IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its member organizations, their members, and these members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

COMPLAINT

1. The U.S. Food and Drug Administration (FDA) must protect the health, safety, and welfare of all Americans by rejecting or limiting the use of dangerous drugs.

2. But the FDA failed America's women and girls when it chose politics over science and approved chemical abortion drugs for use in the United States. And it has continued to fail them by repeatedly removing even the most basic precautionary requirements associated with their use.

3. To date, the FDA's review, approval, and deregulation of chemical abortion drugs has spanned three decades, correlated with four U.S. presidential elections, and encompassed six discrete agency actions. Plaintiffs challenge these six FDA actions and ask that the Court hold them unlawful, set them aside, and vacate them.

4. Beginning in January 1993, on his second full day in office, President Bill Clinton directed his cabinet to legalize chemical abortion drugs in the United States.

5. President Clinton and his agency officials then pressured the French manufacturer of the key chemical abortion drug, mifepristone (also known as "RU-486" and "Mifeprex"), to *donate for free* the U.S. patent rights of the drug to the Population Council—as its name suggests, an entity focused on population control.

6. After receiving the patent rights to mifepristone, the Population Council submitted a new drug application, worked closely with the Clinton FDA during the review process, and, not surprisingly, obtained the agency's approval on

September 28, 2000—just over one month before the closely contested 2000 U.S. presidential election.

7. The *only* way the FDA could have approved chemical abortion drugs was to use its accelerated drug approval authority, necessitating the FDA to call pregnancy an "illness" and argue that these dangerous drugs provide a "meaningful therapeutic benefit" over existing treatments.

8. But pregnancy is not an illness, nor do chemical abortion drugs provide a therapeutic benefit over surgical abortion. In asserting these transparently false conclusions, the FDA exceeded its regulatory authority to approve the drugs.

9. What's more, the FDA needed to disavow science and the law because the FDA never studied the safety of the drugs under the labeled conditions of use despite being required to do so by the Federal Food, Drug, and Cosmetic Act (FFDCA). The agency also ignored the potential impacts of the hormone-blocking regimen on the developing bodies of adolescent girls in violation of the Pediatric Research and Equity Act (PREA). And the FDA disregarded the substantial evidence that chemical abortion drugs cause more complications than even surgical abortions.

10. Since then, the FDA has not followed the science, reversed course, or fixed its mistakes—all to the detriment of women and girls. Instead, the FDA has doubled down on its actions and removed the few safeguards that were in place.

11. In March 2016—*fourteen years* after two Plaintiffs filed a citizen petition with the FDA asking the agency to withdraw its approval of chemical

abortion drugs—the FDA rejected these Plaintiffs' petition despite their explanations that the agency violated federal laws by approving these drugs and ignoring the substantial evidence that these drugs harm women and girls.

12. On the *same day* that the FDA rejected the citizen petition and mere months before another U.S. presidential election, the FDA also made "major changes" to the chemical abortion drug regimen, eliminating crucial safeguards for pregnant women and girls.

13. For example, the FDA extended the permissible gestational age of the baby for which a pregnant woman or girl may take chemical abortion drugs—from seven weeks to ten weeks.

14. Numerous studies have demonstrated that there is an increased risk from chemical abortion drugs to pregnant women and girls as the baby's age advances from seven weeks to ten weeks because the surface area of the placenta as well as the size of the baby significantly grow during these three weeks.

15. Also in 2016, the FDA changed the dosage and route of administration for the chemical abortion drugs, reduced the number of required in-person office visits from three to one, expanded who could prescribe and administer chemical abortion drugs beyond medical doctors, and eliminated the requirement for abortionists to report non-fatal complications from chemical abortion drugs—without requiring any objective clinical investigations or studies that evaluated the safety and effectiveness of this new chemical abortion regimen or any safety assessment of its effects on the developing bodies of girls under 18 years of age.

16. These major changes failed to satisfy the rigorous scientific standards of the FFDCA and violated PREA's requirement for a specific safety assessment of these changes on pregnant girls who undergo the revised chemical abortion drug regimen.

17. Realizing a profit-making opportunity in the rapidly growing chemical abortion business, another entity sought the FDA's approval to market and distribute a generic version of mifepristone. In 2019, the FDA obliged and approved the generic drug—without requiring any new clinical investigations or studies that evaluated the drug's safety and effectiveness under the requirements of the FFDCA, nor any specific safety assessments on girls as set forth under PREA.

18. A couple of years later, in April of 2021, shortly after President Joe Biden took office, the FDA's new management issued a "Non-Enforcement Decision" by which the agency would stop enforcing its requirement that abortionists provide in-person dispensing of mifepristone and instead would temporarily allow mail-order chemical abortions during the COVID-19 public health emergency.

19. In December 2021—*two-and-a-half years* after two Plaintiffs filed a citizen petition asking the FDA to restore and strengthen the pre-2016 chemical abortion drug regimen or, at minimum, to preserve the few remaining safeguards for women and girls—the FDA rejected almost all of these Plaintiffs' citizen petition. The FDA issued its denial despite their discussion of how the agency violated the law by ignoring the growing and substantial evidence that these dangerous drugs harm women and girls.

20. On the *same day* that it rejected the citizen petition, the Biden FDA also announced that it would permanently allow abortionists to send chemical abortion drugs through the mail.

21. This decision not only harms women and girls who voluntarily undergo chemical abortions, but it also further helps sex traffickers and sexual abusers to force their victims into getting abortions while preventing the authorities from identifying these victims.[1] In fact, the State of Texas has recognized that "[d]ue to the potentially high number of trafficking victims who undergo abortion procedures, abortion facility employees are uniquely situated to identify and assist victims of sex trafficking."[2]

22. In addition to the legal and scientific infirmities referenced above, all of the FDA's actions on chemical abortion drugs—the 2000 approval, the 2016 major changes, the 2019 generic drug approval, and the two 2021 actions to eliminate the in-person dispensing requirement—failed to acknowledge and address the federal laws that prohibit the distribution of chemical abortion drugs by postal mail,

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[1] *See, e.g.,* Ex. 1, Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61, 73, 77–78 (noting that survivors in study "reported that they often did not freely choose the abortions they had while being trafficked," these "[s]urvivors [] had significant contact with clinical treatment facilities, most commonly Planned Parenthood clinics," and that "these points of contact with healthcare represent rare opportunities for victim identification and intervention.").

[2] Ex. 2, C.S.H.B. 3446, H. Comm. Rpt., 84th Legis. (Mar. 12, 2015), https://capitol.texas.gov/tlodocs/84R/analysis/pdf/HB03446H.pdf (a subsequent, similar version was codified at Tex. Health & Safety Code § 245.025).

express company, or common carrier. *See* 18 U.S.C. §§ 1461, 1462. Instead, the FDA's actions permitted and sometimes even encouraged these illegal activities.

23. After two decades of engaging the FDA to no avail, Plaintiffs now ask this Court to do what the FDA was and is legally required to do: protect women and girls by holding unlawful, setting aside, and vacating the FDA's actions to approve chemical abortion drugs and eviscerate crucial safeguards for those who undergo this dangerous drug regimen.

JURISDICTION AND VENUE

24. This Court has subject-matter jurisdiction under 28 U.S.C. § 1331 because this action raises federal questions under the Administrative Procedure Act (APA), 5 U.S.C. §§ 553, 701–06, and the FFDCA, 21 U.S.C. § 301 *et seq*.

25. This Court also has jurisdiction under 28 U.S.C. § 1346(a) because this is a civil action against the United States.

26. Additionally, this Court has jurisdiction under 28 U.S.C. § 1361 to compel an officer of the United States or any federal agency to perform his or her duty.

27. This Court has jurisdiction to review Defendants' unlawful actions and enter appropriate relief under the APA, 5 U.S.C. §§ 553, 701–06.

28. This Court has jurisdiction to issue equitable relief to enjoin ultra vires agency action under an equitable cause of action. *Larson v. Domestic & Foreign Com. Corp.*, 337 U.S. 682, 689–91 (1949).

29. This case seeks declaratory, injunctive, and other appropriate relief under the Declaratory Judgment Act, 28 U.S.C. §§ 2201–02, 5 U.S.C. §§ 705–06, Federal Rule of Civil Procedure 57, and the Court's inherent equitable powers.

30. This Court may award costs and attorneys' fees under the Equal Access to Justice Act, 28 U.S.C. § 2412.

31. Venue is proper in this Court under 28 U.S.C. § 1391 because a substantial part of the events or omissions giving rise to the claims occurred in this district, and a substantial part of property that is the subject of the action is situated here. This district and this division are where Plaintiffs Alliance for Hippocratic Medicine, including the doctors of its member associations, and Dr. Shaun Jester are situated and are injured by Defendants' actions. Defendants are United States agencies or officers sued in their official capacities. A substantial part of the events or omissions giving rise to the Complaint occurred within the Northern District of Texas.

PLAINTIFFS

32. Four national medical associations and four doctors experienced in caring for pregnant and post-abortive patients bring this case. They seek to protect women and girls from the documented dangers of chemical abortion drugs.

33. Plaintiff Alliance for Hippocratic Medicine is a nonprofit membership organization that upholds and promotes the fundamental principles of Hippocratic medicine: protecting the vulnerable at the beginning and end of life; seeking the ultimate good for the patient with compassion and moral integrity; and providing health care with the highest standards of excellence based on medical science. The

Alliance for Hippocratic Medicine's members currently are the American Association of Pro-Life Obstetricians and Gynecologists, the American College of Pediatricians, the Catholic Medical Association, the Christian Medical & Dental Associations, and the Coptic Medical Association of North America. The Alliance for Hippocratic Medicine is incorporated in the State of Texas and has its registered agent in Amarillo, Texas. The Alliance for Hippocratic Medicine seeks relief on behalf of itself, its current and future member organizations, their members, and these members' patients. Mr. Mario Dickerson and Drs. Donna Harrison, Jeffrey Barrows, and Quentin Van Meter submit declarations in support of the Alliance for Hippocratic Medicine.[3]

34. Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) is a nonprofit organization that encourages and equips its members and other concerned medical practitioners to provide an evidence-based rationale for defending the lives of both the pregnant mother and her unborn child. AAPLOG aims to make known the evidence-based effects of abortion on women as well as the scientific fact that human life begins at the moment of fertilization, with the goal that all women, regardless of race, creed, or national origin, will be empowered to make healthy and life-affirming choices. AAPLOG is incorporated in the State of Florida, and headquartered in Indiana. AAPLOG has individual members in Texas. AAPLOG seeks relief on behalf of itself, its current and future

[3] Ex. 3, Dickerson Decl. ¶ 7; Ex. 4, Harrison Decl. ¶ 6, 13; Ex. 5, Barrows Decl. ¶ 2; Ex. 6, Van Meter Decl. ¶ 6.

members, and their patients. Drs. Donna Harrison, Christina Francis, Ingrid Skop, and Nancy Wozniak submit declarations in support of AAPLOG.[4]

35. Plaintiff American College of Pediatricians is a national organization of pediatricians and other health care professionals. The American College of Pediatricians is a nonprofit organization founded in 2002, is incorporated in the State of Tennessee, and has its registered agent in Tennessee. The American College of Pediatricians' membership includes more than 600 physicians and other health care professionals drawn from 47 different states across the nation. The American College of Pediatricians has members within this judicial district and elsewhere in the State of Texas. The American College of Pediatricians seeks relief on behalf of itself, its current and future members, and their patients. Dr. Quentin Van Meter submits a declaration in support of the American College of Pediatricians.[5]

36. Plaintiff Christian Medical & Dental Associations is a national nonprofit organization, headquartered in the State of Tennessee, of Christian physicians, dentists, and allied health care professionals, with over 13,000 members nationwide, including 1,237 overall members in Texas, of whom 607 are practicing or retired physicians, and 35 are OB/Gyns. The Christian Medical & Dental Associations sues on behalf of itself, its current and future members, and their

[4] Ex. 4, Harrison Decl. ¶ 5; Ex. 7, Francis Decl. ¶ 4; Ex. 8, Skop Decl. ¶ 4; Ex. 9, Wozniak Decl. ¶ 3.

[5] Ex. 6, Van Meter Decl. ¶ 6.

patients. Drs. Jeffrey Barrows and Steven Foley submit declarations in support of the Christian Medical & Dental Associations.[6]

37. Plaintiff Dr. Shaun Jester, D.O, is a board-certified obstetrician and gynecologist and the Medical Director of Moore County OB/Gyn in Dumas, Texas. His practice includes cesarean section deliveries, hysterectomies, and other women's health treatments. He has treated women who have had abortions, including one woman who suffered an adverse event from a chemical abortion, for which he submitted an adverse event report to the FDA. Dr. Jester sues on his own behalf and on behalf of his current and future patients.

38. Plaintiff Dr. Regina Frost-Clark, M.D., is a board-certified doctor in obstetrics and gynecology. She practices with Ascension Medical Group St. John OB/Gyn Associates in Saint Clair Shores, Michigan. Dr. Frost-Clark has treated several women who have suffered complications from chemical abortions, many who presented to the emergency room. Dr. Frost-Clark sues on her own behalf and on behalf of her current and future patients.

39. Plaintiff Dr. Tyler Johnson, D.O., is an emergency department physician certified by the American Board of Emergency Medicine. Based out of Leo, Indiana, Dr. Johnson serves as the director of emergency medicine at Parkview Dekalb Hospital and practices in the emergency departments of hospitals throughout northern Indiana. He has treated women in the emergency department

[6] Ex. 5, Barrows Decl. ¶ 2; Ex. 10, Foley Decl. ¶ 5.

suffering complications from chemical abortion. Dr. Johnson sues on his own behalf and on behalf of his current and future patients.

40. Plaintiff Dr. George Delgado, M.D., is board-certified in family medicine and in hospice and palliative medicine. He serves as the director of medical affairs of Culture of Life Family Services, which based out of Escondido, California, and provides comprehensive medical care and pro-life pregnancy clinic services for women and children. He also serves as a medical advisor to the Abortion Pill Rescue Network. Dr. Delgado established the Abortion Pill Reversal program—a process that can reverse the effects of the chemical abortion drug regimen and allow women and girls to continue their pregnancies.[7] He has treated women suffering complications from chemical abortion and seeking to reverse the effects of chemical abortion. Dr. Delgado sues on his own behalf and on behalf of his current and future patients.

DEFENDANTS

41. Defendant FDA is an agency of the United States government within the United States Department of Health and Human Services (HHS). The Secretary of HHS has delegated to the FDA the authority to administer the provisions of the FFDCA for approving new drug applications and authorizing a risk evaluation and mitigation strategy (REMS) for dangerous drugs. The address of the FDA's headquarters is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

[7] Abortion Pill Reversal, https://www.abortionpillreversal.com/abortion-pill-reversal/overview (last visited Nov. 17, 2022).

42. Defendant Robert Califf, M.D., who is being sued in his official capacity, is the Commissioner of Food and Drugs at the FDA. He is responsible for supervising the activities of the FDA, including the approval of new drug applications and the issuance, suspension, waiver, or removal of a REMS. Defendant Califf's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

43. Defendant Janet Woodcock, M.D., who is being sued in her official capacity, is the Principal Deputy Commissioner, Office of the Commissioner, at the FDA. She works closely with the Commissioner of Food and Drugs to develop and implement key public health initiatives and oversees the agency's day-to-day functions. Defendant Woodcock served as the Acting Commissioner of Food and Drugs from January 20, 2021, until February 17, 2022, and previously was the Director of the FDA's Center for Drug Evaluation and Research. Defendant Woodcock's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

44. Defendant Patrizia Cavazzoni, M.D., who is being sued in her official capacity, is the Director of the FDA's Center for Drug Evaluation and Research. She is responsible for the regulation of drugs throughout their lifecycle, the development of new and generic drugs, the evaluation of applications to determine whether drugs should be approved, the monitoring of the safety of drugs after they are marketed, and the taking of enforcement actions to protect the public from harmful drugs.

Defendant Cavazzoni's address is 10903 New Hampshire Avenue, Silver Spring, Maryland 20993.

45. Defendant HHS is a federal agency within the executive branch of the U.S. government, including under 5 U.S.C. § 551 and 701(b)(1). Its address is 200 Independence Avenue SW, Washington, D.C. 20201.

46. Defendant Xavier Becerra is the Secretary of HHS and is sued in his official capacity. He is responsible for the overall operations of HHS, including the FDA. His address at HHS is 200 Independence Avenue SW, Washington, D.C. 20201.

47. Collectively and as applicable, all defendants are referred to herein as the "FDA" or "Defendants." Plaintiffs also sue Defendants' employees, agents, and successors in office.

48. The federal officials are subject to the APA. 5 U.S.C. § 701(b); 5 U.S.C. § 551(1).

FACTUAL ALLEGATIONS

I. Introduction

49. This case challenges the FDA's failure to abide by its legal obligations to protect the health, safety, and welfare of women and girls[8] when the agency authorized the chemical abortion drugs mifepristone and misoprostol for use in the

[8] The FDA's approval of chemical abortion lacks an age restriction and, therefore, permits the use of the drug regimen by a pregnant girl of any age under 18 years.

United States and subsequently eliminated necessary safeguards for pregnant women and girls who undergo this dangerous drug regimen.

50. *First*, the FDA never had the authority to approve these drugs for sale. In 2000, the FDA approved chemical abortion drugs under 21 C.F.R. § 314, Subpart H (Subpart H). This regulation authorizes the FDA to grant "accelerated approval" of "certain new drug products that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses* and that provide *meaningful therapeutic benefit* to patients over existing treatments." 21 C.F.R. § 314.500 (emphasis added).

51. But chemical abortion drugs do not treat serious or life-threatening illnesses. Indeed, pregnancy is a normal physiological state that many females experience one or more times during their childbearing years. Pregnancy rarely leads to complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability.[9]

52. Likewise, chemical abortion drugs do not provide a "meaningful therapeutic benefit" to women and girls over existing treatments.

53. To the contrary, the FDA's approval of chemical abortion drugs has potentially serious and life-threatening effects on women and girls, especially when

[9] Ex. 11, Byron Calhoun, *The maternal mortality myth in the context of legalized abortion,* 80 The Linacre Quarterly 264, 264–276 (2013); James Studnicki & Tessa Longbons, *Pregnancy Is* Not *More Dangerous Than Abortion*, Nat'l Rev. (Aug. 28, 2022, 6:30 AM), https://www.nationalreview.com/2022/08/pregnancy-is-not-more-dangerous-than-abortion/.

compared to surgical abortion, which uses medical devices and tools to physically remove a baby from inside the pregnant mother.

54. Even though endocrine disruptors such as mifepristone could have significant impacts on an adolescent girl's developing body and reproductive system, the FDA never required an assessment that evaluated the safety and effectiveness of chemical abortion drugs on pregnant girls under 18 years of age.

55. *Second*, the FDA has not only continued to keep chemical abortion drugs on the market, but the agency has also eliminated the few safeguards it initially established to protect women and girls who go through the chemical abortion drug regimen.

56. In particular, in 2016, the FDA (1) increased the gestational age for which a pregnant woman or girl may have a chemical abortion from 49 days' gestation to 70 days' gestation; (2) changed the dosage and route of administration for the chemical abortion drugs; (3) reduced the number of required in-person office visits from three to one; (4) allowed non-doctors to prescribe and administer chemical abortions; (5) failed to require a clinical study to determine the safety of these changes to the chemical abortion drug regimen on pregnant girls under 18 years of age; and (6) eliminated the requirement for prescribers to report nonfatal adverse events from chemical abortion—thus ensuring that the FDA and the public would never learn of the dangers and injuries that would befall women and girls from removing these safeguards.

57. What is more, in 2021, the FDA announced that it would allow abortionists to dispense the chemical abortion drugs by mail or mail-order pharmacy—an action that a longstanding federal law independently and expressly prohibits.

58. Plaintiffs now ask this Court to protect women and girls by holding unlawful, setting aside, and vacating the FDA's actions to approve and eliminate the safeguards for those who take chemical abortion drugs.

II. The Chemical Abortion Regimen and Its Adverse Health Effects

59. The chemical abortion drug regimen requires the use of two drugs: (1) mifepristone (also known as "RU-486" and "Mifeprex") and (2) misoprostol.

60. As an endocrine disruptor, mifepristone is a synthetic steroid that blocks progesterone receptors in the uterus of a woman or girl. The hormone progesterone is necessary for the healthy growth of a baby and the maintenance of a pregnancy. When a woman or girl ingests the chemical abortion drug mifepristone, the drug blocks the action of the natural hormone progesterone, chemically destroys the baby's environment in the uterus, blocks nutrition to the baby, and ultimately starves the baby to death in the mother's womb.[10]

61. Because mifepristone alone works less than 25 percent of the time to complete the abortion, the FDA's chemical abortion drug regimen mandates the use

[10] *See* Ex. 4, Harrison Decl. at ¶ 21; Ex. 8, Skop Decl. at ¶ 10; Ex. 12, *The FDA and RU-486: Lowering the Standard for Women's Health: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform*, 109th Cong. 4 (2006).

of a second drug—misoprostol—to induce cramping and contractions in an attempt to expel the baby from the mother's womb.[11]

62. The only other FDA-approved use of misoprostol is to reduce the risk of gastric ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs) in patients at high risk of complications from gastric ulcers and patients at high risk of developing gastric ulceration.[12] Misoprostol's label warns that the drug "should not be taken by pregnant women to reduce the risk of ulcers" by NSAIDs.[13]

63. The use of these two chemical abortion drugs causes significant injuries and harms to pregnant women and girls.

64. For example, upwards of ten percent (10%) of women who take chemical abortion drugs will need follow-up medical treatment for an incomplete or failed chemical abortion,[14] with an average of thirty-nine percent (39%) of women requiring surgery if taken in the second trimester.[15]

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[11] *See* Ex. 4, Harrison Decl. at ¶ 21; Ex. 13, 2002 Citizen Petition of AAPLOG to FDA at 41 n.187 (Aug. 8, 2002); *see also* FDA-Approved Label for Mifepristone (Mifeprex) (Mar. 2016), https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

[12] *See, e.g.,* Ex. 14, FDA-Approved Label for Misoprostol (Cytotec) (Jan. 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019268s051lbl.pdf.

[13] *Id.*

[14] Ex. 18, Maarit Niinimaki et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BJM, April 20, 2011, at 4.

[15] Ex. 15, Maarit J. Mentula et al., *Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study*, 26 Hum. Reprod. 927, 931 (2011).

65. Twenty percent (20%) of females will have an adverse event after taking chemical abortion drugs—a rate four times higher than with surgical abortion. This includes over fifteen percent (15%) of females experiencing hemorrhaging and two percent (2%) having an infection during or after taking chemical abortion drugs.[16]

66. Chemical abortions are over fifty percent (50%) more likely than surgical abortions to result in an emergency department visit within thirty days, affecting one in twenty females.[17]

67. The number of chemical abortion-related emergency room visits increased by over five hundred percent (500%) between 2002 and 2015.[18]

68. For those women and girls who take chemical abortion drugs, there is a significant increase in risk of complications as the baby's gestational age increases. One study found that, after nine weeks' gestation, almost four times as many women and girls experience an incomplete abortion, nearly twice as many suffer an infection, and over six times as many women and girls require surgical abortion after consuming the chemical abortion drugs.[19]

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[16] Ex. 16, Maarit Niinimaki et al., *Immediate complications after medical compared with surgical termination of pregnancy*, 114 Obstetrics & Gynecology 795 (2009).

[17] Ex. 17, James Studnicki et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, Health Serv. Rsch. & Managerial Epidemiology, Nov. 9, 2021.

[18] *Id* at 5.

[19] Ex. 18, Niinimaki, *supra* note 14, at 5.

69. Chemical abortion drugs have heightened risks for women and girls with certain blood types. In fact, if a woman or girl with a Rh-negative blood type is not administered certain medication (Rhogam) at the time of her chemical abortion, she could experience isoimmunization, which threatens her ability to have future successful pregnancies. If an Rh-negative woman or girl is left untreated, her future baby will have a fourteen percent (14%) chance of being stillborn and a fifty percent (50%) chance of being born alive but suffering neonatal death or brain injury. Around fifteen percent (15%) of the U.S. population is at risk of this blood condition.[20]

70. Some abortion activists encourage women to lie to an emergency department doctor by saying they are having a miscarriage if they suffer complications requiring urgent care.[21] If a chemical abortion is miscoded as a miscarriage in the emergency room (which occurred sixty percent (60%) of the time in one study), the treating doctor's lack of knowledge results in the woman or girl

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[20] Ingrid Skop, *The Evolution of "Self-Managed" Abortion: Does the Safety of Women Seeking Abortion Even Matter Anymore?*, Charlotte Lozier Institute (Mar. 1, 2022), https://lozierinstitute.org/the-evolution-of-self-managed-abortion/.

[21] *See, e.g., Will a doctor be able to tell if you've taken abortion pills?*, Women Help Women (Sept. 23, 2019), https://womenhelp.org/en/page/1093/will-a-doctor-be-able-to-tell-if-you-ve-taken-abortion-pills; *How do you know if you have complications and what should you do?*, AidAccess, https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do (last visited Nov. 14, 2022).

being at significantly greater risk of needing multiple hospitalizations and follow-up surgery.[22]

71. The risk of chemical abortions is not only physical: women and girls have described that their chemical abortion experiences harmed their mental health and left them feeling unprepared, silenced, regretful, or left with no other choice before undergoing a chemical abortion.[23]

72. Abortionists exacerbate this harm to a woman's or girl's mental health by not adequately informing her about what she will see when she self-administers chemical abortion drugs at home or in a hotel. For example, one woman was surprised and saddened to see that her aborted baby "had a head, hands, and legs" with "[d]efined fingers and toes."[24]

73. Given the FDA's refusal to require an ultrasound, abortionists can egregiously misdate the gestational age of a baby with devastating consequences. One young woman has alleged that she did not receive an ultrasound or any other physical examination to determine her baby's gestational age prior to receiving

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[22] Ex. 19, James Studnicki et al., *A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization*, Health Servs. Rsch. & Managerial Epidemiology, May 20, 2022.

[23] Ex. 20, Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 Health Commc'n 1485 (2021).

[24] Caroline Kitchener, *Covert network provides pills for thousands of abortions in U.S. post Roe*, Wash. Post: Politics (Oct. 18, 2022, 6:00 am), https://www.washingtonpost.com/politics/2022/10/18/illegal-abortion-pill-network/.

chemical abortion drugs from Planned Parenthood.[25] The abortionist misdated the baby's gestational age as six weeks, resulting in the at-home delivery of a "lifeless, fully-formed baby in the toilet," later determined to be around *30-36 weeks old*.[26] Because of this chemical abortion, the woman alleges that she "has endured significant stress, trauma, emotional anguish, physical pain, including laceration and an accelerated labor and delivery unaided by medication, lactation, soreness, and bleeding."[27]

III. The FDA's Authority to Review, Approve, or Deny New Drug Applications

74. The FDA's approval of new drugs must comply with federal laws and regulations that directly govern the agency, in addition to other laws that broadly govern the federal government's actions. Specifically, the FDA must comply with the Federal Food, Drug, and Cosmetic Act (FFDCA), the Pediatric Research Equity Act of 2003 (PREA), and the agency's regulations. When taking regulatory action on new drugs, the FDA must also meet the requirements of other federal laws restricting the distribution of certain drugs.[28]

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[25] Complaint at 9, *Doe v. Shah*, No. 501531/2021, (Sup. Ct. of N.Y., Cnty. of Kings Jan. 20, 2021), https://www.liveaction.org/news/wp-content/uploads/2022/10/Kings-Co-501531_2021_JANE_DOE_v_MEERA_SHAH.pdf.

[26] *Id.* at 10–11.

[27] *Id.* at 11.

[28] For a general overview of the FDA's drug approval process, *see How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, Congressional Research Service (May 8, 2018), https://crsreports.congress.gov/product/pdf/R/R41983.

A. New Drug Applications Under the Federal Food, Drug, and Cosmetic Act

75. Under the FFDCA, anyone seeking to introduce into commerce and distribute any new drug in the United States must first obtain the FDA's approval by filing a new drug application (NDA). 21 U.S.C. § 355(a).

76. A drug may be considered "new" by reason of the "newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4). A drug may also be considered "new" by reason of the "newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug . . . is not a new drug." *Id.* § 310.3(h)(5).

77. The NDA must contain extensive scientific data showing the safety and effectiveness of the drug. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125.

78. Under the FFDCA, the FDA must reject an application if the clinical investigations "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(2).

79. The FDA must also reject an application if "the results of such tests show that such drug is unsafe for use under such conditions or do not show that

such drug is safe for use under such conditions." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(3).

80. The FDA shall refuse an application if, based upon information submitted to the agency or upon the basis of any other information before the agency, the FDA "has insufficient information to determine whether such drug is safe for use under such conditions." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(4).

81. Finally, the FDA must deny an application if "there is a lack of substantial evidence that the new drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b)(5).

82. The FFDCA defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d).

83. If a sponsor of an approved drug subsequently seeks to change the labeling, market a new dosage or strength of the drug, or change the way it manufactures a drug, the company must submit a supplemental new drug

application (sNDA) seeking the FDA's approval of such changes. 21 U.S.C. § 355(b); 21 C.F.R. §§ 314.54, 314.70.

84. Only the sponsor "may submit a supplement to an application." 21 C.F.R. § 314.71(a).

85. "All procedures and actions that apply to an application under [21 C.F.R.] § 314.50 also apply to supplements, except that the information required in the supplement is limited to that needed to support the change." 21 C.F.R. § 314.71(b); *see also* 21 C.F.R. § 314.54(a) ("application need contain only that information needed to support the modification(s) of the listed drug").

86. The sNDA must also show that the drug is safe and effective for "the conditions of use prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. § 355(d).

87. The FFDCA allows a generic drug manufacturer to submit an abbreviated new drug application (ANDA) for approval to introduce into commerce and distribute a generic version of an approved drug. 21 U.S.C. § 355(j).

88. In the ANDA, the generic drug manufacturer must show, among other things, that (a) the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed and (b) the drug product is chemically the same as the already approved drug, allowing it to rely on the FDA's previous finding of safety and effectiveness for the approved drug. The route of administration, dosage form, and strength must also be the same. 21 U.S.C. § 355(j); 21 C.F.R. § 314.94.

B. Assessments on Pediatric Populations

89. In 1998, the FDA issued a regulation, called the Pediatric Rule, requiring an assessment specifically powered to determine the safety and effectiveness of a new drug on pediatric patients.[29] This rule allowed for full or partial waivers of its pediatric assessment requirements, set forth under then 21 C.F.R. § 314.55(c).

90. A federal district court subsequently held that the FDA had exceeded its statutory authority when issuing the Pediatric Rule and thus enjoined the FDA from enforcing the regulation. *See Ass'n of Am. Physicians & Surgeons v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002).

91. In response, President George W. Bush and Congress enacted PREA to codify the Pediatric Rule legislatively. This law expressly requires studies on the safety and effectiveness of drugs intended for pediatric populations, unless certain exceptions apply. The FDA may require an assessment on the drug's safety and effectiveness, extrapolate findings from studies on adult populations, or waive the assessment for pediatric populations. 21 U.S.C. § 355c.

92. In general, PREA requires an application or supplement to an application for a drug to include an assessment on the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations. 21 U.S.C. § 355c(a)(2)(A)(i). This assessment must also support dosing and

[29] Ex. 21, Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998).

administration for each pediatric subpopulation for which the drug is safe and effective. 21 U.S.C. § 355c(a)(2)(A)(ii).

93. Under limited circumstances, PREA allows the FDA to avoid this assessment and, instead, extrapolate the safety and effectiveness of a drug for pediatric populations: "If the course of the *disease* and the effects of the drug are sufficiently similar in adults and pediatric patients, the [FDA] may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients." 21 U.S.C. § 355c(2)(B)(i) (emphasis added).

94. To support this extrapolation, the FDA must include "brief documentation of the scientific data supporting the conclusion" that the course of the *disease* and the effects of the drug are sufficiently similar in adults and pediatric patients. 21 U.S.C. § 355c(B)(iii) (emphasis added).

95. In addition, PREA also allows the FDA to grant a full or partial waiver of the requirement for pediatric assessments or reports on the investigation for a drug if one of the following situations exists: (1) "necessary studies are impossible or highly impracticable"; (2) "there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups"; or (3) the drug "does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients" and it "is not likely to be used in a substantial number of pediatric patients." 21 U.S.C. § 355c(a)(5)(A), (B).

96. PREA also deemed a waiver or deferral issued under the Pediatric Rule between April 1, 1999, and December 3, 2003, to be a waiver or deferral under 21 U.S.C. § 355c(a). 21 U.S.C. § 355c note.

C. Subpart H Regulations for Accelerated Approval of Certain New Drugs for Serious and Life-Threatening Illnesses

97. Both the FFDCA and PREA serve as the primary laws governing the FDA's review and approval of new drugs. The FDA has also implemented certain regulations to effectuate its legal obligations under these laws and to address certain public health crises over the years.

98. For example, on December 11, 1992, the FDA published the final rule, "New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval."[30]

99. This final rule established procedures "under which FDA will accelerate approval of certain new drugs and biological products for *serious or life-threatening illnesses*, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs."[31]

100. The FDA intended these procedures "to provide expedited marketing of drugs for patients suffering from *such illnesses* when the drugs provide a *meaningful therapeutic advantage* over existing treatment."[32]

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[30] Ex. 22, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).

[31] *Id.* (emphasis added).

[32] *Id.* (emphasis added).

101. As codified under Subpart H, the FDA defined the scope of the new regulations:

> This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses* and that provide *meaningful therapeutic benefit* to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

21 C.F.R. § 314.500 (emphasis added).

102. If the FDA's review under Subpart H concludes that a drug is effective but can be safely used *only if* distribution or use is restricted, the agency must "require such postmarketing restrictions as are needed to assure safe use of the drug product." 21 C.F.R. § 314.520(a).

103. Such restrictions may include distribution (1) "restricted to certain facilities or physicians with special training or experience" or (2) "conditioned on the performance of specified medical procedures." 21 C.F.R. § 314.520(a)(1), (2).

104. The limitations must "be commensurate with the specific safety concerns presented by the drug product." 21 C.F.R. § 314.520(b).

105. Under 21 C.F.R. § 314.530, the FDA may withdraw approval of drugs approved under Section 314.520 if:

> (1) A postmarketing clinical study fails to verify clinical benefit;
>
> (2) The applicant fails to perform a required postmarketing study with due diligence;
>
> (3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;
>
> (4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

106. The FDA's preamble to the Subpart H rulemaking stated that "[t]he burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed."[33]

107. The *only* way the FDA can terminate an applicant's Subpart H restrictions is to notify the applicant that "the restrictions . . . no longer apply" because the "FDA [has] determine[d] that safe use of the drug product can be assured through appropriate labeling." 21 C.F.R. § 314.560.

D. Drugs Approved with Previous Subpart H Restrictions Deemed to Have Risk Evaluation and Mitigation Strategies

108. Congress decided to codify into law the FDA's postmarketing regulations under Subpart H when it enacted the Food and Drug Administration Amendments Act of 2007 (FDAAA) and created a new section of the FFDCA under 21 U.S.C. § 355-1. This new section authorizes the FDA to require persons submitting certain new drug applications to submit and implement a risk evaluation and mitigation strategy (REMS) if the FDA determines that a REMS is "necessary to ensure that the benefits of a drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a).

109. Section 909(b)(1) of the FDAAA specified that a "drug that was approved before the effective date of this Act is . . . deemed to have in effect an

[33] Ex. 22, 57 Fed. Reg. at 58,952.

approved [REMS] . . . if there are in effect on the effective date of this Act elements to assure safe use [pursuant to Subpart H, 21 C.F.R. § 514.520]." H.R. 3580, 110th Cong. (2007). Thus, if the FDA previously attached postmarketing restrictions on a drug approved under Subpart H, the FDAAA converted those restrictions into a REMS.

110. Under the FDAAA, to allow safe access to drugs with known serious risks, the FDA may require that the REMS "include such elements as are necessary to assure safe use of the drug, because of its inherent toxicity or potential harmfulness" if the agency determines that the drug "is associated with a serious adverse drug experience." 21 U.S.C. § 355-1(f)(1).

111. These "Elements to Assure Safe Use" (ETASU) may require (1) prescribers of the drug "have particular training or experience" or be "specially certified," (2) practitioners or health care settings that dispense the drug be "specially certified," (3) doctors dispense the drug to patients "only in certain health care settings, such as hospitals," (4) doctors dispense the drug to patients "with evidence or other documentation of safe-use conditions, such as laboratory test results," (5) each patient be subject to "certain monitoring," and (6) each patient be enrolled in a "registry." 21 U.S.C. § 355-1(f)(3).

112. The FDA may also require an applicant to monitor and evaluate implementation of the REMS, in addition to working to improve those elements. 21 U.S.C. § 355-1(g).

113. The FDA may also include a communication plan to health care providers as part of the REMS to disseminate certain information about the drug and its risks. 21 U.S.C. § 355-1(e)(3).

114. An applicant "may propose the addition, modification, or removal of [the REMS] . . . and shall include an adequate rationale to support such proposed addition, modification, or removal." 21 U.S.C. § 355-1(g)(4)(A).

IV. Federal Laws Restrict Distribution of Chemical Abortion Drugs

115. Two federal laws restrict the distribution of abortion-inducing drugs. 18 U.S.C. §§ 1461–62. These laws apply to both upstream and downstream distribution.

116. *First*, 18 U.S.C. § 1461 prohibits the use of postal "mails" to convey or deliver chemical abortion drugs. Specifically, it prohibits the mailing or delivery by any letter carrier of "[e]very article or thing designed, adapted, or intended for producing abortion" and "[e]very article, instrument, substance, drug, medicine, or thing, which is advertised or described in a manner calculated to lead to another to use or apply it for producing abortion."

117. *Second*, 18 U.S.C. § 1462 broadly prohibits the use of "any express company or other common carrier" to transport abortion drugs in interstate or foreign commerce. Specifically, it prohibits the use of any express company or common carrier to distribute "any drug, medicine, article, or thing designed, adapted, or intended for producing abortion."

V. The FDA's Review of the Population Council's Application to Market Chemical Abortion Drugs in the United States

118. The French pharmaceutical company Roussel Uclaf S.A. first developed and tested mifepristone under the name RU-486. By April 1990, the drug had become fully available in France.[34]

119. But Roussel Uclaf's German parent company, Hoechst AG, prohibited the drug manufacturer from attempting to enter the U.S. market and filing a new drug application with the FDA.[35] Hoechst's resistance and desire to keep a low profile was due, in part, to its corporate history and complicity in previous mass genocide.[36]

120. Nevertheless, on January 22, 1993—his second full day in office—President Bill Clinton directed then-HHS Secretary Donna Shalala to assess initiatives to promote the testing and licensing of RU-486 in the United States.[37]

121. According to a Roussel Uclaf official, President Clinton also wrote to Hoechst asking the company to file a new drug application with the FDA, which Hoechst refused to do.[38]

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[34] Ex. 13, 2002 Citizen Petition at 7–8.

[35] *Id* at 8.

[36] Julie A. Hogan, *The Life of the Abortion Pill in the United States*, at 23–24 (2000), http://nrs.harvard.edu/urn-3:HUL.InstRepos:8852153 ("Hoechst traces its corporate history to I.G. Farben, the manufacturer of Zyklon-B, which was used in the gas chambers of Auschwitz," and therefore "did not want to be credited with doing to fetuses what the Nazis had done to the Jews.").

[37] Ex. 13, 2002 Citizen Petition at 8.

[38] *Id.*

122. In early 1993, as HHS later reported, Secretary Shalala and then-FDA Commissioner David Kessler likewise "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[39]

123. Specifically, according to HHS, "[i]n April 1993, representatives of FDA, Roussel Uclaf and the Population Council, a not-for-profit organization, met to discuss U.S. clinical trials and licensing of RU-486." Between April 1993 and May 1994, the parties continued their negotiations.[40]

124. "The Population Council is a nonprofit founded in 1952 by John D. Rockefeller III to address supposed world overpopulation. . . . [Rockefeller] served as the organization's first president."[41]

125. The talks between the FDA, the Population Council, and Roussel Uclaf culminated in what HHS called a "donation": Roussel Uclaf transferred, "without remuneration, its United States patent rights to mifepristone (RU-486) to the Population Council."[42]

126. After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States.[43]

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[39] *Id.* (quoting HHS Fact Sheet, *Mifepristone (RU-486): Brief Overview* (May 16, 1994)).

[40] HHS Fact Sheet, *Mifepristone (RU-486): Brief Overview*.

[41] Population Council, https://www.influencewatch.org/non-profit/population-council/ (last visited Nov. 15, 2022).

[42] Ex. 13, 2002 Citizen Petition at 8–9 (quoting HHS Press Release, *Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council*, (May 16, 1994)).

[43] *Id.* at 9.

127. The Population Council then filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[44]

128. The FDA initially accorded the drug standard review; but in a May 7, 1996, letter, the FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[45]

129. On September 18, 1996, the FDA issued a letter stating that the application was "approvable" and requested more information from the Population Council.[46]

130. On February 18, 2000, the FDA issued a second "approvable" letter, setting forth the remaining prerequisites for approval. This letter announced that the FDA had "considered this application under the restricted distribution regulations contained in 21 C.F.R. § 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR § 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[47]

131. The FDA told the Population Council that the agency would proceed under Subpart H because the FDA "concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended."[48]

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[44] *Id.* at 10.
[45] *Id.*
[46] *Id.* at 10–11.
[47] Ex. 23, FDA Letter to Population Council re: NDA (Feb. 18, 2000) at 5.
[48] *Id.*

132. Given the known dangers of chemical abortion drugs, the FDA needed to approve the Population Council's application under Subpart H because this regulatory authority provided the FDA with the *only* means to restrict the drugs' distribution and use "to assure safe use." 21 C.F.R. 314.520.

133. In response to the proposed Subpart H consideration, the Population Council objected and explained that its application for mifepristone did not fall within the scope of Subpart H.[49]

134. The Population Council thus wrote a letter to the FDA just three weeks before the final approval of mifepristone, arguing that "it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[50]

135. The Population Council stated that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[51]

136. Moreover, as the Population Council observed, "[n]either is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[52]

137. And after quoting the preamble to the FDA's Subpart H Final Rule, the Population Council's letter stated that "[t]he plain meaning of these terms does

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[49] Ex. 13, 2002 Citizen Petition at 20.
[50] *Id.*
[51] *Id.*
[52] *Id.*

not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[53]

138. The letter added that unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[54]

139. The Population Council explained that "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[55]

140. Despite these last-minute objections, the Population Council ultimately ceased its opposition to the FDA's intention to approve chemical abortion drugs under Subpart H on September 15, 2000.[56]

VI. The FDA's Approval of the Population Council's Application to Market Chemical Abortion Drugs in the United States.

141. On September 28, 2000, the FDA approved chemical abortion drugs under Subpart H "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[57]

142. The FDA informed the Population Council that Subpart H "applies when FDA concludes that a drug product shown to be effective can be safely used

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[53] *Id.*

[54] *Id.*

[55] *Id.*

[56] Ex. 24, 2000 FDA Approval Memo. to Population Council re: NDA 20-687 Mifeprex (mifepristone) at 6 (Sept. 28, 2000).

[57] Ex. 25, 2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets at 1 (Sept. 28, 2000).

only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[58]

143. The FDA would not have been able to approve the chemical abortion drugs without invoking Subpart H, as it was the only authority available to the agency to allow it to apply postmarketing restrictions on the drugs.[59]

144. To defend its use of Subpart H, the FDA agency declared that "the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H" and asserted that "[t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[60]

145. The FDA stated that the chemical abortion drugs' "labeling is now part of a total risk management program." In particular, "[t]he professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program."[61]

146. The 2000 approval required the Population Council to include on the drugs' label a "black box warning for special problems, particularly those that may lead to death or serious injury."[62]

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[58] Ex. 24, 2000 FDA Approval Memo. at 6.

[59] Ex. 26, 2003 Citizen Petitioners' Response to Opposition Comments filed by The Population Council, Inc. and Danco Laboratories, LLC to Comments at 2–4 (Oct. 10, 2003) https://www.aaplog.org/wp-content/uploads/2002/08/ResponseToDanco10-03reRU-486.pdf (2003 Response).

[60] Ex. 24, 2000 Approval Memo. at 6.

[61] *Id.* at 2.

[62] *Id.*

147. The approved regimen in 2000 contained measures to assure safe use, including requiring at least three office visits: (1) the Day 1 in-person dispensing and administration of mifepristone; (2) the Day 3 in-person dispensing and administration of misoprostol; and (3) the Day 14 return to the doctor's office to confirm no fetal parts or tissue remain.[63]

148. The FDA explained that "[r]eturning to the health care provider on Day 3 for misoprostol . . . assures that the misoprostol is correctly administered," and it "has the additional advantage of contact between the patient and health care provider to provide ongoing care, and to reinforce the need to return on Day 14 to confirm that expulsion has occurred."[64]

149. The FDA's Subpart H restrictions included the following requirements for abortionists: the ability to assess the duration of pregnancy accurately and to diagnose ectopic pregnancies (chemical abortion drugs cannot end an ectopic pregnancy, but the symptoms of these drugs resemble hemorrhaging from a life-threatening ectopic pregnancy[65]); the requirement to report any hospitalization, transfusion, or other serious events; and the ability to provide surgical intervention or to ensure that the patient has access to other qualified physicians or medical facilities.[66]

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[63] *Id.* at 2–3.

[64] *Id.* at 3.

[65] Ex. 8, Skop Decl. ¶ 29; *AAPLOG Statement on FDA removing Mifepristone safety protocols (REMS)*, at 2, https://aaplog.org/wp-content/uploads/2021/04/AAPLOG-Statement-on-FDA-removing-mifepristone-REMS-April-2021-1.pdf.

[66] Ex. 24, 2000 Approval Memo. at 6.

150. The FDA's restrictions on the distribution of mifepristone included:

- In-person dispensing from the doctor to the woman or girl;
- Secure shipping procedures;
- Tracking system ability;
- Use of authorized distributors and agents; and
- Provision of the drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing.[67]

151. The FDA did not include prohibitions on the upstream distribution of the chemical abortion drugs—from the manufacturer or importer to the abortionist—by mail, express company, or common carrier as proscribed by federal laws, nor did the FDA acknowledge and address these laws.[68]

152. The FDA also outlined the Population Council's two post-approval study commitments.[69] The Population Council was to conduct "a monitoring study to ensure providers who did not have surgical-intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial)."[70]

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[67] *Id.*

[68] *Id.*

[69] Ex. 25, 2000 Approval Letter at 2–3.

[70] Ex. 24, 2000 Approval Memo. at 7.

The Population Council also agreed "to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system."[71]

153. In the 2000 Approval, the FDA informed the Population Council that the agency was "waiving the pediatric study requirement for this action on this application."[72] Without explanation of the effects of chemical abortion drugs on puberty or substantiation of its decision, the FDA asserted that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen." [73]

154. The FDA nonetheless highlighted the findings of one limited study that included 51 subjects under 20 years of age. The agency explained that the approved labeling states that the safety and efficacy for girls under 18 years of age "have not been studied" because the raw data from this limited study had not been submitted for review, the pediatric population was not part of the NDA indication, the data on safety and effectiveness were only reviewed for the indication's age group (18–35 years of age), and the clinical trials excluded patients younger than 18 years old.[74]

155. The FDA believed it would eventually overcome this data deficiency because the Population Council would "collect outcomes in their [post-approval]

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[71] *Id.*
[72] Ex. 25, 2000 Approval Letter at 3.
[73] Ex. 24, 2000 Approval Memo. at 7.
[74] *Id.*

studies of women of all ages to further study this issue"[75]—even though those studies were not designed to evaluate the safety and effectiveness of mifepristone on girls under the age of 18 years.

156. But the FDA released the Population Council from its obligation to conduct these studies in 2008.[76]

157. Therefore, since the 2000 Approval, the FDA has continued to allow pregnant girls of *any age* to take chemical abortion drugs—despite never requiring a study specifically designed to determine the safety and effectiveness of these drugs.

158. With the FDA approval in hand, the Population Council then granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, an exclusive license to manufacture, market, and distribute Mifeprex in the United States.[77]

VII. 2002 Citizen Petition

159. The FDA's regulations prohibit a litigant from going straight to court to challenge the agency's approval of a new drug. Instead, the FDA's regulations require the submission of a "citizen petition" requesting the agency take or refrain from taking any form of administration action before filing a lawsuit. 21 C.F.R. §§ 10.30, 10.45(b). These regulations allow the FDA to indefinitely delay a final response to a citizen petition. 21 C.F.R. § 10.30(e)(2)(iv). The FDA's eventual

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[75] *Id.*

[76] Ex. 27, 2016 FDA Letter to AAPLOG, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA-2002-P-0364, at 31 (Mar. 29, 2016) (2016 Petition Denial).

[77] Ex. 13, 2002 Citizen Petition at 9.

decision on a citizen petition constitutes a final agency action for the underlying FDA action and the related citizen petition, and both are reviewable in the courts under the APA. 21 C.F.R. § 10.45(c).

160. In August 2002, Plaintiffs AAPLOG and Christian Medical & Dental Associations, along with the Concerned Women for America, (collectively, 2002 Petitioners), submitted a citizen petition (2002 Citizen Petition) with the FDA pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500–314.560); and Section 505 of the FFDCA (21 U.S.C. § 355).[78]

161. The 2002 Petitioners requested that the FDA impose an immediate stay of the approval of mifepristone and ultimately revoke the approval, in addition to requesting a full FDA audit of the underlying clinical studies.[79]

162. The 2002 Petitioners stated that the FDA's approval of mifepristone in 2000 violated the APA for many reasons, including because it was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law, given that (1) the FDA lacked the authority to approve mifepristone under Subpart H and (2) the FDA incorporated misoprostol as part of the chemical abortion regimen despite not receiving an sNDA for this new use of the drug.[80]

163. The 2002 Petitioners explained how the 2000 Approval violated Subpart H because pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of this accelerated approval authority. "Thus,

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[78] *Id.* at 1.

[79] *Id.*

[80] *Id.* at 18–23, 41–48.

pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point."[81]

164. Moreover, "there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions." Nor does mifepristone "treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion." Indeed, as the 2000 Mifeprex label acknowledged, because "medical abortion failures should be managed with surgical termination," the option for surgical abortion must be available for any woman or girl who undergoes chemical abortion.[82]

165. Nor did the clinical trials compare chemical abortion with the existing "therapy," surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments."[83]

166. The 2002 Petitioners also pointed out that the clinical trials that the Population Council submitted to support its NDA failed to present "substantial evidence" that the mifepristone regimen is safe and effective.[84]

167. In fact, as the 2002 Citizen Petition demonstrated, the FDA's 2000 Approval has endangered women's lives because it lacked the necessary safeguards for this dangerous regimen. For instance, the FDA failed to require an ultrasound,

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[81] *Id.* at 19.
[82] *Id.* at 21–22.
[83] *Id.* at 37.
[84] *Id.* at 24–41.

which is necessary both to determine an accurate gestational age of the baby and to rule out an ectopic pregnancy. The FDA also did not restrict the regimen to physicians who have received proper training and possess admitting privileges to emergency facilities. In light of the FDA's subsequent acknowledgment that women had serious adverse events since the 2000 Approval, the 2002 Citizen Petition urged the FDA to "react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials."[85]

168. What is more, the 2002 Petitioners challenged the 2000 Approval because the U.S. clinical trial for mifepristone did not mirror the anticipated conditions of use under the approved label despite the FFDCA's requirements under 21 U.S.C. § 355(d). Under the conditions of the U.S. clinical trial:

(a) the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy and exclude women with ectopic pregnancies;

(b) the physicians had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization; and

[85] *Id.* at 49–71.

(c) all patients needed to be within one hour of emergency facilities or the facilities of the principal investigator; and

(d) women were monitored for four hours for adverse events after taking misoprostol.[86]

169. Because the FDA's 2000 Approval did not require these safeguards for women and girls using chemical abortion drugs, the 2002 Petitioners reasoned that the agency should not have extrapolated conclusions about the safety and effectiveness of chemical abortion drugs under the approved label.[87]

170. The 2002 Citizen Petition also requested that the FDA withdraw the 2000 Approval of the chemical abortion drugs because the sponsor had not been enforcing the limited restrictions on the use of the drug regimen. Among the deviations from the approved regimen, physicians were offering chemical abortion drugs to women with pregnancies beyond the maximum seven weeks and eliminating the second of the three prescribed visits (i.e., in-facility administration of misoprostol).[88]

171. Subpart H authorizes the FDA to withdraw approval of a drug approved under Section 514.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon." 21 C.F.R. § 314.530(a)(4). Because "the burden is on the applicant to ensure that the conditions of use under which the

[86] *Id.* at 75–76.
[87] *Id.* at 76.
[88] *Id.* at 71–75.

applicant's product was approved are being followed," the 2002 Petitioners asked the FDA to exercise its authority to withdraw its approval for mifepristone.[89]

172. The 2002 Petitioners also challenged the FDA's decision to waive the agency's regulatory requirement to conduct a pediatric study—the failure of which endangered the health and safety of girls—because it did not meet the requirements for such a waiver.[90]

173. The 2002 Citizen Petition next pointed out that the FDA impermissibly reduced the Population Councils' post-approval studies during the final stages of the FDA's review in 2000. "Not only did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the [post-approval] trials that it would perform."[91]

174. Finally, the FDA then "compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate [post-approval] study."[92] Because chemical abortion drugs "could conceivably interfere with

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[89] Ex. 13, 2002 Citizen Petition at 75.
[90] *Id.* at 76–83.
[91] *Id.* at 84–85.
[92] *Id.* at 86.

pubertal development," girls under 18 years of age deserve separate consideration in studies with significant numbers of participants.[93]

175. On October 10, 2003, the 2002 Petitioners filed a response ("2003 Response") to opposition comments by the Population Council and Danco. The 2003 Response not only responded to these comments, but it also provided the FDA with additional evidence that the safety and effectiveness of chemical abortion drugs have not been established in accordance with the requirements of the FFDCA or the FDA's own regulations.[94]

VIII. Implementation of a REMS for Mifepristone

176. After receiving the 2002 Citizen Petition, the FDA's next significant regulatory action on chemical abortion drugs involved incorporating Congress's mandate to convert Subpart H postmarketing restrictions for previously approved drugs into a REMS.

177. As previously discussed, Section 909(b)(1) of the FDAAA specified that a "drug that was approved before the effective date of this Act is . . . deemed to have in effect an approved [REMS] . . . if there are in effect on the effective date of this Act elements to assure safe use [pursuant to 21 C.F.R. § 514.520]."

[93] *Id.* at 86, n. 377.

[94] Ex. 26, 2003 Response.

178. In a March 27, 2008, Federal Register notice, the FDA identified chemical abortion drugs as one of "those drugs that FDA has determined will be deemed to have in effect an approved REMS."[95]

179. In 2011, pursuant to the 2008 notice, the FDA approved a REMS for chemical abortion drugs in accordance with section 909(b)(1) of the FDAAA.[96]

180. The FDA "determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications."[97]

181. The REMS incorporated the previous Subpart H restrictions and consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.[98]

182. The REMS required "prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications."[99]

183. The FDA also instructed Danco that, "[a]s part of the approval under Subpart H, as required by 21 CFR § 314.550, you must submit all promotional

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[95] Ex. 28, Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313, 16,314 (Mar. 27, 2008).

[96] Ex. 29, 2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC at 1 (June 6, 2011) (2011 Approval Letter).

[97] *Id.* at 1.

[98] *Id.* at 1; Ex. 30, 2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011) (2011 REMS).

[99] Ex. 29, 2011 Approval Letter at 1; Ex. 30, 2011 REMS.

materials, including promotional labeling as well as advertisements, at least 30 days before the intended time of initial distribution of the labeling or initial publication of the advertisement."[100]

IX. The FDA's Denial of the 2002 Citizen Petition

184. Almost *fourteen years* after receiving the 2002 Citizen Petition—on March 29, 2016—the FDA denied the 2002 Citizen Petition ("2016 Denial").[101]

185. The FDA abused its regulatory authority under 21 C.F.R. § 10.30(e)(2)(iv) to delay a final response to the 2002 Citizen Petition.

186. In the 2016 Denial, the FDA asserted that it appropriately approved chemical abortion drugs under Subpart H because "[a]s FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening *conditions*, as well as to illnesses or diseases."[102]

187. The FDA further asserted that the Subpart H premable "also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations."[103]

188. The FDA asserted that "[u]nwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses

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[100] Ex. 29, 2011 Approval Letter at 2–3.
[101] Ex. 27, 2016 Petition Denial.
[102] *Id.* at 4 (emphasis added).
[103] *Id.*

or conditions, can be serious for certain populations or under certain circumstances."[104]

189. The FDA also asserted that chemical abortion "provides a meaningful therapeutic benefit to some patients over surgical abortion" because chemical abortion "provides an alternative to surgical abortion," which itself can lead to complications such as "a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure."[105]

190. The FDA also asserted that the clinical trials constituted "substantial evidence" of effectiveness, while contending that the "FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled."[106]

191. The FDA then asserted that its decision not to require studies of pediatric patients "was consistent with FDA's implementation of the regulations in effect at that time." The agency also asserted that its 2000 Approval "determined that there were sufficient data from studies of mifepristone." Even though the 2000 Approval said the FDA was waiving the requirement for a pediatric assessment, the 2016 Petition Denial stated that the 2000 Approval "should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal

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[104] *Id.*

[105] *Id.* at 5.

[106] *Id.* at 9.

pediatric patients, rather than stating that we were waiving the requirements for all pediatric groups."[107]

192. In response to the 2002 Citizen Petition's argument that the FDA's inclusion of misoprostol as part of the mifepristone regimen was illegal because the sponsor of that drug had not submitted an sNDA, the FDA asserted that "[n]either the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex."[108]

193. The FDA provided "[e]xamples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the reference drug."[109] But the FDA did not purport to provide an example of drug labeling where that second drug was not approved for the use of the new indication.

X. The FDA's 2016 Major Changes to the Mifepristone Regimen

194. On the *same day* that the FDA denied the 2002 Citizen Petition—March 29, 2016—the FDA also approved major changes to the mifepristone regimen (2016 Major Changes) in response to an sNDA that Danco had submitted to the FDA on May 28, 2015.[110]

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[107] *Id.* at 29.

[108] *Id.* at 15.

[109] *Id.*

[110] Ex. 31, 2016 FDA Letter to Danco Laboratories re: NDA 020687, Supp 20 (Mar. 29, 2016).

195. The FDA acknowledged that the 2000 Approval hinged on necessary safeguards to protect women and girls from the dangers of chemical abortion drugs. The FDA's "Summary Review" of the 2016 Major Changes recalled that "[a]t the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520." After summarizing the history and provisions of the REMS for mifepristone, the FDA noted that "[t]he REMS for Mifeprex incorporated the restrictions under which the drug was originally approved."[111] But the FDA decided to remove these crucial protections after reconsidering and reopening the 2000 Approval.

196. The FDA acknowledged that "these major changes are interrelated," demonstrating the agency's awareness that each change impacted the others.[112]

197. The 2016 Major Changes included the following revisions to the 2000 Approval's safeguards for women and girls:

(a) extending the maximum gestational age at which a woman or a girl can abort her baby from 49 days to 70 days;

(b) altering the mifepristone dosage from 600 mg to 200 mg, the misoprostol dosage from 400 mcg to 800 mcg, and misoprostol administration from oral to buccal (cheek pouch);

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[111] Ex. 32, FDA, Center for Drug Evaluation and Research, Summary Review of Application Number: 020687Orig1s020, at 4 (Mar. 29, 2016) (2016 Summary Review).

[112] *Id.* at 6.

(c) eliminating the requirement that administration of misoprostol occur in-clinic;

(d) broadening the window for misoprostol administration to include a range of 24-48 hours after taking mifepristone, instead of 48 hours afterwards;

(e) adding a repeat 800 mcg buccal dose of misoprostol in the event of an incomplete chemical abortion;

(f) removing the requirement for an in-person follow-up examination after an abortion; and

(g) allowing "healthcare providers" other than physicians to dispense and administer the chemical abortion drugs.[113]

198. Despite these major changes to the regimen, the FDA eliminated the requirement for prescribers to report all nonfatal serious adverse events from chemical abortion drugs. Rather than require future adverse event reports from abortionists about whether revising the dosages and removing the initial safeguards harmed women and girls, the FDA simply asserted that "after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged." The FDA at least conceded that "[i]t is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends."[114]

[113] *Id.* at 6–10.

[114] *Id.* at 27.

199. As with the 2000 Approval, the 2016 Major Changes did not include prohibitions on the upstream distribution of chemical abortion drugs by mail, express company, or common carrier as proscribed by federal laws, nor did the FDA acknowledge and address these laws.

A. The FDA's Evidence for the Safety and Effectiveness of the 2016 Major Changes

200. The FDA lacked substantial evidence that the 2016 Major Changes would have the effect it purported or was represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.

201. The FDA's review and approval did not include a single adequate and well-controlled investigation that evaluated the safety and effectiveness of mifepristone and misoprostol under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

202. Instead, the FDA relied on studies that evaluated only one or just a few of the major changes that the FDA enacted in 2016; as the FDA acknowledged, "in some cases data from a given study were relied on to provide evidence to support multiple changes"[115]—but no study supported all the changes.

203. For example, the FDA relied on a study lead by a former longtime employee of the Population Council to support extending the maximum gestational age to 70 days, changing the dosing regimen, and authorizing a repeat dose of

[115] Ex. 32, 2016 Summary Review at 6.

misoprostol if the first dose fails.[116] In this study, the abortionists (1) confirmed gestational age (and presumably screened for ectopic pregnancies) "based on routine ultrasound practices," (2) required the study participants to return to the study site 7 to 14 days after using mifepristone "for clinical assessment, which included ultrasonography," and (3) "intervened surgically if they deemed it medically necessary or at the patient's request."[117] But the labeling that the FDA approved with the 2016 Major Changes did not require (1) an ultrasound to confirm gestational age or screen for an ectopic pregnancy, (2) an in-person follow-up exam using ultrasonography, and (3) an ability of abortionists to personally perform surgical abortion if necessary. Such variations between the study conditions and the approved labeling fail to comply with the requirements of the FFDCA.

204. Moreover, the studies on which the FDA relied for each individual major change all contained at least one fatal flaw, including the following substantial weaknesses: significant loss to follow-up; safeguards not required under the labeling; small sample size lacking statistical significance; not powered to evaluate safety; and bias.

205. In fact, many of these studies showed that the new chemical abortion regimen was *unsafe* for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof, or they failed to show that chemical abortion was safe under such conditions.

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[116] Ex. 33, Beverly Winikoff et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012).
[117] *Id.* at 1071.

B. The FDA's Lack of Research on Pediatric Populations for the 2016 Major Changes

206. The FDA's 2016 Major Changes continued to allow pregnant girls of any age to use chemical abortion drugs—despite not knowing whether these dangerous drugs could have an adverse impact on the health, safety, and welfare of developing girls.

207. The FDA did not require Danco to submit an assessment on the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, nor did the FDA require Danco to submit an assessment that supported the dosing and administration for each pediatric subpopulation for which the drug is safe and effective.[118]

208. The FDA "granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarchal females." The FDA then concluded that Danco "fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old." The FDA cited three published studies in support of this conclusion.[119]

209. The primary study on which the FDA relied, *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, by Mary Gatter and Deborah Nucatola of Planned Parenthood of Los Angeles and

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[118] Ex. 32, 2016 Summary Review at 18–20.

[119] *Id.* at 18–19.

Kelly Cleland of Princeton University's Office of Population Research, evaluated the proposed dosing regimen followed by home administration of misoprostol through 63 days' gestation. The study also included postmenarcheal girls in the study population, from which the FDA extrapolated its conclusion.[120]

210. For the pediatric population under 18 years of age, the Planned Parenthood study stated that it had a loss to follow-up of twenty percent (20%). Therefore, the authors lacked any knowledge of whether these girls died, were hospitalized, or experienced other serious adverse events.[121] The authors also recognized that "[l]oss to follow-up was significantly higher among the *youngest* age group."[122]

211. The FDA minimized this significant data gap by asserting that "loss to follow-up was *slightly higher* in those less than 18 years old."[123] Despite this significant data gap, the FDA went on to conclude that "age did not adversely impact efficacy outcomes."[124]

212. Furthermore, in this study, Planned Parenthood also performed an ultrasound examination on *all* females prior to the chemical abortions, in addition to giving them "routine antibiotic coverage" at the beginning of the chemical

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[120] *Id.* at 19 (citing Ex. 34, Mary Gatter et al., *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, 91 Contraception 269 (2015).

[121] Ex. 34, Gatter at 4–5.

[122] *Id.* (emphasis added).

[123] Ex. 32, 2016 Summary Review at 19 (emphasis added).

[124] *Id.*

abortion regimen.[125] But the FDA did not require any of these safeguards for women and girls under the 2016 Major Changes.

213. The FDA did not address or discount any potential conflict of interest or bias in the study—despite the study disclosing that Planned Parenthood Federation of America provided funding for the study. Nor did the FDA address or discount any potential conflict of interest or bias in the study even though its authors, Mary Gatter[126] and Deborah Nucatola,[127] had significant incentives to increase their income and Planned Parenthood's profits through abortion-related actions outside of performing surgical abortion.[128]

214. A second study that the FDA cited in support of its PREA conclusion was based on a nationwide registry of induced abortions and hospital register data in Finland.[129] For the adolescent cohort who had chemical abortions, the study

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[125] Ex. 34, Gatter at 2.

[126] *See, e.g.*, The Center for Medical Progress, *Second Planned Parenthood Senior Executive Haggles Over Body Parts Prices, Changes Abortion Methods*, YouTube (July 21, 2015), https://www.youtube.com/watch?v=MjCs_gvImyw (video capturing Gatter saying she "want[s] a Lamborghini" when discussing the price that she would charge for selling intact aborted fetal body parts).

[127] *See, e.g.,* The Center for Medical Progress, *Planned Parenthood Uses Partial-Birth Abortions to Sell Baby Parts*, YouTube (July 14, 2015), https://www.youtube.com/watch?v=jjxwVuozMnU (video capturing Nucatola stating that Planned Parenthood affiliates would be "happy" selling intact aborted fetal body parts for a "reasonable" price that is "a little better than break even").

[128] The Fifth Circuit has recognized the overall authenticity and veracity of the undercover videos capturing Planned Parenthood's desire to profit from the trafficking of aborted fetal body parts. *See Planned Parenthood of Greater Tex. Family Planning & Preventative Health Servs., Inc. v. Smith*, 913 F.3d 551, 559 n. 6 (5th Cir. 2019), *on reh'g en banc sub nom. Planned Parenthood of Greater Tex. Fam. Plan. & Preventative Health Servs., Inc. v. Kauffman*, 981 F.3d 347 (5th Cir. 2020).

[129] Ex. 32 2016 Summary Review at 19–20 (citing Ex. 18, Niinimaki, *supra* note 14).

found that 12.8% experienced hemorrhaging, 7.0% had incomplete abortions, and 11.0% needed surgical evacuation of "retained products of conception."[130] Because these statistics were similar to those of the adult cohort, the FDA found these statistics "reassuring" to support the safety profile of chemical abortion drugs for a pediatric population.[131]

215. The third and final study that the FDA cited in support of its PREA conclusion was a study of 28 adolescents, ages 14 to 17 years old, with pregnancies under 57 days' gestation.[132] Even though the authors of this study cautioned that a larger study was needed to make any generalizable conclusions for pediatric populations, the FDA likewise found this small study "reassuring."[133]

216. The FDA did not require any studies on the long-term effects of chemical abortion drugs in pediatric populations with developing reproductive systems.

XI. 2019 Citizen Petition

217. In response to the 2016 Major Changes, on March 29, 2019, Plaintiffs AAPLOG and American College of Pediatricians (2019 Petitioners) submitted to the FDA a citizen petition (2019 Citizen Petition) pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500–314.560); and Section 505 of the FFDCA (21 U.S.C. § 355). The 2019 Petitioners asked the FDA to (1) "restore and

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[130] Ex. 18, Niinimaki, *supra* note 14 at 3–4.
[131] Ex. 32, 2016 Summary Review at 20.
[132] *Id.* at 19.
[133] *Id.* at 20.

strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000" and, in the event that the FDA denied that request, (2) "retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescribers."[134]

218. The 2019 Citizen Petition asked the FDA to take the following actions to restore and strengthen elements of the chemical abortion drug regimen and prescriber requirements approved in 2000 to protect the health, safety, and welfare of women and girls:

- Reduce the maximum gestational age from 70 days to 49 days;
- Limit the ability to prescribe and dispense chemical abortion drugs to qualified, licensed physicians—not other "healthcare providers";
- Mandate certified abortionists to be physically present when dispensing chemical abortion drugs;
- Require that the prescriber perform an ultrasound to assess gestational age, identify ectopic pregnancies, ensure compliance with FDA restrictions, and adequately inform the woman of gestational age-specific risks, which rise with increasing gestational age;
- Restore the requirement for in-person administration of misoprostol;

[134] Ex. 35, 2019 Citizen Petition of AAPLOG to FDA (Mar. 29, 2019).

- Restore the requirement for an in-person follow-up visit to confirm abortion and rule out life-threatening infection through clinical examination or ultrasonographic scan;
- Restore the 2000 label language that stated that chemical abortion drugs are contraindicated if a woman lacks adequate access to emergency medical care; and
- Restore the prescriber reporting requirements for all serious adverse events, including any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the chemical abortion regimen.[135]

219. The 2019 Petitioners also asked the FDA to require a formal study of outcomes for at-risk populations, including the pediatric female population, patients with repeat chemical abortions, patients who have limited access to emergency room services, and patients who self-administer misoprostol.[136]

220. The 2019 Citizen Petition explained that "[t]he developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system." Therefore, "[t]he use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

[135] *Id.*

[136] *Id.* at 13–14.

likely to significantly impact the developing reproductive system of the adolescent female."[137]

221. If the FDA refused to restore and strengthen the chemical abortion regimen and prescriber requirements approved in 2000, the 2019 Citizen Petition requested that the FDA retain the mifepristone REMS and continue limiting the dispensing of mifepristone to clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. In other words, the FDA should do no further harm to the few remaining safeguards for women and girls who undergo the chemical abortion drug regimen.[138]

222. In particular, the 2019 Petitioners explained that eliminating or relaxing the REMS to facilitate internet or telephone prescriptions would be dangerous to women and girls.[139] The 2019 Citizen Petition also raised concerns about dispensing from a pharmacy instead of a clinical facility.[140]

223. The 2019 Citizen Petition provided the FDA with detailed analysis and data to support these requests.

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[137] *Id.*
[138] *Id.* at 14–25.
[139] *Id.* at 18–20.
[140] *Id.* at 20–23.

XII. The FDA's Approval of a Generic Version of Mifeprex and a Single, Shared System REMS

224. On April 11, 2019, the FDA approved GenBioPro, Inc.'s[141] generic version of Mifeprex, "Mifepristone Tablets, 200 mg" (2019 ANDA Approval). The FDA determined GenBioPro's Mifepristone Tablets, 200 mg, "to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC." GenBioPro's generic version of mifepristone has the same labeling and REMS as does Danco's Mifeprex.[142]

225. On the same day, the FDA approved modifications to the existing REMS for chemical abortion drugs to establish a single, shared system REMS for mifepristone products for the "medical termination of intrauterine pregnancy," thus allowing the FDA to have a uniform REMS for the chemical abortion drugs that two companies were now marketing. The FDA did not make any substantive modifications to the REMS approved in 2016.[143]

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[141] GenBioPro, Inc. is located at 3651 Lindell Road, Suite D1041, Las Vegas, Nevada. https://www.dnb.com/business-directory/company-profiles.genbiopro_inc.f925af03300887aacd053afe151fefb2.html.

[142] Ex. 36, 2019 FDA ANDA Approval Letter to GenBioPro, Inc. (Apr. 11, 2019), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/091178Orig1s000ltr.pdf.

[143] Ex. 37, 2019 FDA Supplemental Approval Letter to Danco Laboratories, LLC (Apr. 11, 2019), Supplement Approval, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/020687Orig1s022ltr.pdf.

XIII. 2020 ACOG-SMFM Letter to the FDA

226. On April 20, 2020, the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) sent a joint letter (2020 ACOG-SMFM Letter), rather than a citizen petition, to the FDA asking the agency to remove in-person dispensing requirement for mifepristone during the COVID-19 pandemic and instead allow dispensing by mail or mail-order pharmacy.[144]

227. Following the letter, in May 2020, ACOG and others filed suit to enjoin the FDA's in-person dispensing requirement for mifepristone during the pandemic. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183 (D. Md. 2020).

228. The district court granted a nationwide preliminary injunction and lifted the in-person dispensing requirement for the pandemic. *Id.* at 233, order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020). The Fourth Circuit refused to stay the injunction. Court Order Denying Motion for Stay Pending Appeal, *Am. Coll. of Obstetricians & Gynecologists v. FDA,* Nos. 20-1824 (4th Cir. Aug. 13, 2020), ECF No. 30.

229. The FDA then filed for an emergency stay of the injunction with the U.S. Supreme Court. On January 12, 2021, the U.S. Supreme Court granted the FDA an emergency stay of the district court's injunction.[145]

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[144] Ex. 38, 2020 Letter from ACOG and SMFM, to FDA about Mifepristone REMS (Apr. 20, 2020) (2020 ACOG-SMFM Letter).

[145] *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (2021).

XIV. 2021 FDA Letter in Response to 2020 ACOG-SMFM Letter

230. President Joe Biden took office just eight days later. Acting under new management, the FDA responded to the 2020 ACOG-SMFM letter on April 12, 2021, and stated that the agency "intends to exercise enforcement discretion" during the COVID pandemic with respect to the in-person dispensing requirement of the REMS for mifepristone (2021 Non-Enforcement Decision).[146]

231. The FDA's 2021 Non-Enforcement Decision relied, in part, on the supposed lack of reported adverse events caused by chemical abortion drugs occurring between January 2020 and January 2021—despite the agency's elimination of non-fatal reporting requirements for abortionists in 2016. Nevertheless, in 2021, the FDA still "found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events."[147]

232. The FDA's 2021 Non-Enforcement Decision neither acknowledged nor addressed the federal laws expressly prohibiting the distribution of mifepristone by mail, express company, or common carrier—despite explicitly recognizing that this action would allow "dispensing of mifepristone through the mail . . . or through a mail-order pharmacy."[148]

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[146] Ex. 39, 2021 FDA Letter to ACOG and SMFM About Mifepristone REMS, at 2 (Apr. 12, 2021) (2021 Non-Enforcement Decision).

[147] *Id.*

[148] *Id.*

XV. 2021 "Minor" Changes

233. On May 14, 2021, the FDA approved "minor" changes to the Patient Agreement Form to use "gender neutral language," replacing the pronouns "she" and "her" with "the patient." The FDA made similar revisions to the REMS document to reflect the removal of the gender-specific pronouns in the Patient Agreement Form.[149]

234. Despite these changes, the FDA did not require Danco to submit studies showing the safety and effectiveness of chemical abortion on women and girls who may be taking puberty blockers, testosterone injections, or other hormones in addition to the chemical abortion drugs.

235. Currently, the May 14, 2021, "minor" changes are the last updates to the REMS for chemical abortion drugs that the FDA has approved.[150] As discussed below, the FDA is requiring additional changes to the REMS.

XVI. The FDA's December 2021 Announcement of Further Reductions in Safeguards

236. On December 16, 2021, Defendant Cavazonni, Director of the FDA's Center for Drug Evaluation and Research, wrote a letter to Graham Chelius, M.D., of the Society of Family Planning and the California Academy of Family Physicians

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[149] Ex. 40, FDA Supplemental Approval Letter to Danco Laboratories, LLC (May 14, 2021), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/020687Orig1s024ltr.pdf.

[150] Ex. 41, 2021 Updated REMS for Mifepristone Tablets, 200mg (May 14, 2021), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.

to inform him that the FDA had completed its review of the REMS for mifepristone.[151]

237. Although the FDA "determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks," the agency "determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks."[152]

238. The letter identified specific new modifications to the REMS: "(1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the 'in-person dispensing requirement'); and (2) adding a requirement that pharmacies that dispense the drug be specially certified," signaling that the FDA will soon allow pharmacies to dispense chemical abortion drugs.[153]

239. Defendant Cavazzoni also noted that the FDA had answered the "related" 2019 Citizen Petition and would post the agency's response in the public docket.[154]

XVII. The FDA's Denial and Granting of the 2019 Citizen Petition

240. Accordingly, on December 16, 2021—the *same day* that Defendant Cavazzoni sent the letter to Dr. Chelius and *over 2.5 years* after receiving the 2019

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[151] Ex. 42, 2021 FDA Center for Drug Evaluation & Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021).

[152] *Id.*

[153] *Id.*

[154] *Id.*

Citizen Petition—the FDA denied in part and granted in part the 2019 Citizen Petition (2021 FDA Response).[155]

241. The FDA granted the 2019 Citizen Petition only to the extent that the agency agreed that a REMS is necessary to ensure that the "benefits" of mifepristone in a regimen with misoprostol outweigh the risks. But the FDA retained only the Prescriber Agreement Form and the Patient Agreement Form as the remaining elements of the REMS.[156]

242. Aside from retaining these two remaining requirements, the FDA denied the 2019 Citizen Petition's requests (1) to restore and strengthen the mifepristone and prescriber requirements approved in 2000 and (2) to continue limiting the dispensing of mifepristone to women in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[157]

243. Before addressing the merits of the 2019 Citizen Petition, the FDA discussed how chemical abortion drugs came to be regulated, starting with the 2000 Approval under Subpart H and the associated restrictions "needed to assure the safe use of the drug product." The FDA noted that it restricted the distribution of chemical abortion drugs under Subpart H, 21 C.F.R. § 314.520. The agency also

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[155] Ex. 43, 2021 FDA Letter to AAPLOG and Am. Coll. of Pediatricians denying in part and granting in part 2016 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2021 FDA Response).

[156] *Id.* at 21–23.

[157] Ex. 43, 2021 FDA Response.

explained how and why chemical abortion drugs have an associated REMS to "assure safe use" due to the drug's approval under Subpart H.[158]

244. After providing this regulatory background, the FDA defended its decision in the 2016 Major Changes to reconsider and revise the safeguards codified in the original 2000 Approval and the subsequent REMS. The agency also disregarded the analyses and data set forth in the 2019 Citizen Petition.

245. The FDA repeated its previous justifications not to require studies in the pertinent pediatric population in the underlying 2000 Approval and the 2016 Major Changes, and it again asserted—without evidence—that "the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents."[159]

246. In response to the 2019 Citizen Petition's request to preserve the few safeguards after the 2016 Major Changes, the FDA stated that the REMS for mifepristone "must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks."[160]

247. In support of its claim that in-person dispensing is unnecessary, the FDA relied on the "small" number of adverse events voluntarily reported in the FDA Adverse Event Reporting System (FAERS) database to justify the elimination

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[158] *Id.* at 2–3.
[159] *Id.* at 38.
[160] *Id.* at 25

of this safeguard, even though the FDA had years ago removed the requirement for abortionists to report nonfatal adverse events.[161]

248. The FDA relied on the FAERS database despite conceding these facts: "FAERS data does have limitations"; the "FDA does not receive reports for every adverse event"; and thus "FAERS data cannot be used to calculate the incidence of an adverse event . . . in the U.S."[162]

249. The FDA likewise admitted that FAERS "is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events" and the adverse events reported to the FDA "represent a fraction of the actual adverse events occurring in American women."[163] The FDA also agreed that there are reporting "discrepancies [that] render the FAERS inadequate to evaluate the safety of mifepristone abortions."[164]

250. The complicated FAERS electronic submission process further hinders the reporting of adverse events and exacerbates the unreliability of the number of

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[161] *Id.* at 25–36.

[162] Ex. 44, Questions and Answers on FDA's Adverse Event Reporting System (FAERS), https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers.

[163] Ex. 45, Kathi A. Aultman et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 26 Law & Medicine 3, 25–26 (2021).

[164] Ex. 46, Christiana A. Cirucci et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch & managerial Epidemiology 1 (2021).

adverse event reports. Doctors or other interested individuals seeking to submit an adverse event report must navigate a confusing webpage.[165] Recognizing this difficulty in submitting adverse event reports, the FDA provides a 48-page manual as guidance on the technical specifications for submitting an adverse event form.[166]

251. The FDA also relied on some published studies in making its 2021 decision to deny the 2019 Citizen Petition. The agency, however, noted that "the ability to generalize the results of these studies to the United States population is hampered," "the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy," and the FDA "did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States."[167]

252. Despite these limitations, the FDA concluded that mifepristone would "remain safe and efficacy [would] be maintained" if it removed the in-person dispensing requirement from the REMS program.[168]

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[165] Ex. 47, FDA, *FDA Adverse Event Reporting System (FAERS) Electronic Submissions*, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[166] Ex. 48, *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (April 2021), https://www.fda.gov/media/132096/download.

[167] Ex. 43, 2021 FDA Response at 28.

[168] *Id.*

253. The FDA's 2021 Petition Response neither acknowledged nor addressed the federal laws expressly prohibiting the distribution of mifepristone by mail, express company, or common carrier.

254. In summary, the following chart illustrates the changes to the mifepristone regimen over the years:

Regulation	**2000 Approval**	**2016 Major Changes**	**2021 Non-Enforcement Decision and Petition Denial**
Maximum Gestational Age	49 days	70 days	70 days
Dosage	• 600 mg of mifepristone • 400 mcg of misoprostol	• 200 mg of mifepristone • 800 mcg of misoprostol	• 200 mg of mifepristone • 800 mcg of misoprostol
Route of misoprostol administration	Vaginal	Buccal	Buccal
Timing of misoprostol administration	48 hours after mifepristone	24-48 hours after mifepristone	24-48 hours after mifepristone
Repeat dose of 800 mcg misoprostol	No	Yes	Yes
Dispensed only by or under the supervision of a physician	Yes	No	No
In-person *administration* of drug regimen	Yes	No	No
In-person *dispensing* of drug regimen	Yes	Yes	No
Follow-up in-person evaluation post-abortion	Yes	No	No
Requiring prescribers to report all non-fatal serious adverse events	Yes	No	No

XVIII. Injuries to Plaintiffs and Their Patients

255. The Alliance for Hippocratic Medicine, the AAPLOG, the American College of Pediatricians, and the Christian Medical & Dental Associations have members in Texas and around the country who have treated and will continue to treat women and girls who have suffered complications from the FDA's unlawful approval of chemical abortion drugs and subsequent elimination of the safeguards necessary to protect women and girls.

256. These medical associations sue on their own behalf and on behalf of their members and their members' patients—all of whom have been harmed and will continue to be harmed by the FDA's actions.

257. Dr. Jester practices medicine in Texas and has treated a woman who suffered complications from the FDA's unlawful approval of chemical abortion drugs and elimination of the safeguards necessary to protect women and girls. Dr. Frost-Clark, Dr. Johnson, and Dr. Delgado have also treated women and girls who have suffered complications from the FDA's unlawful approval of chemical abortion drugs and elimination of the safeguards necessary to protect women and girls.

258. These doctors sue on behalf of themselves and their patients—both of whom have been harmed and will continue to be harmed by the FDA's actions.[169]

[169] *June Med. Servs. LLC v. Russo*, 140 S. Ct. 2103, 2118–20 (2020) (holding that doctors and medical providers had third-party standing on behalf of their patients because the Court has "long permitted" them "to invoke the rights of their actual or potential patients").

259. The sworn declarations attached to the Complaint detail how each Plaintiff has been, is, and/or will be personally and professionally injured by the FDA's actions. As many of their injuries overlap, the injuries discussed below cite the specific Plaintiff declaration(s) associated with those injuries. The Complaint incorporates by reference each of the allegations in these declarations.

A. Injuries to Patients

260. The FDA's 2000 Approval legalized an unsafe drug regimen.[170]

261. Chemical abortion drugs cause women and girls to suffer many intense side effects, including cramping, heavy bleeding, and severe pain.[171]

262. Women and girls who take chemical abortion drugs experience significantly more complications than those who have surgical abortions.[172]

263. The FDA's 2000 Approval has caused women and girls to suffer complications from chemical abortion.[173]

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[170] *See* Compl. ¶¶ 141–158.

[171] Ex. 4, Harrison Decl. ¶ 23; Ex. 9, Wozniak Decl. ¶ 17; Ex. 8, Skop Decl. ¶ 13; Ex. 49, Johnson Decl. ¶ 8; Ex. 50, Frost-Clark Decl. ¶ 9; Ex. 51, Delgado Decl. ¶ 11.

[172] Ex. 4, Harrison Decl. ¶ 22; Ex. 9, Wozniak Decl. ¶ 15; Ex. 8, Skop Decl. ¶ 19; Ex. 10, Foley Decl. ¶ 8; Ex. 51, Delgado Decl. ¶ 11.

[173] Ex. 4, Harrison Decl. ¶ 24; Ex. 7, Francis Decl. ¶ 10; Ex. 9, Wozniak Decl. ¶ 8; Ex. 8, Skop Decl. ¶¶11–13, 16–19, 22–23; Ex. 52, Jester Decl. ¶ 16; Ex. 49, Johnson Decl. ¶¶ 9–11; Ex. 10, Foley Decl. ¶ 3; Ex. 50, Frost-Clark Decl. ¶ 7; Ex. 3, Dickerson Decl. ¶ 11.

264. Since the 2016 Major Changes, the rate of women and girls who have suffered complications from chemical abortion and required critical medical treatment has increased and will continue to increase.[174]

265. The FDA's decision to expand the gestational age for approved mifepristone use to 70 days (10 weeks) harms women.[175]

266. This expansion of the permissible gestational age is especially dangerous for women and girls when combined with the FDA's elimination of the in-person dispensing and follow-up visit requirements.[176]

267. The FDA's failure to require an ultrasound, its subsequent elimination of in-person drug administration, physician supervision, and patient follow-up, and, finally, its removal of the requirement of in-person dispensing in specified health care settings, exposes women and girls to increased risk of suffering complications from chemical abortion and requiring further medical attention following the drug regimen.[177]

268. Because the FDA does not require it, many abortionists do not remain physically near women and girls during the most painful and excruciating periods of

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[174] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 18; Ex. 52, Jester Decl. ¶ 23; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 10; Ex. 51, Delgado Decl. ¶¶ 16, 18; Ex. 3, Dickerson Decl. ¶ 11.

[175] Ex. 9, Wozniak Decl. ¶ 10; Ex. 52, Jester Decl. ¶ 17.

[176] Ex. 52, Jester Decl. ¶ 13.

[177] Ex. 4, Harrison Decl. ¶¶ 24–31; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶¶ 8–10, 14; Ex. 8, Skop Decl. ¶¶ 20, 25–29; Ex. 5, Barrows Decl. ¶¶ 15–18; Ex. 52, Jester Decl. ¶¶ 15–18, 22–23, 25; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15.

the chemical abortion drug regimen, often sending them home with the drugs. Given their lack of admitting privileges and treatment capabilities, abortionists usually instruct women to go to the emergency department of the closest hospital for treatment of any severe adverse events.[178]

269. The FDA has eliminated all procedural safeguards that would rule out ectopic pregnancies, verify gestational age, identify any contraindications to prescribing mifepristone, or identify potential complications like sepsis and hemorrhage, remaining fetal parts, and others until the patient is at a critical time or it is too late to help the patient. As a result, women and girls often suffer unexpected episodes of heavy bleeding or severe pain and must rush to the emergency department of the nearest hospital.[179]

270. As more women and girls require treatment in emergency departments, the other patients of the treating doctors are adversely affected. With the increase in women and girls suffering emergency complications from chemical abortion or seeking to reverse the effects of the chemical abortion regimen, there is a direct correlation in the decrease in time, attention, and resources that emergency department doctors have to treat their other patients.[180]

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[178] Ex. 4, Harrison Decl. ¶ 19; Ex. 10, Foley Decl. ¶ 11.

[179] Ex. 8, Skop Decl. ¶¶ 13, 17–18, 22–23, 28–29; Ex. 5, Barrows Decl. ¶¶ 17–18; Ex. 52, Jester Decl. ¶¶ 13, 15–16, 23; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15.

[180] Ex. 9, Wozniak Decl. ¶¶ 17–18, 27; Ex. 7, Francis Decl. ¶ 12; Ex. 49, Johnson Decl. ¶¶ 14, 16; Ex. 8, Skop Decl. ¶ 32; Ex. 10, Foley Decl. ¶ 10; Ex. 51, Delgado Decl. ¶ 18; Ex. 3, Dickerson Decl. ¶ 14.

271. Abortionists commonly violate the remaining safeguards and the FDA-approved label for chemical abortion drugs by giving the drugs to women who are contraindicated for chemical abortion (i.e., could experience deadly adverse events if they take the drugs) and then subsequently harmed by these drugs, demonstrating that the FDA's remaining safeguards for women and girls are ineffective in protecting them.[181]

272. The FDA's decision not to require abortionists to report all adverse events for chemical abortion drugs harms women and girls because it creates an inaccurate and false safety profile for the use of chemical abortion drugs.[182]

273. Due to inadequate adverse event reporting, the true rates of risks associated with chemical abortion drugs remain undercounted and therefore are unknown. Because abortion providers cannot know the accurate risk levels that their patients face when ingesting these drugs, these providers cannot properly inform their patients about the risks associated with chemical abortion. This prevents women and girls from giving informed consent to these providers.[183]

274. Many women and girls do not fully understand the nature of chemical abortion drugs and the risks that these drugs present to them.[184]

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[181] Ex. 9, Wozniak Decl. ¶ 24.

[182] Ex. 4, Harrison Decl. ¶ 35; Ex. 52, Jester Decl. ¶ 24.

[183] Ex. 4, Harrison Decl. ¶¶ 36–38; Ex. 9, Wozniak Decl. ¶¶ 19–20; Ex. 49, Johnson Decl. ¶ 17.

[184] Ex. 4, Harrison Decl. ¶ 31; Ex. 8, Skop Decl. ¶¶ 13, 27; Ex. 52, Jester Decl. ¶ 24; Ex. 49, Johnson Decl. ¶ 12; Ex. 10, Foley Decl. ¶¶ 12, 15; Ex. 51, Delgado Decl. ¶ 15.

275. Abortionists who prescribe or dispense chemical abortion drugs are not providing women with an adequate, accurate assessment of the known risks and effects associated with chemical abortion. Therefore, women and girls are unable to give informed consent to the drugs they are receiving, and thus they are not consenting at all to taking the chemical abortion drugs—resulting in physical and mental injuries.[185]

276. Women and girls often suffer distress and regret after undergoing chemical abortion, sometimes seeking to reverse the effects of mifepristone.[186]

277. A woman or girl can experience these emotions and feelings upon viewing the body of her lifeless baby after taking chemical abortion drugs.[187]

278. Even with medical oversight, abortionists can sometimes coerce women into taking chemical abortion drugs—without their true informed consent.[188]

279. The FDA's actions to eliminate in-person dispensing and administration also harm women because the lack of oversight will likely exacerbate human trafficking. Many trafficked women experience abortions and doctors potentially serve as an important resource to intervene on behalf of these trafficked women and girls.[189]

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[185] Ex. 4, Harrison Decl. ¶ 37; Ex. 8, Skop Decl. ¶¶ 14, 16, 27; Ex. 49, Johnson Decl. ¶ 12; Ex. 10, Foley Decl. ¶ 15; Ex. 50, Frost-Clark Decl. ¶ 20; Ex. 51, Delgado Decl. ¶ 15.

[186] Ex. 8, Skop Decl. ¶¶ 15–16; Ex. 10, Foley Decl. ¶¶ 12, 16; Ex. 51, Delgado Decl. ¶ 14.

[187] Ex. 8, Skop Decl. ¶ 15.

[188] Ex. 51, Delgado Decl. ¶ 15.

[189] Ex. 8, Skop Decl. ¶ 31.

280. Women and girls will continue to suffer complications from chemical abortion drugs.[190]

B. Injuries to Plaintiff Doctors

281. Because the FDA's 2000 Approval of chemical abortion drugs legalized an unsafe drug regimen, women and girls have suffered many intense side effects and increasing complications—requiring crucial medical attention and treatment.[191]

282. The FDA's 2000 Approval has caused medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, to treat women and girls who have suffered complications from mifepristone and misoprostol.[192]

283. Since the 2016 Major Changes and the associated elimination of necessary safeguards for women and girls, medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, have seen and will continue to see an additional increase in the rate of women and girls who have suffered complications from chemical abortion—complications requiring critical treatment from these doctors.[193]

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[190] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 29; Ex. 8, Skop Decl. ¶ 21; Ex. 52, Jester Decl. ¶ 20; Ex. 49, Johnson Decl. ¶ 18.

[191] Ex. 4, Harrison Decl. ¶ 23; Ex. 9, Wozniak Decl. ¶¶ 15, 17; Ex. 8, Skop Decl. ¶¶ 13, 18; 23; Ex. 5, Barrows Decl. ¶ 17; Ex. 49, Johnson Decl. ¶ 8; Ex. 50, Frost-Clark Decl. ¶ 9; Ex. 51, Delgado Decl. ¶ 11; Ex. 10, Foley Decl. ¶ 8; Ex. 3, Dickerson Decl. ¶ 11.

[192] Ex. 4, Harrison Decl. ¶ 24; Ex. 7, Francis Decl. ¶ 10; Ex. 8, Skop Decl. ¶¶ 12–21; Ex. 52, Jester Decl. ¶ 17; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 3; Ex. 50, Frost-Clark Decl. ¶ 7; Ex. 3, Dickerson Decl. ¶¶ 11, 13.

[193] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 18; Ex. 52, Jester Decl. ¶¶ 18, 23, 25; Ex. 49, Johnson Decl. ¶ 9; Ex. 10, Foley Decl. ¶ 9; Ex. 50, Frost-Clark Decl. ¶¶ 12–15; Ex. 51, Delgado Decl. ¶¶ 13, 16; Ex. 3, Dickerson Decl. ¶ 12.

284. The FDA's approved regimen for chemical abortion drugs harms not only women and girls but also medical professionals, including Plaintiff doctors and the members of Plaintiff medical associations, who respond and treat these complications and other effects from chemical abortion drugs.[194]

285. The FDA's elimination of most of the safeguards protecting women and girls from the dangers of mifepristone has made chemical abortion more widely available and with less medical supervision—causing more women and girls to experience complications from chemical abortion and, therefore, increasing emergency situations. An increase in complications only compounds the harm to doctors, including Plaintiff doctors and the members of Plaintiff medical associations.[195]

286. When women and girls suffer complications from chemical abortion drugs, these adverse events can overwhelm the medical system and consume crucial limited medical resources, including blood for transfusions, physician time and attention, space in hospitals and medical centers, and other equipment and

[194] Ex. 4, Harrison Decl. ¶¶ 26–30; Ex. 7, Francis Decl. ¶¶ 12–13; Ex. 9, Wozniak Decl. ¶ 17; Ex. 8, Skop Decl. ¶¶ 25, 32; Ex. 52, Jester Decl. ¶¶ 17, 18; Ex. 49, Johnson Decl. ¶ 14; Ex. 51, Delgado Decl. ¶ 13; Ex. 3, Dickerson Decl. ¶ 12.

[195] Ex. 52, Jester Decl. ¶¶ 20, 25; Ex. 50, Frost-Clark Decl. ¶ 8; Ex. 4, Harrison Decl. ¶¶ 26–30, 28; Ex. 7, Francis Decl. ¶ 14; Ex. 8, Skop Decl. ¶¶ 20, 28, 32; Ex. 49, Johnson Decl. ¶ 14; Ex. 10, Foley Decl. ¶ 10.

medicines.[196] This need for blood transfusions exacerbates the current critical national blood shortage.[197]

287. The increased occurrence of complications related to chemical abortion drugs multiplies the workload of health care providers, including Plaintiff doctors and the members of Plaintiff medical associations, in some cases by astronomical amounts. This is especially true in maternity care "deserts" (i.e., geographic areas where there are not a large number of OB/Gyn providers for patients).[198]

288. When there is a complication from chemical abortion drugs, the typical care doctors provide patients moves from simple patient management to complicated patient management. Accordingly, a patient who suffers complications from chemical abortion drugs requires significantly more time and attention from providers than most patients require.[199]

289. For example, Plaintiff Dr. Jester needed to treat a woman who had traveled from Texas to New Mexico to obtain chemical abortion drugs from Planned Parenthood. The woman returned to Texas, suffered from two weeks of moderate to heavy bleeding, and then developed a uterine infection. At the hospital, Dr. Jester provided her with intravenous antibiotics and performed a dilation and curettage

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[196] Ex. 4, Harrison Decl. ¶ 28; Ex. 7, Francis Decl. ¶ 17; Ex. 9, Wozniak Decl. ¶ 17.

[197] Ex. 4, Harrison Decl. ¶ 19; *see also* Current National Blood Supply, https://americasblood.org/for-donors/americas-blood-supply/ (last visited Nov. 16, 2022); Catherine Garcia, *The urgent American blood shortage, explained*, The Week (Oct. 26, 2022), https://theweek.com/health-and-wellness/1017643/the-urgent-american-blood-shortage-explained.

[198] Ex. 4, Harrison Decl. ¶ 29; Ex. 7, Francis Decl. ¶ 14; Ex. 9, Wozniak ¶¶ 17–18.

[199] Ex. 4, Harrison Decl. ¶ 30.

(i.e., the surgical procedure to remove a dead baby and pregnancy tissue from inside the uterus). If she had waited a few more days before receiving care from Dr. Jester, she could have been septic and died.[200]

290. Dr. Nancy Wozniak, a member of Plaintiff AAPLOG, needed to treat a woman who had contraindications to chemical abortion drugs (due to her taking anti-coagulants) but still received chemical abortion drugs from Planned Parenthood in Indiana. The woman consumed the first chemical abortion drug, mifepristone, at Planned Parenthood and took an Uber for a ride home. During her Uber ride, she began to experience bleeding and other adverse side effects from the mifepristone. Instead of taking her home, the Uber driver took her to the emergency department of Dr. Wozniak's hospital. Dr. Wozniak treated the woman and advised her not to take the second chemical abortion drug, misoprostol, because of the grave risk that she could bleed out and die.[201]

291. The FDA's elimination of the in-person dispensing requirement for chemical abortion drugs—allowing mail-order abortion—further harms the practice of medicine. The increasing number of chemical abortions through mail-order or telemedicine methods means that more women and girls will suffer complications and require medical attention from doctors, including Plaintiff doctors and the

[200] Ex. 52, Jester Decl. ¶ 17.

[201] Ex. 9, Wozniak Decl. ¶¶ 24–25.

members of Plaintiff medical associations, especially given that remote abortionists often cannot or do not treat such complications.[202]

292. To circumvent state laws that regulate abortions and protect the health and safety of women and girls, abortionists are relying on access to chemical abortion drugs through mail-order schemes or telemedicine, further increasing the use of these drugs and the complications associated with them.[203]

293. As more emergency situations arise, emergency room doctors, such as Plaintiff doctors and the members of Plaintiff medical associations, are having to treat more patients, including performing hysterectomies or removing fetal parts remains. The more patients suffering emergency complications from chemical abortion or seeking to reverse the chemical abortion process, the less time and attention these doctors have to treat their other patients.[204]

294. Because abortionists do not adequately describe what happens during a chemical abortion and give these drugs to women and girls to take outside of the abortion facility, doctors have needed to treat and care for many women who have come to the emergency department for their intense bleeding and other effects of

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[202] Ex. 9, Wozniak Decl. ¶ 14; Ex. 5, Barrows Decl. ¶ 17; Ex. 52, Jester Decl. ¶¶ 22–23; Ex. 50, Frost-Clark Decl. ¶ 12–15; Ex. 10, Foley Decl. ¶ 10.

[203] Ex. 9, Wozniak Decl. ¶ 13; Ex. 10, Foley Decl. ¶ 10; *see also* Ruth Reader, *State abortion bans prove easy to evade*, Politico (Nov. 11, 2022, 2:24 PM), https://www.politico.com/news/2022/11/01/state-abortion-bans-medication-00064407; Emily Bazelon, *Risking Everything to Offer Abortions Across State Lines*, New York Times (Oct. 4, 2022), https://www.nytimes.com/2022/10/04/magazine/abortion-interstate-travel-post-roe.html.

[204] Ex. 9, Wozniak Decl. ¶¶ 17–18, 27; Ex. 7, Francis Decl. ¶ 14; Ex. 49, Johnson Decl. ¶¶ 14, 16; Ex. 8, Skop Decl. ¶ 32; Ex. 51, Delgado Decl. ¶ 18.

the chemical abortion drugs—although not considered complications from the regimen.[205]

295. Doctors, including Plaintiff doctors and the members of Plaintiff medical associations, experience enormous pressure, stress, and chaos in these emergency situations that the FDA created through its approval of chemical abortion drugs and elimination of necessary safeguards.[206]

296. Some of these emergency situations force pro-life doctors, including Plaintiff doctors and the members of Plaintiff medical associations, into situations in which they feel complicit in an elective chemical abortion by needing to remove a baby with a beating heart or pregnancy tissue as the only means to save the life of the woman or girl. This feeling of complicity in the act of an elective chemical abortion causes great emotional suffering, mental anguish, and spiritual distress among these doctors.[207]

297. For example, Dr. Ingrid Skop, a member of Plaintiff AAPLOG, needed to treat a young woman who had been bleeding for six weeks after she took chemical abortion drugs at a Planned Parenthood facility. After two follow-up appointments, Planned Parenthood had given her an additional dose of the second chemical abortion drug, misoprostol, which failed to resolve her complications. When Dr. Skop treated the young woman, Dr. Skop performed a sonogram,

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[205] Ex. 10, Foley Decl. ¶ 15; Ex. 49, Johnson Decl. ¶ 11.

[206] Ex. 9, Wozniak Decl. ¶ 17; Ex. 5, Barrows Decl. ¶ 19; Ex. 52, Jester ¶ 20; Ex. 49, Johnson ¶ 15; Ex. 3, Dickerson Decl. ¶ 14.

[207] Ex. 8, Skop Decl. ¶ 34; Ex. 7, Francis Decl. ¶ 13; Ex. 5, Barrows Decl. ¶ 26; Ex. 3, Dickerson Decl. ¶ 16.

identified a significant amount of pregnancy tissue remaining in the woman's uterus, and had to perform a suction aspiration to resolve her complication.[208]

298. The members of Plaintiff medical associations oppose being forced to end the life of a human being in the womb for no medical reason, including by having to complete an incomplete elective chemical abortion. The objections are both ethical and medical as they stem from the purpose of medicine itself, which is to heal and not to electively kill human beings regardless of their location. Accordingly, Plaintiff medical associations and their members are harmed by the FDA's repeated removal of necessary safeguards, which may force them to treat women and girls seeking the completion of an elective chemical abortion. This concern is real and imminent, especially in light of the Biden HHS's impermissible actions to compel doctors to complete elective chemical abortions under the Emergency Medical Treatment and Active Labor Act (EMTALA).[209]

299. The FDA's loosening of chemical abortion regulations impacts the standard of care for chemical abortion drugs and the demands and expectations that hospitals will put on their physicians.[210]

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[208] Ex. 8, Skop Decl. ¶ 23.

[209] Ex. 4, Harrison Decl. ¶ 44; Ex. 5, Barrows Decl. ¶ 26; Ex. 3, Dickerson Decl. ¶ 16; *see also Reinforcement of EMTALA Obligations specific to Patients who are Pregnant or are Experiencing Pregnancy Loss (QSO-21-22-Hospitals- UPDATED JULY 2022)*, https://www.cms.gov/files/document/qso-22-22-hospitals.pdf.

[210] Ex. 5, Barrows Decl. ¶ 25.

300. It grieves Plaintiff doctors and members of Plaintiff medical associations to treat women and girls harmed by chemical abortion drugs, including those who regret their decision to have a chemical abortion.[211]

301. When their patients have chemical abortions, doctors lose the opportunity to provide professional services and care for the woman and child through pregnancy, which causes harms to providers who no longer can care for their patients and bring about a successful delivery of a new life.[212]

302. The FDA's elimination of the requirement for abortionists to report all adverse events related to chemical abortion drugs leads to unreliable reporting. Without an accurate understanding of the adverse effects of widespread chemical abortion drug use, Plaintiff doctors and members of Plaintiff medical associations cannot effectively practice evidence-based medicine. Health care providers cannot assess the risks of a particular course of treatment if the FDA is not collecting and tracking the risks. And, therefore, they cannot accurately advise their patients and the public about these risks.[213]

303. Many doctors likely do not know about the importance of reporting adverse events related to chemical abortion drugs to the FDA. Similarly, many doctors likely do not know how to report adverse events.[214]

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[211] Ex. 52, Jester Decl. ¶ 27; Ex. 8, Skop Decl. ¶ 33; Ex. 51, Delgado ¶ 14.

[212] Ex. 51, Delgado Decl. ¶ 17; Ex. 52, Jester Decl. ¶ 19.

[213] Ex. 9, Wozniak Decl. ¶¶ 19–20; Ex. 5, Barrows Decl. ¶ 19; Ex. 8, Skop Decl. ¶ 30; Ex. 4, Harrison Decl. ¶¶ 36–39; Ex. 52, Jester Decl. ¶¶ 24, 26; Ex. 49, Johnson Decl. ¶ 17; Ex. 10, Foley Decl. ¶ 17; Ex. 50, Frost-Clark Decl. ¶ 22.

[214] Ex. 4, Harrison Decl. ¶ 33.

304. Even when Plaintiff doctors and members of Plaintiff medical associations want to voluntarily report adverse events associated with chemical abortion to the FDA, they must go through the complicated, cumbersome, and time-consuming FAERS submission process. The adverse event reporting requirements and the FAERS submission process harm medical practices by taking away significant time from a doctor to treat and meet with patients.[215]

305. In addition, even when doctors want to voluntarily report adverse events to the manufacturer, Danco, the doctor must print, fill out by hand, and then either mail or email back the form to Danco. Much of the information required by this form is impossible to obtain by the physician seeing the patient if they were not the one who dispensed the medication (such as lot number and dosage)—forcing the doctor to leave several fields blank. There is no confirmation whether the reported complications were recorded by Danco or reported to the FDA. Regardless, this submission process harms medical practices by taking away significant time from a doctor to treat and meet with patients.[216]

306. Even when doctors want to report adverse events to their state regulators, their reports can be rejected for improper reasons (e.g., asserting that there was no adverse event because the doctor saved and treated the woman injured by chemical abortion drugs).[217]

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[215] Ex. 7, Francis Decl. ¶¶ 16–18; Ex. 4, Harrison Decl. ¶ 33–34; Ex. 50, Frost-Clark Decl. ¶ 23.

[216] Ex. 7, Francis Decl. ¶¶ 16–18.

[217] Ex. 9, Wozniak Decl. ¶ 26.

307. Because many women and girls suffering complications from chemical abortion drugs tell emergency department doctors that they are experiencing miscarriages, these doctors might not report these incidences as adverse events and so these complications are significantly underreported or not fully known.[218]

308. The inability or refusal of a patient to disclose why she is presenting herself in the emergency department or what drugs she has received also impedes the ability of doctors, including Plaintiff doctors and the members of Plaintiff medical associations, to practice medicine and provide proper treatment to these patients.[219]

309. The lack of accurate information on adverse events also harms the doctor-patient relationship with all medical care providers because the patients no longer trust that their health care providers are telling them the truth. This harms even doctors who do not support or practice chemical abortions, such as the members of the AAPLOG.[220]

310. The FDA's removal of necessary safeguards for women and girls who use chemical abortion drugs increases physicians' exposure to potential liability. Emergency department physicians often have no prior relationship with the patient, lack access to the patient's medical history, and encounter patients who do not know what drugs they consumed or conceal the fact that they attempted a

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[218] Ex. 9, Wozniak Decl. ¶ 28; Ex. 10, Foley Decl. ¶ 14.

[219] Ex. 9, Wozniak Decl. ¶ 28; Ex. 49, Johnson Decl. ¶¶ 13, 15; Ex. 10, Foley Decl. ¶ 14; Ex. 50, Frost-Clark Decl. ¶¶ 16–17, 19.

[220] Ex. 4, Harrison Decl. ¶ 37.

chemical abortion. These factors place physicians in higher-risk situations with less critical information about patients, thus increasing their exposure to allegations of malpractice and potential liability.[221]

311. As this exposure increases, so does the cost to practice medicine, including insurance costs.[222]

312. Doctors, such as Dr. Jester and Dr. Delgado, serve patients as professional health care providers. They provide care to all women and unborn children, and they give them the best professional services possible. Just like all other health care providers, a hospital or practice will bill for the costs of medical services rendered. When their patients have chemical abortions, they lose the opportunity to provide professional medical care for the woman and child through pregnancy and bring about a successful delivery of a new life.[223]

313. Plaintiffs expect to continue to treat women and girls who suffer complications from chemical abortion drugs.[224]

C. Injuries to Plaintiff Medical Associations

314. Plaintiffs medical associations have also suffered organizational harms from the FDA's approval and deregulation of chemical abortion drugs.

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[221] Ex. 9, Wozniak Decl. ¶¶ 21–22; Ex. 5, Barrows Decl. ¶¶ 22–24; Ex. 52, Jester Decl. ¶ 21; Ex. 49, Johnson Decl. ¶ 15; Ex. 10, Foley Decl. ¶ 14; Ex. 50, Frost-Clark Decl. ¶¶ 16–18; Ex. 3, Dickerson Decl. ¶ 15.

[222] Ex. 5, Barrows Decl. ¶ 24.

[223] Ex. 52, Jester Decl. ¶ 19; Ex. 51, Delgado ¶ 17.

[224] Ex. 4, Harrison Decl. ¶ 26; Ex. 7, Francis Decl. ¶ 11; Ex. 9, Wozniak Decl. ¶ 29; Ex. 8, Skop Decl. ¶ 21; Ex. 52, Jester Decl. ¶¶ 12, 20; Ex. 49, Johnson Decl. ¶ 18.

315. For example, the inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates Plaintiff medical associations' purpose to support women's health and to educate doctors, their patients, and the public about these dangers.[225]

316. In addition, Plaintiff AAPLOG has needed to divert limited time, energy, and resources to compensate for this lack of information by conducting their own studies and analyses of the available data. This diversion of time, energy, and resources comes to the detriment of other advocacy and educational efforts of Plaintiff AAPLOG, including their efforts about the dangers of surgical abortion, the conscience rights of doctors, and the sanctity of life at all stages.[226]

317. Plaintiffs AAPLOG and Christian Medical & Dental Associations submitted a citizen petition in 2002 challenging the FDA's 2000 Approval of chemical abortion drugs and requesting an audit of the clinical studies. Both associations were concerned about women's health issues and recognized that the FDA's violations of its standards and rules in approving chemical abortion drugs put the lives and health of women and girls at risk. It took considerable time, energy, and resources to draft their 92-page petition and the 30-page response to comments letter, in addition to compiling and analyzing supporting sources and

[225] Ex. 4, Harrison Decl. ¶¶ 38–39; Ex. 7, Francis Decl. ¶¶ 19–20; Ex. 5, Barrows Decl. ¶¶ 20–21; Ex. 6, Van Meter Decl. ¶¶ 19–20; Ex. 3, Dickerson Decl. ¶¶ 21–22.
[226] Ex. 4, Harrison Decl. ¶ 40; Ex. 7, Francis Decl. ¶ 21.

studies. This effort caused both associations to divert limited time, energy, and resources from its other priorities and routine functions.[227]

318. Similarly, Plaintiffs AAPLOG and American College of Pediatricians submitted another citizen petition in 2019 challenging the FDA's 2016 Major Changes to the chemical abortion drug regimen. It also took considerable time, energy, and resources to draft the 26-page petition, in addition to compiling and analyzing supporting sources and studies. This effort caused both associations to divert limited time, energy, and resources from its other priorities and routine functions.[228]

319. The Catholic Medical Association, a member of the Alliance for Hippocratic Medicine, has also taken actions to challenge the FDA's approval and deregulation of chemical abortion drugs—at the expense of other priorities.[229]

320. Because abortion activists continue to file their own citizen petitions and letters with the FDA asking the agency to eliminate all protections for women and girls who take chemical abortion drugs, and knowing the Biden administration's relentless, politicized efforts to push these drugs throughout the country, Plaintiff medical associations continue to expend considerable time, energy, and resources on its public advocacy and educational activities about chemical abortion drugs—to the detriment of their other priorities and functions.

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[227] Ex. 4, Harrison Decl. ¶ 41; Ex. 7, Francis Decl. ¶ 22; Ex. 5, Barrows Decl. ¶ 27.
[228] Ex. 4, Harrison Decl. ¶ 42; Ex. 7, Francis Decl. ¶ 23; Ex. 6, Van Meter Decl. ¶ 21.
[229] Ex. 3, Dickerson Decl. ¶¶ 17–20.

This diversion of time, energy, and resources will not cease until the FDA's approval and deregulation of chemical abortion drugs cease.[230]

XIX. The Need for Judicial Relief

321. Injunctive relief is necessary to prevent these harms, and judicial relief is appropriate to vacate, set aside, enjoin, and declare these acts unlawful.

322. All of the agency actions at issue—the 2000 Approval, the 2016 Petition Denial, the 2016 Major Changes, the 2019 ANDA Approval, the 2021 Non-Enforcement Decision, and the 2021 Petition Response, as well as the agency's failure to act and prohibit or restrict chemical abortion drugs—are final agency actions subject to judicial review under the APA.

323. All the acts of Defendants described above, and their officers, agents, employees, and servants, were executed and are continuing to be executed by Defendants under the color and pretense of the policies, statutes, ordinances, regulations, customs, and usages of the United States.

324. Under 5 U.S.C. § 701(a), no statute precludes judicial review of the agency's actions, and the actions are not committed to agency discretion by law.

325. Under the APA, a reviewing court must "hold unlawful and set aside agency action, findings, and conclusions" if they are "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(C).

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[230] Ex. 4, Harrison Decl. ¶ 43; Ex. 7, Francis Decl. ¶ 24; Ex. 5, Barrows Decl. ¶ 27; Ex. 6, Van Meter Decl. ¶ 22; Ex. 3, Dickerson Decl. ¶ 20.

326. Under the APA, a reviewing court must "hold unlawful and set aside agency action, findings, and conclusions" if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

327. Likewise, a court must "compel agency action unlawfully withheld." 5 U.S.C. § 706(1).

328. Plaintiffs have no adequate remedy available at law.

329. Plaintiffs have no adequate or available administrative remedy. In the alternative, any administrative remedy would be futile or unnecessary.

330. Defendants would suffer no harm from the relief requested, and the relief requested would serve the public interest.

CLAIMS FOR RELIEF

CLAIM ONE

2000 APPROVAL

ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

331. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

332. Defendants lacked legal authority in 2000 to approve mifepristone under the FDA's Subpart H regulations.

I. Subpart H

333. The FDA's Subpart H regulations apply only to "certain new drugs that have been studied for their safety and effectiveness in treating serious or life-

threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)." 21 C.F.R. § 314.500.

334. Pregnancy is not an illness.

335. Pregnancy is neither "serious" nor "life-threatening," as those terms are understood in Subpart H.

336. Chemical abortion does not provide a "meaningful therapeutic benefit to patients over existing treatments."

337. Defendants lacked the authority to approve mifepristone for chemical abortion under Subpart H in 2000.

338. Because the French and American trials did not compare the Mifeprex regimen with the then-existing method for ending pregnancies (i.e., surgical abortion), the trials did not demonstrate a "meaningful therapeutic benefit over existing therapy."

339. Thus, the FDA's 2000 Approval of mifepristone for chemical abortion was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with Subpart H's provision for the accelerated approval of certain new drugs.

II. FFDCA

340. Defendants lacked legal authority in 2000 to approve mifepristone under the FFDCA.

341. The FDA's 2000 Approval violated the FFDCA because the clinical trials on which the agency relied did not use the full set of design features the

agency typically requires to produce unbiased investigations of drug safety and effectiveness.

342. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex regimen.

343. The FDA also failed to perform a statistical analysis of the data from the U.S. Clinical Trial.

344. The FDA impermissibly extrapolated conclusions about the safety and effectiveness of mifepristone from the U.S. Clinical Trial even though the agency did not retain the requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care. The U.S. Clinical Trial failed to meet the requirements of the FFDCA that the trial demonstrates safety and effectiveness under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. Instead, the FDA had insufficient information on whether mifepristone was safe under such conditions.

345. Finally, the FDA violated the FFDCA and the agency's implementing regulations because the agency mandated the use of misoprostol for chemical abortion as part of the 2000 Approval—despite the requirement that the sponsor submit an sNDA for a new use of a previously approved drug.

346. Therefore, Defendants lacked the authority to approve mifepristone for chemical abortion under the FFDCA. Given these infirmities, the 2000 Approval

was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with the FFDCA.

III. PREA

347. Defendants lacked legal authority in 2000 to approve mifepristone under PREA.

348. In the 2000 Approval, the FDA stated that it was "waiving the pediatric study requirement for this action on this application."[231]

349. Because the 2000 Approval failed to meet any of the qualifications for a waiver, *see* 21 U.S.C. § 355c(a)(5)(A), (B), the FDA lacked authority when waiving the pediatric study requirement without explanation, and the 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right when the FDA waived the pediatric study requirement without explanation. For the same reason, the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law when the FDA waived the pediatric study requirement without explanation.

350. In 2016, despite contrary evidence in the administrative record, the FDA sought to provide an impermissible post-hoc rationalization that it inaccurately stated in the 2000 Approval that it was "waiving" the pediatric study requirements and, instead, should have said it had found that the requirements

[231] Ex. 25, 2000 Approval Letter at 3.

were met for post-menarchal pediatric patients by extrapolating from studies of adult populations.[232]

351. In addition to such a post-hoc rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA. The 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Because the agency was allowed to extrapolate from studies of adult populations *only if* the course of a "disease" is substantially similar in adults and the pediatric population. Because pregnancy is not a disease, PREA did not permit the FDA to make such an extrapolation.

352. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA. The 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the FDA failed to satisfy the requirement for documentation of the scientific data that supports its extrapolation that the course of the "disease" and the effects of the drug are sufficiently similar in adult women and pediatric girls.

[232] Ex. 27, 2016 Petition Denial at 29.

353. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the FDA lacked authority under PREA, the 2000 Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, and not in accordance with law because PREA allows the agency to extrapolate from adequate and well-controlled studies in adults and, as discussed above, the U.S. Clinical Trial did not include adequate and well-controlled studies in adults.

354. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the 2000 Approval was arbitrary, capricious, and an abuse of discretion because the FDA's explanation that it expected girls—under the age of 18 years and going through reproductive development—to have the same physiological outcome with the drug regimen as adult women was unreasonable and not supported by the administrative record.

355. In addition to such a rationalization being impermissible and an inaccurate representation of the agency's decision-making at the time, the 2000 Approval was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law because the FDA did not require an assessment that evaluated the safety and effectiveness of the drug for girls under 18 years of age.

356. Therefore, Defendants lacked the authority to approve mifepristone for chemical abortion under PREA, and the 2000 Approval was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with PREA.

IV. Pretext

357. The FDA's illegal and unreasonable rationales for the 2000 Approval—in light of the political context of the agency's actions—indicate that the stated reasons for the 2000 Approval are pretext. Therefore, the FDA's 2000 Approval is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

V. Reopener and Request

358. "The reopening doctrine . . . create[s] 'an exception to statutory limits on the time for seeking review of an agency decision.'" *Nat'l Ass'n of Reversionary Prop. Owners v. Surface Transp. Bd.*, 158 F.3d 135, 141 (D.C. Cir. 1998). "Under the reopening doctrine, the time for seeking review starts anew where the agency reopens an issue." *Sierra Club v. EPA*, 551 F.3d 1019, 1024 (D.C. Cir. 2008). The U.S. Court of Appeals for the Fifth Circuit has adopted the "reopening doctrine." *See Texas v. Biden*, 20 F.4th 928, 951–55 (5th Cir. 2021), *rev'd on other grounds*, *Biden v. Texas*, 142 S. Ct. 2528 (2022).

359. The FDA's 2016 Major Changes decision and the 2021 Petition Response reopened the FDA's underlying 2000 Approval of chemical abortion drugs for chemical abortion. When issuing these decisions, the FDA undertook a serious, substantive reconsideration of the safeguards required in the 2000 Approval decision and affirmed in the 2016 Petition Denial. Ultimately, by removing these

safeguards, the FDA completely changed the regulatory context and created a different regulatory construct for chemical abortion drugs.

360. For the reasons stated above, the FDA's 2000 Approval of chemical abortion drugs must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM TWO

2016 PETITION DENIAL

**ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706)
IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT;
ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

361. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

362. The 2002 Citizen Petition provided the FDA with substantial legal arguments that the 2000 Approval exceeded the agency's authority and was not in accordance with law under Subpart H, the FFDCA, and the Pediatric Rule.

363. The 2002 Citizen Petition also provided the FDA with significant scientific and factual reasons to withdraw the 2000 Approval.

364. By disregarding the arguments, facts, and reasons set forth in the 2002 Citizen Petition, the FDA's 2016 Petition Denial was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; and it was arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. The FDA's 2016 Petition Denial was unreasonable and not supported by the administrative record.

365. The FDA's illegal and unreasonable rationales for the 2016 Petition Denial—in light of the political context of the agency's actions—indicate that the stated reasons for the 2016 Petition Denial are pretext. Therefore, the FDA's 2016 Petition Denial is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

366. "The reopening doctrine . . . create[s] 'an exception to statutory limits on the time for seeking review [of an agency decision].'" *Surface Transp. Bd.*, 158 F.3d at 141. "Under the reopening doctrine, the time for seeking review starts anew where the agency reopens an issue." *Sierra Club*, 551 F.3d at 1024. The U.S. Court of Appeals for the Fifth Circuit has adopted the "reopening doctrine." *See Texas v. Biden*, 20 F.4th at 951–55.

367. The FDA's 2016 Major Changes decision and the 2021 Petition Response have reopened the FDA's 2016 Petition Denial. When issuing these decisions, the FDA undertook a serious, substantive reconsideration of the safeguards enshrined in the 2000 Approval decision. Ultimately, by removing the safeguards in the 2000 Approval, the FDA created a different regulatory construct and completely changed the regulatory context for the chemical abortion drug regimen.

368. Therefore, the FDA's 2016 Petition Denial must be held unlawful, set aside, and preliminarily and permanently enjoined under the APA.

CLAIM THREE

2016 MAJOR CHANGES

**ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706)
IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT;
ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

369. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

370. Defendants lacked legal authority to make the 2016 Major Changes.

I. FFDCA

371. The FDA's 2016 Major Changes violated the FFDCA because they did not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

372. The 2016 Major Changes violated the FFDCA because the results of the tests on which the FDA relied for its 2016 Major Changes showed that chemical abortion is unsafe for use under such conditions, or they did not show that such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

373. The 2016 Major Changes violated the FFDCA because the FDA had insufficient information to determine whether mifepristone is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.

374. The FDA's 2016 Major Changes lacked substantial evidence that the new drug will have the effect it purports or is represented to have under the

conditions of use prescribed, recommended, or suggested in the proposed labeling thereof.

375. In violation of the FFDCA, none of the studies on which the FDA relied for its 2016 Major Changes evaluated the safety and effectiveness of the chemical abortion regimen under the conditions of the label approved in 2016, or they failed to satisfy the substantial evidence requirement for showing the safety and effectiveness of the regimen under the conditions of the label approved in 2016.

376. Therefore, Defendants lacked legal authority to make the 2016 Major Changes. The FDA's 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right under the FFDCA. The FDA's 2016 Major Changes were unreasonable and not supported by the administrative record.

II. PREA

377. The FDA lacked legal authority under PREA to make the 2016 Major Changes, and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious, an abuse of discretion, and not in accordance with law, because PREA allows the FDA to extrapolate from studies of adult populations only if the course of a "disease" is substantially similar in adults and the pediatric population. Because pregnancy is not a disease, PREA did not permit the FDA to make such an extrapolation.

378. Defendants lacked legal authority under PREA to make the 2016 Major Changes and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious,

an abuse of discretion, and not in accordance with law, because the FDA failed to satisfy the requirement for documentation of the scientific data that supports its extrapolation that the course of the "disease" and the effects of the drug are sufficiently similar in adult women and pediatric girls.

379. Defendants lacked legal authority under PREA to make the 2016 Major Changes and the 2016 Major Changes were in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and were arbitrary, capricious, an abuse of discretion, and not in accordance with law, because the FDA did not require an assessment that evaluated the safety and effectiveness of mifepristone for girls under 18 years of age.

III. Pretext

380. The FDA's illegal and unreasonable rationales for the 2016 Major Changes—in light of the political context of the agency's actions—indicate that the stated reasons for the 2016 Major Changes are pretext. Therefore, the FDA's 2016 Major Changes is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

IV. Request

381. For the reasons stated above, the FDA's 2016 Major Changes must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM FOUR

2019 ABBREVIATED NEW DRUG APPROVAL

**ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706)
IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT;
ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW**

382. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

383. Defendants lacked legal authority to issue the 2019 ANDA Approval.

384. Because the FDA relied on the unlawful 2000 Approval of Mifeprex as a means to approve GenBioPro's generic drug, Mifepristone Tablets, 200 mg, if the Court finds that the 2000 Approval was unlawful, as set forth above, then the 2019 ANDA Approval needed independently to satisfy the requirements of the FFDCA and PREA.

385. Unable to rely on an unlawful approval, the FDA's approval of the 2019 ANDA Approval violated the FFDCA because it lacked the clinical investigations, adequate testing, sufficient information, and substantial evidence to show the safety and effectiveness of mifepristone under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof as required by 21 U.S.C. § 355(d).

386. Unable to rely on an unlawful approval, the FDA's approval of the 2019 ANDA also violated PREA because the submission lacked the necessary assessment on the safety and effectiveness of mifepristone on the pediatric population as required by 21 U.S.C. § 355c(a).

387. For these reasons, the 2019 ANDA Approval was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right, and the 2019 ANDA Approval was arbitrary, capricious, an abuse of discretion, and not in accordance with law.

388. The FDA's illegal and unreasonable rationales for the 2019 ANDA Approval—in light of the political context of the agency's actions—indicate that the stated reasons for the 2019 ANDA Approval are pretext. Therefore, the FDA's 2019 ANDA Approval is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

389. Therefore, the 2019 ANDA Approval must be held unlawful, set aside, and preliminarily and permanently enjoined.

CLAIM FIVE

2000 APPROVAL, 2016 MAJOR CHANGES, 2019 ANDA APPROVAL, 2021 NON-ENFORCEMENT DECISION, AND 2021 PETITION RESPONSE

ULTRA VIRES; ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

390. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

391. The FDA lacked legal authority when issuing its 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response.

392. None of these FDA actions comply with the federal laws that expressly prohibit the mailing or delivery by any letter carrier, express company, or other

common carrier of any substance or drug intended for producing abortion. 18 U.S.C. §§ 1461–62.

393. Since the 2000 Approval, the FDA has failed to restrict the upstream distribution of chemical abortion drugs from manufacturer or importer to abortionists in violation of these federal laws.

394. The FDA's 2021 Non-Enforcement Decision and 2021 Petition Response also violated these federal laws because they impermissibly removed the in-person dispensing requirement for chemical abortion drugs and, accordingly, authorized the downstream distribution of chemical abortion drugs by mail, express company, and other common carriers.

395. Because a federal agency cannot permit what federal law expressly prohibits, the FDA lacked legal authority when issuing its 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response.

396. Therefore, the FDA's 2000 Approval, 2016 Major Changes, 2021 Non-Enforcement Decision, and 2021 Petition Response must be held unlawful, set aside, and preliminarily and permanently enjoined under the Court's inherent equitable power to enjoin *ultra vires* actions, *Larson*, 337 U.S. at 689–91.

CLAIM SIX

2021 PETITION RESPONSE

ADMINISTRATIVE PROCEDURE ACT (5 U.S.C. § 706) IN EXCESS OF STATUTORY JURISDICTION, AUTHORITY, OR LIMITATIONS, OR SHORT OF STATUTORY RIGHT; ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

397. Plaintiffs re-allege and incorporate, as though fully set forth, paragraphs 1–330 of this complaint.

398. The 2019 Citizen Petition provided the FDA with significant data and reasons to justify restoring the pre-2016 REMS.

399. The 2019 Citizen Petition also provided the FDA with significant data and reasons to justify strengthening the REMS for chemical abortion drugs, including the requirement that the abortionist uses an ultrasound to assess gestational age and diagnose ectopic pregnancies.

400. Finally, the 2019 Citizen Petition asked the FDA to require a formal study of outcomes for at-risk populations, including girls under the age of 18 years, as the agency has never studied these outcomes.

401. By disregarding the data and reasons set forth in the 2019 Citizen Petition, the FDA's 2021 Petition Response was unreasonable and not supported by the administrative record.

402. The FDA's 2021 Petition Response was in excess of statutory jurisdiction, authority, or limitations, or short of statutory right and arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law.

403. The FDA's illegal and unreasonable rationales for the 2021 Petition Denial—in light of the political context of the agency's actions—indicate that the stated reasons for the 2021 Petition Denial are pretext. Therefore, the FDA's 2021 Petition Denial is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law in violation of the APA. 5 U.S.C. § 706(2)(A).

404. Therefore, the FDA's 2021 Petition Response must be held unlawful, set aside, and preliminarily and permanently enjoined under the APA.

PRAYERS FOR RELIEF

For these reasons, Plaintiffs respectfully request that the Court enter an order as to Defendants, including their employees, agents, successors, and all persons in active concert or participation with them.

A. Issue a preliminary and permanent injunction ordering Defendants to withdraw mifepristone and misoprostol as FDA-approved chemical abortion drugs and to withdraw Defendants' actions to deregulate these chemical abortion drugs.

B. Hold unlawful, set aside, and vacate the 2000 Approval.

C. Hold unlawful, set aside, and vacate the 2016 Petition Denial.

D. Hold unlawful, set aside, and vacate the 2016 Major Changes.

E. Hold unlawful, set aside, and vacate the 2019 ANDA Approval.

F. Hold unlawful, set aside, and vacate the 2021 Non-Enforcement Decision.

G. Hold unlawful, set aside, and vacate the 2021 Petition Response.

H. Declare that the chemical abortion drugs mifepristone and misoprostol fall outside the scope of the FDA's regulation entitled "Subpart H–Accelerated

Approval of New Drugs for Serious or Life-Threatening Illnesses" (codified at 21 C.F.R. §§ 314.500, et seq.) because pregnancy is not an "illness" and these drugs do not "provide meaningful therapeutic benefit to patients over existing treatments."

I. Declare that the Federal Food, Drug, and Cosmetic Act requires the FDA to rely on clinical investigations and studies that show a drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof when reviewing and approving a new drug application or a supplemental new drug application.

J. Declare that the Federal Food, Drug, and Cosmetic Act prohibits the FDA from relying on studies that incorporate safeguards and protections not included under the conditions prescribed, recommended, or suggested in the proposed labeling when reviewing and approving a new drug application or a supplemental new drug application.

K. Declare that the Federal Food, Drug, and Cosmetic Act prohibits the FDA from relying exclusively on studies that fail to evaluate all the requested changes in the proposed labeling thereof when reviewing and approving a new drug application or a supplemental new drug application.

L. Declare that 18 U.S.C. § 1461 and 18 U.S.C. § 1462 prohibit the FDA from approving a new drug application or a supplemental new drug application that fails to limit distribution of chemical abortion drugs in accordance with these laws.

M. Retain jurisdiction of this matter for the purpose of enforcing this Court's order.

N. Award Plaintiffs' costs, attorneys' fees, and other disbursements for this action.

O. Grant any other relief this Court deems equitable, just, and appropriate.

Respectfully submitted this November 18, 2022.

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**Pro Hac Vice Application forthcoming*

TABLE OF EXHIBITS

Exhibit	Description
1	Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61.
2	Bill Analysis, C.S.H.B. 3446, Committee Report.
3	Declaration of Mario R. Dickerson
4	Declaration of Dr. Donna Harrison
5	Declaration of Dr. Jeffrey Barrows
6	Declaration of Dr. Quentin Van Meter
7	Declaration of Dr. Christina Francis
8	Declaration of Dr. Ingrid Skop
9	Declaration of Dr. Nancy Wozniak
10	Declaration of Dr. Steven A. Foley
11	Byron Calhoun, *The maternal mortality myth in the context of legalized abortion,* 80 The Linacre Quarterly 264 (2013).
12	*The FDA and RU-486: Lowering the Standard for Women's Health: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform*, 109th Cong. 4 (2006).
13	2002 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to U.S. Food & Drug Admin. (FDA) (Aug. 20, 2002).
14	FDA-Approved Label for Misoprostol (Cytotec) (Jan. 2017).
15	Maarit J. Mentula et al., *Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study*, 26 Hum. Reprod. 927 (2011).
16	Marrit Niinimaki et al., *Immediate Complications After Medical Compared With Surgical Termination of Pregnancy*, 114 Obstetrics & Gynecology 795 (2009).
17	James Studnicki et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, Health Servs. Rsch. & Managerial Epidemiology, Nov. 9, 2021.

18	Maarit Niinimaki, et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BJM, April 20, 2011.
19	James Studnicki et al., *A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization*, Health Servs. Rsch. & Managerial Epidemiology, May 20, 2022.
20	Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*. 36 Health Commc'n 1485 (2021).
21	Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,632 (Dec. 2, 1998).
22	New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992).
23	FDA Letter to Population Council re: NDA (Feb. 18, 2000).
24	2000 FDA Approval Memorandum to Population Council re: NDA 20-687 Mifeprex (mifepristone) (Sept. 28, 2000).
25	2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets (Sept. 28, 2000).
26	2003 Citizen Petitioners' Response to Opposition Comments filed by The Population Council, Inc. and Danco Laboratories, LLC (Oct. 10, 2003).
27	2016 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA-2002-P-0364 (Mar. 29, 2016) (2016 Petition Denial).
28	Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313, 16,314 (Mar. 27, 2008).
29	2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC (June 6, 2011).
30	2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011).
31	2016 FDA Letter to Danco Laboratories re: NDA 020687, Supp 20 (Mar. 28, 2016).

32	FDA, Center for Drug Evaluation and Research, Summary Review of Application Number: 020687Orig1s020 (March 29, 2016) (2016 Summary Review).
33	Beverly Winikoff, et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012).
34	Mary Gatter, et al., *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, 91 Contraception 269 (2015).
35	2019 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to FDA (Mar. 29, 2019).
36	2019 FDA Abbreviated New Drug Application (ANDA) Approval Letter to GenBioPro, Inc. (Apr. 11, 2019).
37	2019 FDA Supplemental Approval Letter to Danco Laboratories, LLC (Apr. 11, 2019).
38	2020 Letter from Am. Coll. of Obstetricians & Gynecologists and Soc'y for Maternal-Fetal Med., to FDA about Mifepristone REMS (Apr. 20, 2020).
39	2021 FDA Letter to Am. Coll. of Obstetricians & Gynecologists and Soc'y for Maternal-Fetal Med. about Mifepristone REMS (Apr. 12, 2021).
40	2021 FDA Supplemental Approval Letter to Danco Laboratories, LLC (May 14, 2021).
41	2021 Updated REMS for Mifepristone Tabets, 200mg (May 14, 2021).
42	2021 FDA Center for Drug Evaluation and Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021).
43	2021 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists and Am. Coll. of Pediatricians denying in part and granting in part 2019 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2021 FDA Response).
44	Questions and Answers on FDA's Adverse Event Reporting System (FAERS), https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers.
45	Kathi A. Aultman et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 26 Law & Medicine 3 (2021).
46	Christina A. Cirucci et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch. & Managerial Epidemiology 1 (2021).

47	FDA, *FDA Adverse Event Reporting System (FAERS) Electronic Submissions.*
48	*Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (April 2021).
49	Declaration of Dr. Tyler Johnson
50	Declaration of Dr. Regina Frost-Clark
51	Declaration of Dr. George Delgado
52	Declaration of Dr. Shaun Jester

Exhibit 1

Laura J. Lederer & Christopher A. Wetzel, *The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities*, Annals of Health Law, Winter 2014 at 61

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The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities

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The Health Consequences of Sex Trafficking and Their Implications for Identifying Victims in Healthcare Facilities

Laura J. Lederer* and Christopher A. Wetzel**

INTRODUCTION

> [W]hen I turned 13 I'd had enough of the abuse in home and I ran away. I didn't know where to go so I went to the center of town and stood by the town hall. A man saw me hanging around there and he said that he was looking for a 'protégé.' I didn't know what it was but it sounded fine to me. He said that I could stay at his house if I didn't have a place to stay. . . . When we got to his house he pulled out a bottle of gin and had me drink and drink. The next thing I remember is waking up drunk in his bed all wet and hurt. He took me out on the street and told me what to do . . . During that time I saw 10 to 20 men a day. I did what he said because he got violent when I sassed him. I took all kinds of drugs—even though I didn't really like most of them . . . Over the years I had pimps and customers who hit me, punched me, kicked me, beat me, slashed me with a razor. I had forced unprotected sex and got pregnant three times and had two abortions at [a clinic]. Afterward, I was back out on the street again. I have so many scars all over my body and so many injuries and so many illnesses. I have hepatitis C and stomach and back pain and a lot of psychological issues. I tried to commit suicide several times.
>
> –Kayla, survivor[1]

Kayla's story is typical of women and girls trafficked for commercial sex

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1. All survivor names have been changed to protect their privacy.

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in the United States. Experiences like the ones she describes were reported by trafficking survivors who answered questions about their trafficking experience in a series of focus groups. Her story represents not the worst that occurs in sex trafficking, but rather, the common experience of women and girls trafficked into commercial sex by a criminal industry that generates an estimated $33.9 billion per year worldwide.[2]

This paper explores the health consequences and healthcare experiences of women and girls trafficked in the United States for commercial sex. The paper is based on an original study of over one hundred domestic sex trafficking victims and survivors. It provides evidence that women and children who are trafficked into prostitution are physically, mentally, and emotionally devastated by the crime, and this devastation is lasting – with injuries, illnesses, and impairments continuing for decades. It illustrates how our healthcare system is failing trafficked women and children. It makes the case that health care providers of all kinds – in emergency wards, healthcare clinics, and private practices – are seeing trafficking victims but failing to identify them, thereby unwittingly contributing to continuing criminal activity and exacerbating both public and private physical and mental health problems for this segment of the population. It offers recommendations on ways that public policy and healthcare practice can combat sex trafficking by more readily identifying victims and catalyzing rescues. Finally, it argues that law, policy, and protocols must change in order to adequately address the health consequences of sex trafficking.

Section I briefly summarizes previous studies on health and human trafficking and puts the current study in context. Section II describes the current study, including methodology used to collect information from survivors. Section III presents the results of the study, detailing findings on survivors' physical and mental health issues. In addition, it describes victims' contact with healthcare providers during the time they were trafficked. Section IV summarizes critical issues in the provision of health care for sex trafficking victims, with particular attention to reproductive health care. Finally, Section V sets forth recommendations for legislators, policymakers, and healthcare professionals.

I. PREVIOUS LITERATURE AND CONTEXT

The current study fills a gap in the growing body of literature on health and violence in the context of sex trafficking. A majority of trafficking-

2. Patrick Belser, Forced Labor and Human Trafficking: Estimating the Profits 14 (Int'l Labour Office, Working Paper No. 42, 2005), available at http://digitalcommons.ilr.cornell.edu/cgi/viewcontent.cgi?article=1016&context=forcedlabor.

related studies have focused on trafficking outside of the United States. These studies have often concentrated narrowly on one or two aspects of sex trafficking, such as the prevalence of sexually transmitted diseases/infections (STDs/STIs)[3] or mental health issues,[4] though a few took a more comprehensive approach to examining the health and violence-related experiences of women in the commercial sex industry.[5] International studies established that trafficking victims are subject to a myriad of physical and psychological symptoms stemming from extensive abuse.[6]

Recently, some researchers have undertaken domestic studies on sex trafficking as well.[7] Three early studies surveyed 100 or more women and

3. See, e.g., Audrey E. Pettifor et al., Increased Risk of Chlamydial and Gonococcal Infection in Adolescent Sex Workers in Madagascar, 34 SEXUALLY TRANSMITTED DISEASES 475 (2007); Jay G. Silverman et al., HIV Prevalence and Predictors Among Rescued Sex-Trafficked Women and Girls in Mumbai, India, 43 J. ACQUIRED IMMUNE DEFICIENCY SYNDROMES 588 (2006); Jay G. Silverman et al., Syphilis and Hepatitis B Co-Infection Among HIV-Infected, Sex-Trafficked Women and Girls, Nepal, 14 EMERGING INFECTIOUS DISEASES 932 (2008); see also Arun Kumar Acharya, Sexual Violence and Proximate Risks: A Study on Trafficked Women in Mexico City, 12 GENDER, TECHNOLOGY & DEVELOPMENT 77 (2008).

4. See, e.g., Geetha Suresh et al., An Assessment of the Mental Health of Street-Based Sex Workers in Chennai, India, 25 J. CONTEMP. CRIM. JUST. 186 (2009); Hyunjung Choi et al., Posttraumatic Stress Disorder (PTSD) and Disorders of Extreme Stress (DESNOS) Symptoms Following Prostitution and Childhood Abuse, 15 VIOLENCE AGAINST WOMEN 933 (2009); See, e.g., Mazeda Hossain et al., The Relationship of Trauma to Mental Disorders Among Trafficked and Sexually Exploited Girls and Women, 100 AM. J. PUB. HEALTH 2442 (2010);

5. See, e.g., Melissa Farley et al., Prostitution and Trafficking in Nine Countries: An Update on Violence and Posttraumatic Stress Disorder, 2 J. TRAUMA PRAC. 33 (2003); See, e.g., Cathy Zimmerman et al., The Health of Trafficked Women: A Survey of Women Entering Posttrafficking Services in Europe, 98 AM. J. PUB. HEALTH 55 (2008).

6. Olga Gajic-Veljanoski & Donna E. Stewart, Women Trafficked into Prostitution: Determinants, Human Rights, and Health Needs, 44 TRANSCULTURAL PSYCHIATRY 338, 352-53 (2007).

7. See, e.g., Celia Williamson & Michael Prior, Domestic Minor Sex Trafficking: A Network of Underground Players in the Midwest, 2 J. CHILD & ADOLESCENT TRAUMA 46 (2009); KEVIN BALES & STEVEN LIZE, TRAFFICKING IN PERSONS IN THE UNITED STATES: A REPORT TO THE NATIONAL INSTITUTE OF JUSTICE 16-17 (2005), available at https://www.ncjrs.gov/pdffiles1/nij/grants/211980.pdf.; Rochelle L. Rochelle L. Dalla, Night Moves: A Qualitative Investigation of Street-Level Sex Work, 26 PSYCHOL. WOMEN Q. 63 (2002). These studies are qualitative in nature, communicating important narratives but not providing quantitative data. Other literature focuses on experiences of violence and/or substance abuse among victims but does not provide substantial data on victims' physical and mental health consequences. See, e.g., Steven P. Kurtz et al., Sex Work and "Date" Violence, 10 VIOLENCE AGAINST WOMEN 357 (2004) [hereinafter Kurtz et al., Violence]; Jody Raphael & Deborah L. Shapiro, Violence in Indoor and Outdoor Prostitution Venues, 10 VIOLENCE AGAINST WOMEN 126 (2004) [hereinafter Raphael & Shapiro, Violence]; Amy M. Young et al., Prostitution, Drug Use, and Coping with Psychological Distress, 30 J.

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touched on the problems that the instant study examines, but were each limited to a single city and examined a comparatively small number of health consequences.[8] The most comprehensive early study interviewed victims in five U.S. regions and discussed violence at length while touching on both physical and mental health consequences.[9] However, it was small and somewhat narrow in focus.[10]

While other studies have been conducted,[11] two Minnesota-based studies

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DRUG ISSUES 789 (2000); Nabila El-Bassel et al., Correlates of Partner Violence Among Female Street-Based Sex Workers: Substance Abuse, History of Childhood Abuse, and HIV Risks, 15 AIDS PATIENT CARE & STDS 41 (2001).

8. See Roberto J. Valera et al., Violence and Post Traumatic Stress Disorder in a Sample of Inner City Street Prostitutes, 16 AM. J. HEALTH STUD. 149, 149 (2000) (studying violence generally and PTSD, but not physical symptoms); Roberto J. Valera et al., Perceived Health Needs of Inner-City Street Prostitutes: A Preliminary Study, 25 AM. J. HEALTH BEHAV. 50, 50 (2001) (discussing five types of violence, sixteen physical symptoms, PTSD, and substance use); JODY RAPHAEL & DEBORAH L. SHAPIRO, CTR. FOR IMPACT RESEARCH, SISTERS SPEAK OUT: THE LIVES AND NEEDS OF PROSTITUTED WOMEN IN CHICAGO 4 (2005) [hereinafter RAPHAEL & SHAPIRO, SISTERS], available at http://www.impactresearch.org/documents/sistersspeakout.pdf (interviewing 222 victims in Chicago on 39 chronic physical health problems as well as experiences of violence and substance abuse, but not mental health).

9. JANICE G. RAYMOND & DONNA M. HUGHES, COAL. AGAINST TRAFFICKING IN WOMEN, SEX TRAFFICKING OF WOMEN IN THE UNITED STATES 7 (2001), available at http://action.web.ca/home/catw/attach/sex_traff_us.pdf.

10. Id. at 29 (interviewing only ten participants).

11. In 2004-2005, researchers published a series of Miami-based studies focusing on drug use, social service needs and barriers to them, and the connections between an abusive past, mental health problems, and HIV risk. See Hilary L. Surratt et al., Sex Work and Drug Use in a Subculture of Violence, 50 CRIME & DELINQUENCY 43, 46 (2004); Steven P. Kurtz et al., Barriers to Health and Social Services for Street-Based Sex Workers, 16 J. HEALTH CARE POOR & UNDERSERVED 345, 345 (2005) [hereinafter Kurtz et al., Barriers]; Hilary L. Surratt et al., The Connections of Mental Health Problems, Violent Life Experiences, and the Milieu of the "Stroll" with the HIV Risk Behaviors of Female Street Sex Workers, 17 J. PSYCHOL. & HUM. SEXUALITY 23, 23 (2005). These studies saw high rates of participation and asked respondents about their overall health condition but did not discuss specific physical health symptoms and limited participation to victims who were current drug users and still active in the commercial sex trade. See, e.g., Surratt et al., supra, at 46; Kurtz et al., Barriers, supra, at 346. Another 2004 study made unique contributions to the literature, revealing disturbing mortality rates among women in prostitution in Colorado and concluding that "[w]omen engaged in prostitution face the most dangerous occupational environment in the United States." John J. Potterat et al., Mortality in a Long-term Open Cohort of Prostitute Women, 159 AM. J. EPIDEMIOLOGY 778, 780-82, 784 (2004). The study also found that "active prostitutes were almost eighteen times more likely to be murdered than women of similar age and race during the study interval." Id. at 782. The study did not, however, address specific physical and mental health symptoms. Another 2005 study examined the role of medical care providers, but interviewed only twenty-one victims in three cities and was primarily qualitative. FAMILY VIOLENCE PROT. FUND, TURNING PAIN INTO
POWER: TRAFFICKING SURVIVORS' PERSPECTIVES ON EARLY INTERVENTION STRATEGIES

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are especially relevant. A 2010 survey of 117 Minneapolis women examined the impact of victims' age of entry into commercial sex on substance abuse and HIV risk.[12] Because of these emphases, however, it discussed physical and emotional health consequences only at a high level of generality, such as whether participants "ever had an STD" or "ever experienced emotional violence."[13] Another 2011 study of 105 Native American women engaged in commercial sex in Minnesota[14] covered a substantial range of violent experiences, physical and health symptoms, and drugs, as well as Post-Traumatic Stress Disorder (PTSD).[15] The study contains some discussion of other mental health symptoms, but primarily in the context of determining whether the victims suffered from PTSD.

These studies set the stage for our current, more expansive study, which looks at over 200 health issues in more detail and across a broader geographic and ethnic spectrum. As far can be determined, our study is the first to examine many of the reproductive health issues experienced by sex trafficking victims, including birth control usage, pregnancies, miscarriages, and forced and elective abortions. In addition, it analyzes health care access and interactions and collects data on symptoms experienced both during and after trafficking.

II. METHODS

This study collected data from female sex trafficking survivors.[16] The study used a mixed-methods approach, combining qualitative data collection from focus groups and structured interviews with quantitative analysis. An initial feasibility study using a single focus group was conducted in November of 2011. Following this initial focus group, a

(2005), available at http://www.futureswithoutviolence.org/userfiles/file/ImmigrantWomen/Turning%20Pain%20intoPower.pdf.

12. Lauren Martin et al., Meaningful Differences: Comparison of Adult Women Who First Traded Sex as a Juvenile Versus as an Adult, 16 VIOLENCE AGAINST WOMEN 1252, 1252 (2010).

13. Id. at 1262.

14. MELISSA FARLEY ET AL., PROSTITUTION RESEARCH & EDUC., GARDEN OF TRUTH: THE PROSTITUTION AND TRAFFICKING OF NATIVE WOMEN IN MINNESOTA, 22 (2011) [hereinafter FARLEY ET AL., PROSTITUTION RESEARCH], available at http://www.prostitutionresearch.com/pdfs/Garden_of_Truth_Final_Project_WEB.pdf.

15. Id. at 28-30, 35-40.

16. The terms "survivor" and "trafficking survivor" will be used throughout to refer to the individuals interviewed in this study. "Victim" and "trafficking victim" will refer generally to individuals who are victims of trafficking as defined by the Trafficking Victims Protection Act of 2000. 22 U.S.C.A. § 7102(15) (West, WestlawNext through P.L. 106-386). The statute defines "sex trafficking" as "the recruitment, harboring, transportation, provision, or obtaining of a person for the purpose of a commercial sex act." § 7102(10).

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series of eleven similar focus groups were conducted in cities across the United States from January 2012 to December 2012.[17] Local leaders in the anti-trafficking movement, often survivor-led service providers, were asked to assist in locating survivors in their cities who wished to participate in the study. The focus groups included 107 participants, all domestic survivors of sex trafficking, ranging in age from fourteen to sixty. During these focus groups, participants commented on and discussed a range of topics, including subjects such as any early childhood trauma, the age at which they were trafficked, how they were recruited, how long they were held in captivity, and the overarching health issues they experienced. Following the focus group sessions, survivors completed an extensive health survey.[18]

The health survey included three components. In the first component, survivors reported on more than one hundred discrete health conditions drawn primarily from the World Health Organization's Statistical Classification of Diseases and Related Health Problems.[19] These health problems ranged from neurological and gastrointestinal symptoms to respiratory, cardiovascular, and dermatological conditions. Survivors answered questions about conditions in categories including, general health, communicable and non-communicable diseases, dental health, substance abuse, as well as nearly thirty psychological symptoms and disorders. The first component also asked about a range of sexually transmitted infections, gynecological and urinary tract conditions, birth control usage, pregnancy, and pregnancy outcomes.

Because of the ubiquity of violence in sex trafficking,[20] the first component also sought information about violence that the trafficking victim endured. The questionnaire asked whether the victim had been

17. The cities chosen included Columbus, Ohio; Honolulu, Hawaii; San Diego, San Francisco, and Sacramento, and Los Angeles, California; Minneapolis, Minnesota; St. Paul, Minnesota; St. Louis, Missouri; Washington, D.C.; Asheville, North Carolina; Nashville, Tennessee. The initial "feasibility" group was conducted in Washington, D.C. in November of 2011, with a pilot study in Columbus, Ohio, shortly thereafter. The average focus group size was just under nine trafficking victims, with the largest group being twenty-two participants (St. Louis), and the lowest being two participants (Los Angeles). The participants came from survivor centered service providers and shelters including, but not limited to, Courtney's House; Breaking Free; Kwanzaa Northside Women's Space; Pacific Alliance to Stop Slavery; Save Our Adolescents from Prostitution (SOAP); Courage House; Magdalene; Generate Hope; Veronica's Voice; and On Eagles Wings.

18. See infra, Appendix for a sample questionnaire completed by a survivor.

19. See generally WORLD HEALTH ORG., INTERNATIONAL CLASSIFICATION OF DISEASES (2010), available at http://www.who.int/classifications/icd/en/.

20. See, e.g., RAYMOND & HUGHES, supra note 9, at 63-65, 67-68, 75-77; Raphael & Shapiro, Violence, supra note 7, at 132-36; Kurtz et al., Violence, supra note 7, at 367-78; RAPHAEL & SHAPIRO, SISTERS, supra note 8, at 18-20.

subjected to physical abuse, such as being beaten, punched, kicked, raped, penetrated with foreign objects, threatened with a weapon, burned with cigarettes, strangled, stabbed, slashed, or forced to have unprotected sex. In addition to physical violence, victims indicated whether they were violated in other ways, such as being asked to participate in pornography, recreate a scene from pornographic material, or submit to abuse by a person in authority.

The second component of the survey consisted of a series of open-ended questions about health care. It asked such questions as whether and how long the victim used birth control during the time she was trafficked, where the birth control was obtained, who escorted the victim to the facility where birth control was obtained, and the type of birth control used. Because previous studies have identified health care providers as critical potential identifiers of trafficking victims,[21] the second component also asked what types of facilities survivors had visited to receive medical treatment and whether the healthcare provider asked or knew about their situations. Each victim also answered more detailed reproductive health questions, including her history of pregnancies, miscarriages, abortions and live births, where the abortions and/or births occurred, and whether she maintained custody of any children she had. With respect to abortion, the victim indicated how many abortions she had undergone, at what stage of pregnancy, and whether the abortion was coerced.

The final component of the questionnaire asked victims about the symptoms they experienced after escaping trafficking. This component covered the same range of physical and psychological symptoms as the first component. A full copy of a completed questionnaire is included in this article's Appendix.

Answers from the questionnaires were coded and entered in a spreadsheet. For questions in the first and third components where survivors circled symptoms to indicate that they had experienced them, a binary coding system (1 if circled, 0 if not) was used. For the open-ended second component, common answers were assigned a number and for questions where survivors gave an unwieldy variety of answers, the least common answers were grouped into a single "other" category.[22] When

21. See, e.g., Helen Cole, Human Trafficking: Implications for the Role of the Advanced Practice Forensic Nurse, 14 J. AM. PSYCHIATRIC NURSES ASS'N 463, 466 (2009) (citing Jeffrey Barrows & Reginald Finger, Human Trafficking and the Healthcare Professional, 101 S. MED. J. 521 (2008)); ERIN WILLIAMSON ET AL., DEP'T HEALTH & HUMAN SERVS., NATIONAL SYMPOSIUM ON THE HEALTH NEEDS OF HUMAN TRAFFICKING VICTIMS: POST-SYMPOSIUM BRIEF 4-8 (2008).

22. Coded data came almost exclusively from the questionnaires. Survivors' focus

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survivors did not answer a question, the response was coded as "N/A."

This coding system allowed the spreadsheet program to count how many survivors gave each response by counting how many cells in a column were filled with a given number. The totals were then calculated as percentages both of all survivors and of those who answered the particular question. The results section analyzes the frequency with which individual symptoms and experiences were reported by the survivors in this study as well as the percentages of victims who reported at least one symptom or experience in a given category.

III. RESULTS

A. Physical Health Symptoms

> I am telling you that you have to not be in your sober mind to run these tricks—you just can't do it straight so everyone on the street is hooked on some drug. I've done drugs so long I have really hurt my body. I have kidney disease, liver problems, hepatitis C, high blood pressure, polymyositis [an inflammatory muscular disease], and fibroid tumors.
>
> –Taylor, survivor

Survivors suffered tremendously, virtually without exception. Out of 106 survivors,[23] 105 (99.1%) reported at least one physical health problem during trafficking. The most frequently reported physical problems were neurological—91.5% of respondents[24] reported at least one neurological symptom and 82.1% specifically reporting memory problems, insomnia, or poor concentration. Headaches or migraines (53.8%) and dizziness (34.0%) were also common symptoms. The trafficking experience ravaged the general health of victims as well, with 85.7% reporting at least one symptom in the general health category. In particular, the respondents' dietary health was often poor. Severe weight loss (42.9%), malnutrition (35.2%), loss of appetite (46.7%), and eating disorders (36.2%) were especially common; 71.4% of respondents reporting at least one of these diet-related symptoms.

The toll of constant commercial sexual exploitation and physical abuse on the victims led to a range of additional conditions. Physical injuries

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group statements were consulted only in the few instances where a questionnaire answer was unambiguous and the survivor's statements clarified it.

23. One participant did not fill out the first component of the survey.

24. Because many interviewees did not answer every question, percentages given are of respondents who answered the particular question, not necessarily of all 107 interviewees.

were rampant, with nearly 70% of victims reported physical injuries, most commonly to the head or face. Symptoms not conventionally associated with sexual abuse were only slightly less common: 67.9% of respondents experienced some type of cardiovascular or respiratory difficulty and 61.3% suffered from gastrointestinal symptoms while being trafficked. More than half of the survivors (54.3%) reported dental problems, with tooth loss the most common problem (42.9%). The only major health category in which less than half of respondents reported a symptom was dermatological issues, which were nonetheless reported by 27.4% of respondents. This study's findings of widespread physical health consequences are generally consistent with the results of previous domestic studies and build on their findings by revealing a more comprehensive picture of the health issues that plague trafficking victims.[25]

Table 1. Physical Health Problems

Category	**% of respondents reporting at least one symptom**[26]
Any Physical Health Problem	99.1% (N=106)
Neurological	91.7% (N=106)
General Health	86.0% (N=105)
Injuries	69.2% (N=102)
Cardiovascular/Respiratory	68.5% (N=106)
Gastrointestinal	62.0% (N=106)
Dental	54.3% (N=105)

B. Psychological Symptoms

> "The mental health problems are the worst and most long lasting. I was diagnosed with chronic depression, have anxiety, post-traumatic stress syndrome, nightmares, flashbacks, disorientation. I've been suicidal at

25. See, e.g., FARLEY ET AL, PROSTITUTION RESEARCH, supra note 14, at 29-30, 31; RAYMOND & HUGHES, supra note 9, at 79.

26. The small differences in the number of respondents are due to some subjects electing to fill out some portions of the questionnaire but not others. Judgment occasionally had to be exercised by coders as to whether a given victim had not answered a section or had indicated not experiencing any of the symptoms. However, such judgment was required on only a small minority of surveys and was made with a presumption against selective completion of the questionnaire.

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> times. I don't think anyone is out on the street without having these long lasting effects."
>
> —Amanda, survivor

Survivors were overwhelmingly traumatized not only physically, but also mentally. The brutal treatment they endured created ongoing psychological and mental conditions in many of these victims and exploited existing mental instability in others. All but two of those who responded to the survey (104/106, 98.1%) reported at least one psychological issue during their captivity and survivors noted an average of more than a dozen (12.11). The most frequently reported problems included depression (88.7%), anxiety (76.4%), nightmares (73.6%), flashbacks (68.0%), low self-esteem (81.1%), and feelings of shame or guilt (82.1%). The picture painted by these surveys and the personal interviews that accompanied many of them is one of complete mental devastation. A substantial number of survivors suffered from other psychological disorders, including acute stress (38.7%), bipolar (30.2%), depersonalization (19.8%), multiple personality (13.2%), and borderline personality (13.2%) disorders.

Two additional and particularly chilling reporting rates confirm the extent of mental trauma that survivors suffered: 41.5% had attempted suicide (one victim reported 9 such attempts) and 54.7% suffered from Post Traumatic Stress Disorder. The psychological consequences that the trafficking victims in these focus groups reported were wide-ranging, severe, and in some cases nearly universal. As with physical symptoms, the findings on the psychological consequences of trafficking are consistent with other studies.[27]

Even the escape from their trafficking circumstances was far from a remedy for the psychological suffering of survivors. When reporting on their health experiences after trafficking, 96.4% of survivors reported at least one psychological symptom and an average of 10.5. As the table below indicates, there were only minor improvements in the number of psychological problems experienced when the victims escaped from their trafficking situations. Sex trafficking took a lasting mental and emotional as well as physical toll on nearly every survivor in the study.

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27. See, e.g., FARLEY ET AL., PROSTITUTION RESEARCH, supra note 14, at 31; RAYMOND & HUGHES, supra note 9, at 83; Melissa Farley & Howard Barkan, Prostitution, Violence, and Posttraumatic Stress Disorder, 27 WOMEN & HEALTH 37, 42 (1998), available at http://www.prostitutionresearch.com/Farley%26Barkan%201998.pdf.

Table 2. Psychological Health Problems

	During Trafficking (N=106)	**After Trafficking** (N=83)[28]	**Change in % reporting**
Reported at least one psychological issue	98.1%	96.4%	-1.7%
Average number of psychological issues	12.1	10.5	-1.6
Depression	88.7%	80.7%	-8.0%
Flashbacks	68.0%	63.9%	-4.1%
Shame/guilt	82.1%	71.1%	-11.0%
PTSD	54.7%	61.5%	+6.8%
Attempted suicide	41.5%	20.5%	-21.0%

C. Reproductive Issues

> If I hadn't had my children when I was young, I wouldn't be able to have them because I have had so many STDs and gynecological problems—including pelvic inflammatory disease, cervical infections, gonorrhea, herpes, chlamydia—I can't have children now.
>
> –Megan, survivor

Not surprisingly, survivors also reported significant numbers of reproductive health problems while they were being trafficked. Most notably, more than two-thirds of these women (67.3%) contracted some form of sexually-transmitted disease or infection (STD/STI). Survivors reported significantly higher rates of chlamydia (39.4%) and gonorrhea

28. Some respondents answered only the questions about symptoms experienced during trafficking, accounting for the difference in number of respondents for during and post-trafficking questions.

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(26.9%) than the next most common disease (Hepatitis C, 15.4%). Well over half of survivors (63.8%) reported at least one gynecological symptom other than STDs/STIs, with pain during sex (46.2%), urinary tract infections (43.8%), and vaginal discharge (33.3%) among the most common such symptoms. The extent of reproductive health issues that survivors reported is hardly surprising due to the extreme levels of sexual abuse these women endured. On average, the respondents reported being used for sex by approximately thirteen buyers per day,[29] with a median response of ten. Some respondents reported typical days of as many as thirty to fifty buyers.

Reporting problems complicated the data regarding pregnancies and their results, with some respondents answering related questions inconsistently.[30] While these reporting issues make precision impossible, the data merits concluding with confidence that pregnancy, miscarriage, and abortion were all common experiences for survivors in the study. Even without accounting for possible underreporting, forty-seven of the sixty-six women (71.2%) who gave an answer for the number of pregnancies they had during trafficking reported at least one pregnancy while being trafficked; fourteen of these (21.2% of respondents) reported five or more pregnancies. Of the

29. Where victims gave a range for the number of buyers per day, the answer was coded as the median of that range, using the lower median where the range contained an even number of possibilities. For example, an answer of 5-7 was coded as 6 and an answer of 10-15 was coded as 12.

30. For example, thirty-four respondents circled "pregnancy" as something they experienced during trafficking in the survey's first component, but an additional nineteen women gave a number of one or greater to the open-ended question "How many pregnancies did you have while being trafficked?" in the second component of the survey despite not having circled "pregnancy" earlier, bringing the total to fifty-three. There is reason to believe, however, that even the combined total of fifty-three women may underreport the number who experienced a pregnancy because many of the victims may have had different standards for what counted as a pregnancy. In some cases, the victims appeared not to count pregnancies that ended in abortion or miscarriage, reporting for example, two pregnancies, two live births, two miscarriages, and one abortion. Thus, women whose pregnancies all ended in miscarriage or abortion may not be reflected even in the combined total of fifty-three. Similar discrepancies occurred on a smaller scale with regard to miscarriages (thirty-two subjects circled, ten more did not circle but reported one or more, and two subjects who had circled nonetheless reported zero as the number they had) and abortions (thirty-nine subjects circled, three additional subjects did not circle but reported having one or more). There were additional inconsistent sequences of answers about pregnancies and pregnancy outcomes. Thirty-nine subjects reported numbers of births, miscarriages, and abortions that totaled a different number than the subject reported as her total number of pregnancies or gave otherwise conflicting answers. In most of these cases, there was no obvious explanation that accounted for the difference. Possible explanations include varying standards of what counts as a pregnancy, multiple-child births (twins, triplets, etc.), and answering different questions with reference to different periods of time (i.e., counting only pregnancies occurring during trafficking but counting all miscarriages, births, or abortions whether before, during, or after trafficking).

sixty-four respondents who gave an answer for the number of miscarriages they experienced, thirty-five (54.7%) had at least one miscarriage and nineteen (29.7%) had more than one.[31] Similarly, more than half (55.2%) of the sixty-seven respondents who answered reported at least one abortion, with twenty respondents (29.9%) reporting multiple abortions. Without accounting for possible underreporting, this subset of responding survivors reported a total of 114 abortions.

The prevalence of forced abortions is an especially disturbing trend in sex trafficking. Prior research noted that forced abortions were a reality for many victims of sex trafficking outside the United States[32] and at least one study noted forced abortions in domestic trafficking.[33] The survivors in this study similarly reported that they often did not freely choose the abortions they had while being trafficked. While only thirty-four respondents answered the question whether their abortions were of their own volition or forced upon them, more than half (eighteen) of that group indicated that one or more of their abortions was at least partly forced upon them.[34] One victim noted that "in most of [my six abortions,] I was under serious pressure from my pimps to abort the babies." Another survivor, whose abuse at the hands of her traffickers[35] was particularly brutal, reported

31. The interviewer notes that in some cases, survivors may have used miscarriage as a euphemism for abortion.

32. S. Abdulraheem & A.R. Oladipo, Trafficking in Women and Children: A Hidden Health and Social Problem in Nigeria, 2 INT'L J. SOC. & ANTHROPOLOGY 34, 37 (2010); Acharya, supra note 3, at 90; CATHY ZIMMERMAN ET AL., THE HEALTH RISKS AND CONSEQUENCES OF TRAFFICKING IN WOMEN AND ADOLESCENTS: FINDINGS FROM A EUROPEAN STUDY 24, 51 (2003), available at http://www.oas.org/atip/Global%20Reports/Zimmerman%20TIP%20HEALTH.pdf.

33. RAYMOND & HUGHES, supra note 9, at 18; see also U.S. v. Todd, 627 F.3d 329, 331 (9th Cir. 2009) (mentioning a forced abortion in describing how sex trafficking defendant abused his victims); U.S. v. Stokes, No. 10-00244-04 2011 WL 1585601, at *15 (W.D. Mo. 2011) (mentioning a forcible "abortion" performed by a defendant as one of the "overt acts" in furtherance of a sex trafficking conspiracy).

34. Additionally, several survivors stated in their interviews that they felt forced to choose abortion by the circumstance of being trafficked.

35. Street gangs are increasingly turning to sex trafficking as a source of income. See, e.g., Laura J. Lederer, Sold for Sex: The Link Between Street Gangs and Trafficking in Persons, 4 PROTECTION PROJECT J. HUM. RTS. & CIV. SOC'Y 1, 1 (2011); KAMALA D. HARRIS, CAL. DEP'T OF JUST., THE STATE OF HUMAN TRAFFICKING IN CALIFORNIA 63-64 (2012), available at http://oag.ca.gov/sites/all/files/pdfs/ht/human-trafficking-2012.pdf; Press Release, U. S. Att'y's Office, E. Dist. of Va., Gang Leader Sentenced to 40 Years for Leading Juvenile Sex Trafficking Ring (Sept. 14, 2012), http://www.justice.gov/usao/vae/news/2012/09/20120914stromnr.html; Press Release, U. S. Att'y's Office, E. Dist. of Va., Leader of MS-13 Gang Sentenced to 50 Years in Prison for Sex Trafficking Multiple Teens (June 1, 2012), http://www.fbi.gov/washingtondc/press-releases/2012/leader-of-ms-13-gang-sentenced-to-50-years-in-prison-for-sex-trafficking-multiple-teens. For a case study of gang

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seventeen abortions and indicated that at least some of them were forced on her. Notably, the phenomenon of forced abortion as it occurs in sex trafficking transcends the political boundaries of the abortion debate, violating both the pro-life belief that abortion takes innocent life and the pro-choice ideal of women's freedom to make their own reproductive choices.

D. Violence, Abuse, and Humiliation

> I've had a hard life during this time—16 years on the street, 10 to 20 customers per day. I've been hit, punched, kicked, beaten, whipped with a belt, forced to have sex, threatened with a weapon, shot at, and had my head split open. . . . One of my regulars got together with some friends and kidnapped me. They held me against my will, put a belt around my neck, and forced me to do all kinds of horrible things. When I said I didn't want to they said they would kill my family.
>
> –Nicole, survivor

The survey asked survivors if they had experienced violence or abuse, listing twelve possible forms.[36] These included being threatened with a weapon, shot, strangled, burned, kicked, punched, beaten, stabbed, raped, or penetrated with a foreign object. The survey also asked about other kinds of abuse such as threats, intimidation, verbal abuse and humiliation. Nearly all the survivors (92.2%) reported being the victim of at least one form of physical violence. Many survivors had suffered more than half of these experiences. Respondents reported an average of 6.25 of the 12 forms of violence. Likewise, most of these abuses were the rule rather than the exception—eight of the twelve were reported by half or more of the respondents, including behaviors as extreme as strangulation. In their interviews, survivors described additional ways they were abused. One survivor was whipped and had bleach poured on her, while another was forced to eat feces and was hung by her arms in a closet. As another survivor describes, "[my pimp] had his girls out on the streets every night. It was either you made the [money] for him or you got beat." In addition to the abuses detailed below, almost all survivors reported serious verbal

involvement in sex trafficking near Washington, D.C., see Laura J. Lederer & Justin Davis, Street Gangs and Human Trafficking in the Greater Washington, D.C. Area (Aug. 1, 2013) (unpublished manuscript) (on file with authors).

36. The specific forms on the survey were being threatened with a weapon, strangulation, burning with cigarettes, being kicked, punched, beaten, or beaten with an object, stabbing/slashing, rape (vaginal, oral, or anal), penetration with foreign objects, forced unprotected sex, and abuse by a person of authority.

abuse, including repeatedly being called derogatory names, treated as less than human, and being deprived of basic physical and emotional needs such as food, sleep, and a caring environment.

Table 3. Violence and Abuse in Sex Trafficking

Common Forms of Violence/Abuse	**% Reporting** (N=103)
Some form of violence/abuse	95.1%
Forced sex	81.6%
Punched	73.8%
Beaten	68.9%
Kicked	68.0%
Forced unprotected sex	68.0%
Threatened with weapon	66.0%
Strangled	54.4%
Abused by person of authority	50.5%

In addition to physical mistreatment, some victims were subjected to other forms of degradation, such as recreating scenes from pornography (29.3%) or being forcibly recorded for pornographic purposes (17.1%). Other studies confirm the prevalence of violence against trafficking victims.[37]

E. Substance Abuse

> I started doing drugs, specifically cocaine down at the local go-go bar, and eventually I tried heroin. I was a mess, wrecked my life, wasted it on drugs because I'd been raped and I didn't think I mattered to anyone. When I was 31 years old I started dating a . . . guy who was a drug dealer. We dealt together, did crack together, and he started prostituting me to close drug deals.
>
> —Radeel, survivor

Many survivors were dependent on drugs or alcohol while they were

37. See, e.g., FARLEY ET AL., PROSTITUTION RESEARCH, supra note 14, at 28-29; RAPHAEL & SHAPIRO, SISTERS, supra note 8, at 132-35; RAYMOND & HUGHES, supra note 9, at 75; Melissa Farley, Prostitution and the Invisibility of Harm, 26 WOMEN & THERAPY 247, 251-53 (2003).

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trafficked either because the substances were forced on them as a control mechanism by their traffickers[38] or because substance use was a means of coping with the immense abuse they suffered. 84.3% used alcohol, drugs, or both during their captivity and more than a quarter (27.9%) said that forced substance use was a part of their trafficking experience. More than a quarter of victims reported injected drugs and overdoses (27.2% and 26.0% respectively). As the following table indicates, alcohol, marijuana, and cocaine were the most common substances but others were prevalent as well.

Table 5. Substance Abuse in Sex Trafficking

Substance	**% Reporting Usage** (N=102)
Substance Abuse	84.3%
Alcohol	59.8%
Marijuana	53.4%
Cocaine	50.5%
Crack Cocaine	44.7%
Heroin	22.3%
Ecstasy	13.6%
PCP	9.7%

Overwhelmingly, survivors were the objects of repeated and extreme violence and were frequently driven to substance abuse either by force or by their dire circumstances.

IV. CRITICAL ISSUES IN PROVISION OF HEALTH CARE FOR VICTIMS OF SEX TRAFFICKING

> During the time I was on the street, I went to hospitals, urgent care clinics, women's health clinics, and private doctors. No one ever asked me anything anytime I ever went to a clinic. . . . I was on birth control during the 10 years I was on the streets—mostly Depo-Provera shots which I got at the Planned Parenthood and other neighborhood clinics. I also got the morning-after pill from them. I was young and so I had to

38. For instance, one survivor described how her pimp, "gave us drugs to keep us under his thumb."

> have a waiver signed in order to get these—one of the doctors (a private doctor I think) signed this waiver when my uncle took me to see him.
>
> –Lauren, survivor

Despite their abusive situations, most survivors did receive medical treatment at some point during their trafficking. Of those who answered the questions about their contact with healthcare (N=98), 87.8% had contact with a healthcare provider while they were being trafficked. By far the most frequently reported treatment site was a hospital/emergency room, with 63.3% being treated at such a facility. Survivors also had significant contact with clinical treatment facilities, most commonly Planned Parenthood clinics, which more than a quarter of survivors (29.6%) visited. More than half (57.1%) of respondents had received treatment at some type of clinic (urgent care, women's health, neighborhood, or Planned Parenthood).

Table 6. Victim Contact with Health Care Provider

Treatment Source	**% Reporting** (N=98)
Any contact with healthcare	87.8%
Any type of clinic	57.1%
Hospital/ER	63.3%
Planned Parenthood	29.6%
Regular doctor	22.5%
Urgent care clinic	21.4%
Women's health clinic	19.4%
Neighborhood clinic	19.4%
On-site doctor	5.1%
Other[39]	13.3%

Since pimps and traffickers[40] generally exercise nearly complete control of

39. Those who specified "other" treatment sources mentioned: a methadone clinic for heroin addiction, a psychiatric hospital, prisons (several mentioned treatment in prison facilities), Red Door and YouthLink (public health clinics), a therapist, a city Health Department, a pastor, the Pacific Alliance to Stop Slavery (a Hawaii anti-trafficking organization), and the grandmother of a trafficker.

40. The Oxford Dictionary defines a pimp as "a man who controls prostitutes and arranges clients for them, taking a percentage of their earnings in return." Pimp Definition,

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their victims,[41] these points of contact with healthcare represent rare opportunities for victim identification and intervention.[42] In addition, because of the hearsay exception in the Federal Rules of Evidence for statements made for medical treatment (regardless of whether the declarant testifies),[43] statements by victims to healthcare professionals should usually be admissible in a trafficking prosecution.[44]

These opportunities have largely been missed as even those healthcare professionals who recognized that victims might have been "on the street" rarely understood that they had a pimp/trafficker. Just over half (51.9%) of respondents who answered (N=81) said that at least some of the time the doctor knew they were "on the street," while the remaining respondents did not believe doctors were aware of their situations. Almost half of survivors (43.1%) (N=58) said the doctor asked them something about their lives,[45] but only 19.5% of those who answered (N=41) reported that the doctor knew they had a pimp.[46] At least two prior studies have demonstrated that medical care providers are woefully unprepared to identify trafficking

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OXFORD DICTIONARIES, http://oxforddictionaries.com/definition/english/pimp?q=pimp (last visited Nov. 26, 2013). These actions fall within the TVPA's definition of sex trafficking. 22 U.S.C. § 7102(10) (West, WestlawNext through P.L. 106-386) (defining sex trafficking as "the recruitment, harboring, transportation, provision, or obtaining of a person for the purpose of a commercial sex act."). Pimps are, therefore, one subset of traffickers.

41. See POLARIS PROJECT, DOMESTIC SEX TRAFFICKING: THE CRIMINAL OPERATIONS OF THE AMERICAN PIMP 5, available at http://www.polarisproject.org/resources/resources-by-topic/sex-trafficking (last visited Nov. 26, 2013).

42. See, e.g., Cole, supra note 21, at 466 (citing Jeffrey Barrows & Reginald Finger, Human Trafficking and the Healthcare Professional, 101 S. MED. J. 521 (2008)); WILLIAMSON, supra note 21, at 4.

43. FED. R. EVID. 803(4). The exception permits the admission of statements that are "made for—and [are] reasonably pertinent to—medical diagnosis or treatment" and describe "past or present symptoms or sensations; their inception; or their general cause." Id.

44. While such statements must be "made for . . . medical diagnosis or treatment" purposes, courts have construed this requirement in a manner favorable to sexual assault and rape victims, generally permitting the admission of statements that identify an abuser because the identity of an abuser is pertinent to diagnosis and treatment in sexually abusive contexts. See, e.g., Morgan v. Foretich, 846 F.2d 941, 948-50 (4th Cir. 1988); U.S. v. Renville, 779 F.2d 430, 435-39 (8th Cir. 1988); U.S. v. George, 960 F.2d 97, 99-100 (9th Cir. 1992); U.S. v. Tome, 61 F.3d 1446, 1450 (10th Cir. 1995); U.S. v. Chaco, 801 F. Supp. 2d 1217, 1227 (D.N.M. 2011). This rationale would logically extend to the sex trafficking context as well, especially where the victim is a minor.

45. Several survivors noted in the margins of their surveys that they were unable to answer questions about their lives or situations honestly either because their pimp/trafficker was present or because they feared reprisal from their pimp.

46. Even these numbers may overstate trafficking awareness on the part of medical personnel. One respondent indicated that the physician who treated them had an established relationship with the pimp. If other survivors said their doctors were aware they had a pimp because of similar situations, the awareness statistic would be skewed.

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victims.[47]

As noted above, pregnancy, miscarriage, and abortion were all experienced by half or more of survivors who answered questions about them. Several other survivors said that they had hysterectomies or tubal ligations either during or after trafficking and another two survivors were sold specifically for sodomy in order to avoid pregnancy. Healthcare providers who specialize in these types of care are therefore particularly likely to have opportunities for identification and intervention. Clinics that perform abortions must be especially vigilant in efforts to recognize possible trafficking victims. Roughly two-thirds (67.6%) of survivors who specified a location (N=37) identified a clinic as the site of their abortion(s), far outpacing hospitals (16.2%) and other sites (13.5%). One survivor described her situation:

I got pregnant six times and had six abortions during this time. Several of them were from a doctor who was a client—he did them 'back door'—I came in the back door after hours and paid him off the books. This kept my name off any records…. I think he felt like he was helping. At least one of my abortions was from Planned Parenthood because they didn't ask any questions. But they were expensive and on the street you didn't want to pay $250, $300, or more. So you went 'back door' where the charge was more like $150. I had so much scar tissue from these abortions because there was no follow-up and in a couple of cases I had bad infections, so bad that I eventually lost my fallopian tubes [and had to have a hysterectomy].[48]

Table 7. Where Sex Trafficking Victims Sought Abortions

Where abortions were performed	**% Identifying site** (N=37)
Clinic	67.6%
Hospital	16.2%
Other[49]	13.5%
Different sites at different times	2.7%

47. See J.C. Wong et al., Human Trafficking: An Evaluation of Canadian Medical Students' Awareness and Attitudes, 24 EDUC. FOR HEALTH 1, 3-5 (2011); Makini Chisolm-Straker & Lynne Richardson, Assessment of Emergency Department (ED) Provider Knowledge About Human Trafficking Victims in the ED, 14 ACAD. EMERGENCY MED. (5 SUPPL. 1) S134 (2007), http://onlinelibrary.wiley.com/doi/10.1197/j.aem.2007.03.704/pdf.

48. The abortions were arranged by a series of sex traffickers, not by the victim herself.

49. Those who specified the "other" site of their abortion mentioned an abortionist's home, doctor's offices (including an OB/GYN), and an Arkansas back alley.

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Survivors also interacted with medical professionals for purposes of obtaining birth control. A large majority (80.9%) of those who answered the question (N=73) indicated that they had used some form of birth control for some portion of their time being trafficked. Of those who specified where they obtained the birth control (N=59), approximately half (51.7%) said they had obtained it from a doctor or clinic. More than half (65.2%) of respondents said that they went alone to the doctor or other source where they obtained birth control. Together, these responses indicate that a significant number of trafficking victims see healthcare providers (especially clinics and doctors) to obtain birth control without trafficker supervision, suggesting that medical staff have a rare opportunity to communicate one-on-one with victims.[50]

Table 8. Type of Birth Control Utilized During Sex Trafficking

Birth Control Type[51]	**% Reporting Usage** (N=59)
Condoms	52.5%
Multiple Types	22.0%
Depo-Provera	11.9%
Birth Control Pill	10.2%
IUD	3.4%

VI. RECOMMENDATIONS

A. General Awareness: Common Symptoms and Warning Signs

Medical professionals must be made aware of critical signals for identifying trafficking victims. An important part of this training should be to help the health care professional understand the coercive dynamic of trafficking, especially the extreme degree of control exercised by traffickers, and the prevalence of this criminal exploitation of women and girls. Setting up internal protocols, procedures and regulations can further

50. While condoms (readily available in non-medical settings) were the most common form of birth control, nearly half of survivors (47.5%) used another type of birth control instead of or in addition to condoms. Thus, requests for birth control by noticeably young girls who also show signs of injury or abuse could be viable warning signals of a possible trafficking situation for medical professionals.

51. In addition to the contraceptive forms of birth control listed here, 25% of survivors who answered (N=60) reported use of the "morning-after pill."

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these goals and assist medical care providers in their vital role as identifiers of trafficking victims.

Based on the reported symptoms of survivors, a number of particularly widespread health-related consequences of trafficking should serve as warning signs to medical professionals. The most suggestive physical symptoms are injuries from physical violence, since this was a nearly universal experience for the survivors in the study. Signs of being kicked, punched, or beaten, all of which at least two thirds of respondents reported, should be a major "red flag" along with any signs of forced sex (reported by 81.6%), and head or facial injuries (each reported by more than half of survivors). While these may also be signals of domestic violence, their presence in patients seeking multiple abortions or treatment for sexually transmitted or serious communicable diseases may help healthcare providers to distinguish possible sex trafficking situations. Indications of extreme forms of violence (such as strangulation, stabbing, cigarette burns or gunshot wounds) also may be important clues for identification since these would have far fewer alternate explanations. One researcher notes that tattoos identifying the victim as the "property" of a particular trafficker could also alert care providers,[52] though these may be difficult to recognize.

In addition, those psychological symptoms that were particularly common among trafficking victims should be useful warning signs. Depression was the most common symptom for survivors (88.7%) and anxiety, irritability, nightmares, low self-esteem, and feelings of shame/guilt were all reported by more than 70% of survivors as well. The combination of these symptoms should therefore arouse suspicion when displayed by patients who repeatedly require reproductive health services, when an older or controlling male figure is present with the patient, and when the patient also presents signs of physical abuse. The well-documented rates of PTSD in trafficking victims,[53] (54.7% of survivors in this study) make it another important clue to identifying trafficking victims. Indications of attempted or repeated self-harm would likewise be a reason for considering trafficking as a possibility in these context, since 46.2% of respondents reported suicide ideation and 41.5% had attempted suicide.

The presence of sexually transmitted diseases or infections is another major identifier because nearly two-thirds (67.3%) of survivors reported having at least one such disease. Multiple or serial cases of such diseases or

52. Reena Isaac et al., Health Care Providers' Training Needs Related to Human Trafficking: Maximizing the Opportunity to Screen and Intervene, 2 J. APPLIED RES. ON CHILD 1, 10 (2011).

53. See, e.g., Farley & Barkan, supra note 27, at 42 (reporting that 68% of victims met criteria for PTSD and 76% met criteria for partial PTSD).

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infections is a particularly strong signal that should immediately raise the possibility of a trafficking situation in the minds of healthcare providers. Because of the overwhelming rate of substance abuse (84.3%) that survivors reported, signs of alcohol and/or drug abuse could also be a significant warning sign when observed in patients who require reproductive health services at a young age, appear to be controlled by another person, or also exhibit the physical and psychological symptoms detailed above.

Clinics and other abortion providers should be especially attentive to warning signs particularly with regard to younger patients. Multiple abortions and evidence of coercion (such as the presence of a significantly older or controlling "boyfriend," or the physical and psychological symptoms discussed above) in these patients should prompt the healthcare provider to seek more information about the patient's situation. More than half (52.9%) of survivors (N=34) indicated that at least one abortion was partly or wholly forced on them, making this concern especially grave.

These warning signs are not intended to be exhaustive or authoritative, but they build on and refine the suggestions of prior research.[54] To be sure, there are myriad other physical and psychological symptoms that could alert medical staff to the possibility that a patient is a victim of trafficking and many other contexts in which victims seek medical services. Nonetheless, the symptoms and service contexts most mentioned by survivors should prove particularly relevant to the problem of victim identification by medical professionals and may also lead to conversations that could later assist prosecutors because of their likely admissibility under the Federal Rules of Evidence.

B. Protocols for Identifying Victims and Catalyzing Rescues

Interaction between medical care providers and victims is an extraordinarily delicate situation. Because some victims may come alone, the health provider has an opportunity, if trust level and other considerations allow, to ask questions about the possible victim's situation and to provide her with resources like contact information for rescue and other services. Existing literature and this study both provide some guidance for carefully making the most of these opportunities.

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54. See, e.g., Isaac et al., supra note 52, at 9-10; T.K. Logan et al., Understanding Human Trafficking in the United States, 10 VIOLENCE, TRAUMA, & ABUSE 3, 19-20 (2009); Jeffrey Barrows & Reginald Finger, Human Trafficking and the Healthcare Professional, 101 S. MED. J., 521, 522-23 (2008); Cole, supra note 21, at 468; Patricia A. Crane & Melissa Moreno, Human Trafficking: What is the Role of Health Care Provider?, 2 J. APPLIED RES. ON CHILD 1, 6-7 (2011).

Lederer and Wetzel: The Health Consequences of Sex Trafficking and Their Implications
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Building trust with possible victims is a critical first step and requires patience and cultural sensitivity on the part of medical professionals:

> Building trust with trafficking victims may be a slow process and requires patience and determination. Taking the time to build rapport is critical. . . . The [health care provider] must have the humility to accept and acknowledge that there may be much about the victim's culture they do not understand, and that the impact of such taboos may be significant in that culture. Many small steps are needed to build trust, such as open-ended questions, few interruptions, and a private area to talk. Often more than one visit is needed, and the victim may need to be told to return to the clinic to reevaluate a health care issue when the HCP strongly suspects trafficking and further assessment and questioning is desired to get a patient to open up. Messages for the HCP to convey in private with a suspected victim include a focus on safety, getting healthy, and that the victim's welfare is the highest priority.[55]

Because traffickers often accompany victims to treatment and their presence may prevent truthful answers, victims should be interviewed in private if at all possible.[56] Separation should be done discreetly,[57] perhaps by requesting that the male figure assist with paperwork or remain in the waiting room while staff obtain specimens.[58]

Asking directly whether the patient is a victim of trafficking may be meaningless and directly asking about the most traumatic aspects of trafficking is also "ill-advised."[59] Rather, a serious of "sensitive probing questions" can help uncover or unpack the underlying trafficking situation. For example, the health care sector can borrow from the law profession. Legal aid attorneys working on custody cases noted that when gathering the facts about an abusive husband or boyfriend to help a client gain custody of her child, facts patterns emerged that made it clear that the client was a victim of sex trafficking. The victim did not come through the door self-identifying as a trafficking victim, but slowly over the course of conversation, understood her victimization and was able to seek help from law enforcement to emerge from the trafficking situation. Gradually working with the victim's identifiable health problems to elicit important facts about their over-arching situation is likely to be most effective and

55. Crane & Moreno, supra note 54, at 7-8.
56. Id. at 9.
57. Cole, supra note 21, at 467.
58. Crane & Moreno, supra note 54, at 9.
59. Id.

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least intrusive.[60]

Additionally, where a translator is needed, care needs to be taken to identify someone the right translator to avoid the possibility of complicity with a trafficker.[61] Especially in tight-knit communities, that someone unconnected translates is critical. In addition, other language considerations are key to creating trust and communication. Using informal language (sometimes even slang) rather than formal or clinical terminology may improve communication with victims, bridging conceptual or definitional gaps about trafficking generally, as well as with specific issues like violence and rape. Specific suggested questions include asking about the patient's freedom to contact family and friends, her eating and sleeping conditions (whether basic needs are being met), her ability to come and go freely, who lives with her, and whether she feels happy and cared for.[62] Sometimes it is possible for the provider to ask direct and specific questions about whether the patient has been drugged, raped, coerced, or hurt and get honest answers.

Regardless of the patient's comfort level and degree of cooperation, if a provider strongly suspects the patient is a victim of sex trafficking, he (or she) should call the National Trafficking Hotline.[63] Calls can be made anonymously if necessary. Providers need to have strategies and preparation for how to address potential sex trafficking cases, including coordination with law enforcement and with local NGO service providers.[64] Healthcare providers can play a crucial role in the trafficking rescue process by identifying possible victims and following up on those suspicions with careful, strategic questions, and actions that catalyze rescues or help create exit strategies.

B. Regulations: Training for Healthcare Professionals and Hotline Posting Requirements

Legislators and policymakers also have an important role to play in increasing health care providers' recognition and identification of trafficking victims. State legislators should draft and pass laws that require healthcare providers to undergo training on trafficking generally, including the basic warning signs and indicators for victim identification, techniques

60. Id.
61. Id.; see also Barrows & Finger, supra note 54, at 522.
62. Barrows & Finger, supra note 54, at 522; Crane & Moreno, supra note 54, at 10; and Logan et al., supra note 54, at 20. Each of these sources provides a more complete list of suggested questions.
63. Cole, supra note 21, at 467; Barrows & Finger, supra note 54, at 522.
64. Cole, supra note 21, at 467.

for communicating effectively with possible victims to assess their situations and determine victim status, and appropriate actions to take when a victim is identified. The Obama administration has recognized the need for additional trafficking-related training for federal social service employees and law enforcement.[65] Likewise, medical professionals need training to recognize and appropriately respond to trafficking victims.

New Jersey recently adopted a statute that may serve as a baseline model for such training requirements. Under the new law, the New Jersey Department of Health will "develop, approve, and provide for a one-time training course on the handling and response procedures of suspected human trafficking activities for employees of every licensed health care facility."[66] In order to maintain their licenses, health care facilities must verify completion of the course by a subset of its employees to be defined by regulation.[67] Other states should follow New Jersey's lead by making trafficking-related training a requirement for licensing with a comprehensive definition of the facilities affected.[68] Additionally, other states can build on the New Jersey statute by providing for ongoing trainings,[69] expanding the scope of training to include recognition of victims as well as protocols for handling and response of potential victims, and by requiring that all employees participate in the training course.

Another measure that can be instituted is to require that medical facilities post information about the National Human Trafficking Resource Center

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65. PRESIDENT'S INTERAGENCY TASK FORCE TO MONITOR AND COMBAT TRAFFICKING IN PERSONS, COORDINATION, COLLABORATION, CAPACITY: FEDERAL STRATEGIC ACTION PLAN ON SERVICES FOR VICTIMS OF HUMAN TRAFFICKING IN THE UNITED STATES 25-26 (2013), available at http://www.ncdsv.org/images/HHS-DHS-DOJ_FederalStrategicActionPlanOnServiceForVictimsOfHumanTrafficking_4-2013.pdf.

66. N.J. STAT. ANN. § 2C:13-12(c)(1) (West, WestlawNext through L.2013, c. 169 and J.R. No. 13). Alternatively, the statute permits the state to approve an existing training course provided by a statewide nonprofit group with experience administering similar trainings. Id.

67. Id.

68. See id. (defining "health care facility" as a "facility or institution whether public or private, engaged principally in providing services for health maintenance organizations, diagnosis, or treatment of human disease, pain, injury, deformity, or physical condition," including, inter alia, hospitals, mental hospitals, maternity hospitals, outpatient clinics, diagnostic centers, and treatment centers).

69. One option in states that require Continuing Medical Education (CME) courses would be to institute a trafficking-related CME requirement. For example, the Florida Medical Association offers a CME course comparing domestic violence with human trafficking and training employees to recognize and respond to both. See Fla. Med. Ass'n, Domestic Violence with a Special Focus on Human Trafficking, http://flmedical.inreachce.com/ (follow "public health" hyperlink; then follow "Domestic Violence with a Special Focus on Human Trafficking" hyperlink) (last visited Nov. 26, 2013).

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Hotline, a toll-free phone number that connects callers to law enforcement as well as other services[70] An earlier proposed version of the 2013 TVPRA would have required the Secretary of Health and Human Services and the Attorney General to "make reasonable efforts to encourage [s]tates to adopt legislation" that requires posting of information about the hotline at a variety of establishments, including hospitals and urgent care centers.[71] Measures like this in future federal legislation could be a catalyst to state-level posting requirements. Posting laws improve victim access to the hotline and could even spur otherwise hesitant victims to share their situation with medical staff. In fact, California[72] and Georgia[73] have already adopted posting laws. Other states should follow suit and expand the range of medical facilities covered by the statutes to include abortion and women's health clinics.[74] Some survivors have that while posting laws and brochures are important, even better (or in addition) is a small business card with the hotline number as well as shelter and rescue information on it. A business card can be slipped into a handbag or even a shoe and concealed for use later on.

Finally, both federal and state governments must commit to providing resources to aid survivors of sex trafficking regardless of age. Although the Violence Against Women Reauthorization Act of 2013 provided significant resources for the care of trafficking victims, it only targeted these resources at victims who are minors.[75] These resources need to be extended to cover adult trafficking victims and adult survivors, as their physical and mental health needs are just as great as those of minor sex trafficking victims. Federal and state funding of medical care and other related survivor needs should recognize this reality by eliminating age-based restrictions on funding.

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70. Posting the National Human Trafficking Resource Center Hotline, POLARIS PROJECT, http://www.polarisproject.org/what-we-do/policy-advocacy/capacity-building/posting-the-national-human-trafficking-resource-center-hotline (last visited Nov. 26, 2013). This page of the Polaris Project website also provides model language for state-level posting legislation.

71. H.R. 898, 113th Cong. § 224(c)(1)-(3) (2013).

72. CAL. CIV. CODE § 52.6 (West, WestlawNext through Ch. 800 of 2013 Reg. Sess., 2013-2014 1st Ex. Sess. Laws, and Res. Ch 123).

73. GA. CODE ANN. § 16-5-47 (West, WestlawNext through the end of the 2013 Regular Session).

74. For additional public policy recommendations and more detail on state training and posting requirements, see Laura J. Lederer & Ashley Johnson, Healthcare Professionals' Role in Combating Human Trafficking (Aug. 2, 2013) (unpublished manuscript) (on file with authors).

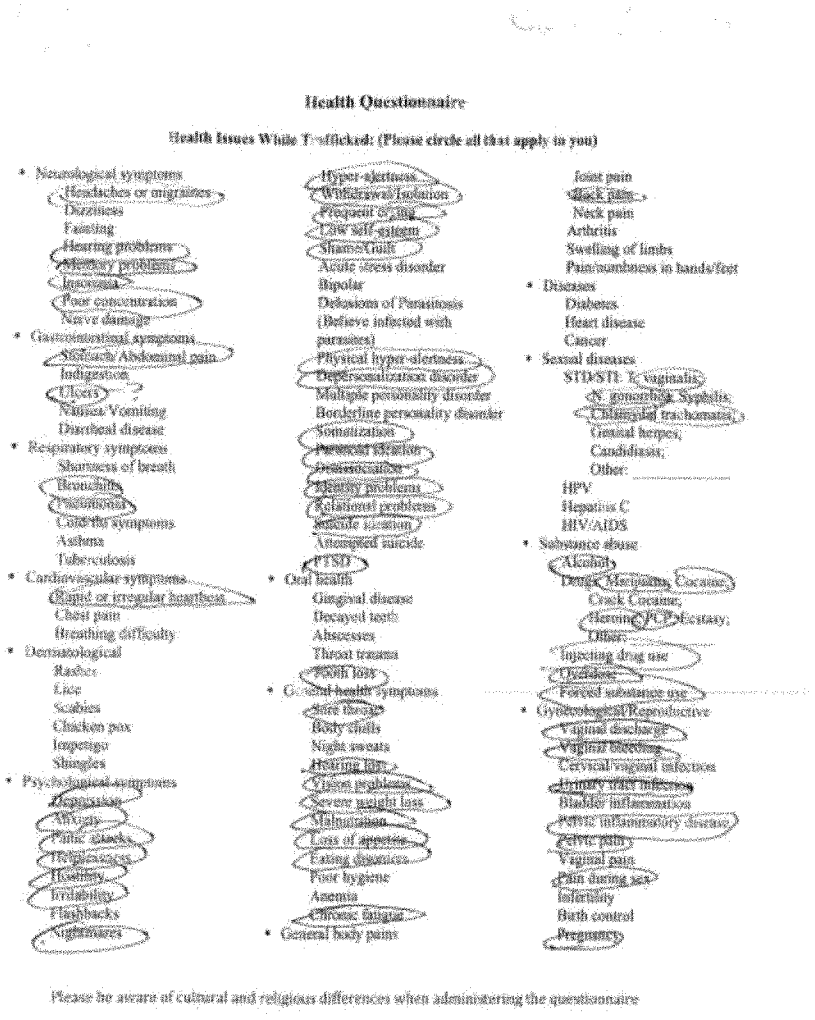
75. Violence Against Women Reauthorization Act of 2013, Pub. L. 113-4, 127 Stat. 136, 136-160 (2013) (codified in various sections of the U.S.C.).

VII. CONCLUSION

Victims of sex trafficking suffer severe physical and psychological health consequences as a result of their trafficking. Victims frequently have contact with medical professionals in a variety of health care settings, including hospital emergency wards, neighborhood clinics, women's health clinics, and Planned Parenthood clinics, as well as private practices. Violence-related injuries, serious illness or disease, pregnancy, birth control, and abortion, substance abuse, addiction and overdose, as well as serious psychological problems, are all reasons why substantial numbers of victims seek treatment.

Because they are "first responders" health care providers have unique opportunities to intervene on behalf of trafficking victims. Health care institutions must develop protocols for training, identifying, and treating sex trafficking victims. Medical personnel must increase efforts to understand the nature and scope of the problem of sex trafficking in the United States in order to improve their capacity to identify victims. This is especially true when they have the ability to speak privately with victims in a context where their statements may be admissible in a later prosecution of their traffickers. To this end, medical staff, particularly in hospital emergency rooms and local clinics should be alert for the most common physical and psychological conditions and symptoms these victims experience, especially in the context of reproductive health. By doing so, the medical community can play a vital role in the ongoing fight to eliminate modern-day slavery.

Appendix – Sample Completed Survey

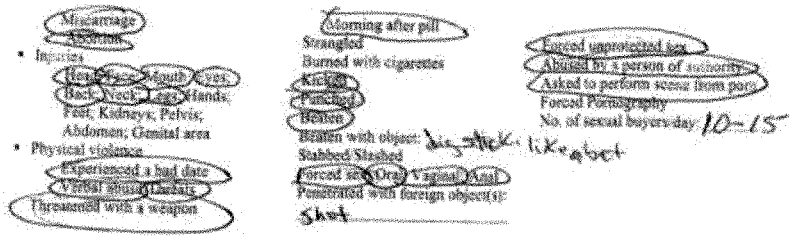


Health Questionnaire

Health Issues While Trafficked: (Please circle all that apply to you)

- Neurological symptoms
  - Headaches or migraines
  - Dizziness
  - Fainting
  - Hearing problems
  - Memory problems
  - Insomnia
  - Poor concentration
  - Nerve damage
- Gastrointestinal symptoms
  - Stomach/Abdominal pain
  - Indigestion
  - Ulcers
  - Nausea/Vomiting
  - Diarrheal disease
- Respiratory symptoms
  - Shortness of breath
  - Bronchitis
  - Pneumonia
  - Cold/flu symptoms
  - Asthma
  - Tuberculosis
- Cardiovascular symptoms
  - Rapid or irregular heartbeat
  - Chest pain
  - Breathing difficulty
- Dermatological
  - Rashes
  - Lice
  - Scabies
  - Chicken pox
  - Impetigo
  - Shingles
- Psychological symptoms
  - Depression
  - Anxiety
  - Panic attacks
  - Forgetfulness
  - Hostility
  - Irritability
  - Flashbacks
  - Nightmares
  - Hyper-alertness
  - Withdrawal/Isolation
  - Frequent crying
  - Low self-esteem
  - Shame/Guilt
  - Acute stress disorder
  - Bipolar
  - Delusions of Parasitosis (Believe infected with parasites)
  - Physical hyper-alertness
  - Depersonalization disorder
  - Multiple personality disorder
  - Borderline personality disorder
  - Somatization
  - Paranoid ideation
  - Dissociation
  - Memory problems
  - Relational problems
  - Suicide ideation
  - Attempted suicide
  - PTSD
- Oral health
  - Gingival disease
  - Decayed teeth
  - Abscesses
  - Throat trauma
  - Tooth loss
- General health symptoms
  - Sore throat
  - Body chills
  - Night sweats
  - Hearing loss
  - Vision problems
  - Severe weight loss
  - Malnutrition
  - Loss of appetite
  - Eating disorders
  - Poor hygiene
  - Anemia
  - Chronic fatigue
- General body pain
  - Joint pain
  - Back pain
  - Neck pain
  - Arthritis
  - Swelling of limbs
  - Pain/numbness in hands/feet
- Diseases
  - Diabetes
  - Heart disease
  - Cancer
- Sexual diseases
  - STD/STI: Vaginalis; N. gonorrhea; Syphilis; Chlamydial trachomatis; Genital herpes; Candidiasis; Other:
  - HPV
  - Hepatitis C
  - HIV/AIDS
- Substance abuse
  - Alcohol
  - Drugs: Marijuana, Cocaine, Crack Cocaine, Heroin, PCP, Ecstasy, Other:
  - Injecting drug use
  - Overdose
  - Forced substance use
- Gynecological/Reproductive
  - Vaginal discharge
  - Vaginal bleeding
  - Cervical/vaginal infection
  - Urinary tract infection
  - Bladder inflammation
  - Pelvic inflammatory disease
  - Pelvic pain
  - Vaginal pain
  - Pain during sex
  - Infertility
  - Birth control
  - Pregnancy

Please be aware of cultural and religious differences when administering the questionnaire



For the above listed health issues, where did you receive treatment?

Hospital/ER
Urgent Care Clinic
Neighborhood Clinic
Planned Parenthood
Women's Health Clinic
General Doctor
On-site Doctor
Other: Dr. my pimp knew

Did the doctor, nurse, health provider know you were "on the street"?

yes

If yes, did the doctor, nurse, health provider ask you anything about your life?

no

If yes, and if you had a pimp, did the health care provider know you had a pimp?

yes - only the one Private Dr,
Not the health clinic's - but they never asked.

Please be aware of cultural and religious differences when administering the questionnaire

If you circled birth control, pregnancy, miscarriage, morning after pill or abortion, please answer the following questions:

How long were you on birth control while being trafficked?
never

What kind of birth control did you use? (Condom, Depo-Provera, Diaphragm, IUCP)
Sponge

Who gave you the birth control? (Trafficker, doctor, clinic worker)
I bought.

Who took you to the clinic, doctor, or hospital where you received birth control?

How many pregnancies did you have while being trafficked?
9 in the life / but 8 pregnancies

Who fathered the child children? (Male sexual buyer, boyfriend/pimp, trafficker)

How many children did you give birth to?
two

Where was each child delivered? (Hospital, clinic, on-site)

Do you have custody of your child?
Yes

How many miscarriages did you have?
1

Were you given the morning after pill? Who supplied the drug?
Dr. three times - not for sure if I was pregnant.

How many abortions did you have?
6

At what term in your pregnancy did you have an abortion?
1st trim - everytime

Was the abortion of your own volition or forced upon you?
experienced both - lack of options to raise a baby

If you had an abortion, where was the abortion performed? (Hospital, clinic, on-site)
Dr. office - clinics

Please be aware of cultural and religious differences when administering the questionnaire.

Health Issues Post-Trafficking: (Please circle all that apply to you)

- Neurological symptoms
  - Headaches or migraines
  - Dizziness
  - Fainting
  - Hearing problems
  - Memory problems
  - Insomnia
  - Poor concentration
  - Nerve damage
- Gastrointestinal symptoms
  - Stomach/Abdominal pain
  - Indigestion
  - Ulcers
  - Nausea/Vomiting
  - Diarrheal disease
- Respiratory symptoms
  - Shortness of breath
  - Bronchitis
  - Pneumonia
  - Cold/flu symptoms
  - Asthma
  - Tuberculosis
- Cardiovascular symptoms
  - Rapid or irregular heartbeat
  - Chest pain
  - Breathing difficulty
- Dermatological
  - Rashes
  - Lice
  - Scabies
  - Chicken pox
  - Impetigo
  - Shingles
- Psychological symptoms
  - Depression
  - Anxiety
  - Panic attacks
  - Helplessness
  - Irritable
  - Irritability
  - Flashbacks
  - Nightmares
  - Hyper-alertness
  - Withdrawal/Isolation
  - Frequent crying
  - Low self-esteem
  - Shame/Guilt
  - Acute stress disorder
  - Bipolar
  - Delusions of Parasitosis (believe infected with parasites)
  - Physical hyper-alertness
  - Depersonalization disorder
  - Multiple personality disorder
  - Borderline personality disorder
  - Somatization
  - Paranoid ideation
  - Dissociation
  - Identity problems
  - Relational problems
  - Suicide ideation
  - Attempted suicide
  - PTSD
  - Phobias: people's motives
- Oral health
  - Gingival disease
  - Decayed teeth
  - Abscesses
  - Throat trauma
  - Teeth loss
- General health symptoms
  - Sore throat
  - Body chills
  - Night sweats
  - Hearing loss
  - Vision problems
  - Severe weight loss
  - Malnutrition
  - Loss of appetite
  - Eating disorders
  - Poor hygiene
  - Anemia
  - Chronic fatigue
- General body pains
  - Joint pain
  - Back pain
  - Neck pain
  - Arthritis
  - Swelling of limbs
  - Pain/numbness in hands/feet
- Diseases
  - Diabetes
  - Heart disease
  - Cancer
- Sexual diseases
  - STD/STI: T. vaginalis; N. gonorrhea; Syphilis; Chlamydia trachomatis; Genital herpes; Candidiasis; Other:
  - HPV
  - Hepatitis C
  - HIV/AIDS
- Substance abuse
  - Alcohol
  - Drugs: Marijuana; Cocaine; Crack Cocaine; Heroine; PCP; Ecstasy; Other:
  - Injecting drug use
  - Overdose
- Gynecological/Reproductive
  - Vaginal discharge
  - Vaginal bleeding
  - Cervical/vaginal infection
  - Urinary tract infection
  - Bladder inflammation
  - Pelvic inflammatory disease
  - Pelvic pain
  - Vaginal pain
  - Pain during sex
  - Infertility
  - Birth control
  - Pregnancy
  - Miscarriage
  - Morning after pill
  - Abortion

Please be aware of cultural and religious differences when administering the questionnaire

Exhibit 2

Bill Analysis, C.S.H.B. 3446,

Committee Report

BILL ANALYSIS

C.S.H.B. 3446
By: Laubenberg
State Affairs
Committee Report (Substituted)

BACKGROUND AND PURPOSE

Human trafficking, child pornography, and international sex tourism reportedly generate billions of dollars a year worldwide and there are indications that a significant number of U.S. citizens and foreign nationals are trafficked within the borders of the United States. Texas law already requires certain places of business to post signs that are visible to employees and patrons that provide a toll-free phone number for a national human trafficking helpline. It has been noted, however, that there is no law requiring these postings at an abortion facility despite the fact that many of the women who undergo abortions may be victims of human trafficking, especially sex trafficking. Due to the potentially high number of trafficking victims who undergo abortion procedures, abortion facility employees are uniquely situated to identify and assist victims of sex trafficking. C.S.H.B. 3446 seeks to require signs relating to human trafficking to be displayed at certain abortion facilities.

CRIMINAL JUSTICE IMPACT

It is the committee's opinion that this bill does not expressly create a criminal offense, increase the punishment for an existing criminal offense or category of offenses, or change the eligibility of a person for community supervision, parole, or mandatory supervision.

RULEMAKING AUTHORITY

It is the committee's opinion that rulemaking authority is expressly granted to the executive commissioner of the Health and Human Services Commission in SECTION 1 of this bill.

ANALYSIS

C.S.H.B. 3446 amends the Health and Safety Code to require a licensed ambulatory surgical center that performs more than 50 abortions in any 12-month period or a licensed abortion facility to conspicuously display in each patient admission area, waiting room, restroom, and patient consulting room signs that contain a phone number for the Department of Public Safety and a toll-free phone number of a nationally recognized information and referral hotline for victims of human trafficking, as well as the following information: a woman cannot be forced to have an abortion against her will, regardless of her age; if a woman is being forced to have an abortion or being abused, the state is able to help the woman; and human trafficking, including sex trafficking, is a violation of state law. The bill prohibits the signs from containing any information other than that information and prescribes the required sign measurements. The bill requires an applicable center or facility to post a sign in English and a sign in Spanish, as well as any other language in which the political subdivision within which the facility is located is required under the Election Code to provide election materials, if applicable. The bill requires the executive commissioner of the Health and Human Services Commission, not later than December 1, 2015, to adopt rules as necessary to implement and enforce the bill's provisions and establishes that an ambulatory surgical center or abortion facility is not required to comply with the bill's provisions before January 1, 2016.

EFFECTIVE DATE

September 1, 2015.

COMPARISON OF ORIGINAL AND SUBSTITUTE

While C.S.H.B. 3446 may differ from the original in minor or nonsubstantive ways, the following comparison is organized and formatted in a manner that indicates the substantial differences between the introduced and committee substitute versions of the bill.

INTRODUCED

SECTION 1. Subchapter B, Chapter 171, Health and Safety Code, is amended by adding Sections 171.0125 and 171.0126 to read as follows:

Sec. 171.0125. REQUIRED SIGNS AT CERTAIN FACILITIES: AVAILABLE RESOURCES. (a) An ambulatory surgical center licensed under Chapter 243 that performs more than 50 abortions in any 12-month period or an abortion facility licensed under Chapter 245 shall conspicuously display a sign that satisfies the requirements of this section in each patient admission area, waiting room, and patient consulting room.

(b) The sign required by this section must be in English and Spanish and display the following text:

You can't be forced. No one can make you have an abortion against your will, even if you are a minor. In fact, forcing a minor to have an abortion is considered child abuse. If you are a minor being forced into making a particular decision, you can report it by calling the Texas Abuse Hotline at 1-800-252-5400. The call is free and the hotline operates 24 hours per day, 365 days per year.

You and the father. The father of your child must provide support for the child, even if he has offered to pay for an abortion. The Child Support Division of the Office of the Attorney General can help you locate your child's father and determine that he is the father. The Child Support Division can also help establish and enforce child support orders and collect money owed, as well as distribute child support payments. To learn more about child support services, call the Child Support Division at (512) 460-6000.

You and adoption. The law allows adoptive parents to pay costs of prenatal care, childbirth, and newborn care. To learn more about adoption services and the organizations available to assist you, call Woman's Right to Know at (512) 776-6917.

You are not alone. Many agencies are willing to help you carry your child to term and to assist you after your child's birth. This includes providing access to health care services for mother and baby, supplies, healthy food items, nutrition education, and in-home support.

HOUSE COMMITTEE SUBSTITUTE

SECTION 1. Subchapter B, Chapter 171, Health and Safety Code, is amended by adding Section 171.0125 to read as follows:

Sec. 171.0125. REQUIRED SIGNS AT CERTAIN FACILITIES: AVAILABLE RESOURCES. (a) An ambulatory surgical center licensed under Chapter 243 that performs more than 50 abortions in any 12-month period or an abortion facility licensed under Chapter 245 shall conspicuously display signs that satisfy the requirements of this section in each patient admission area, waiting room, restroom, and patient consulting room.

(b) The signs required by this section must contain the following information:

(1) a woman cannot be forced to have an abortion against her will, regardless of her age;

(2) if a woman is being forced to have an abortion or being abused, the state is able to help the woman; and

(3) human trafficking, including sex trafficking, is a violation of state law.

(c) The signs required by this section must also contain a phone number for the Department of Public Safety and a toll-free phone number of a nationally recognized information and referral hotline for victims of human trafficking.

(d) The signs required by this section may not contain any information other than the information described by Subsections (b) and (c).

INTRODUCED	
(See subsection (b) above.)	
(c) The executive commissioner of the Health and Human Services Commission shall adopt rules as necessary to implement and enforce this section.	(e) The signs required by this section must each be at least 11 inches in width and 17 inches in length. (f) A facility described by Subsection (a) shall post a sign required by this section in English and a sign in Spanish. If the facility is located in a political subdivision that is required to provide election materials in a language other than English or Spanish under Section 272.011, Election Code, the facility shall also post a sign in that language. (g) The executive commissioner shall adopt rules as necessary to implement and enforce this section.
Sec. 171.0126. REQUIRED SIGNS AT CERTAIN FACILITIES: HUMAN TRAFFICKING. (a) An ambulatory surgical center licensed under Chapter 243 that performs more than 50 abortions in any 12-month period or an abortion facility licensed under Chapter 245 shall conspicuously display a sign that satisfies the requirements of this section in each patient admission area, waiting room, and patient consulting room. (b) The sign required by this section must be in English and Spanish and display the following text: WARNING: Being forced to engage in sexual activity or forced to obtain an abortion is illegal under Texas law. Call the national human trafficking hotline: 1-888-373-7888. (c) The executive commissioner of the Health and Human Services Commission shall adopt rules as necessary to implement and enforce this section.	
SECTION 2. Not later than December 1, 2015, the executive commissioner of the Health and Human Services Commission shall adopt the rules necessary to implement Sections 171.0125 and 171.0126, Health and Safety Code, as added by this Act.	SECTION 2. Not later than December 1, 2015, the executive commissioner of the Health and Human Services Commission shall adopt the rules necessary to implement Section 171.0125, Health and Safety Code, as added by this Act.
SECTION 3. An ambulatory surgical center or abortion facility is not required to comply with Sections 171.0125 and 171.0126, Health and Safety Code, as added by this Act, before January 1, 2016.	SECTION 3. An ambulatory surgical center or abortion facility is not required to comply with Section 171.0125, Health and Safety Code, as added by this Act, before January 1, 2016.
SECTION 4. This Act takes effect September 1, 2015.	SECTION 4. Same as introduced version.

Exhibit 3

Declaration of Mario R. Dickerson

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF MARIO R. DICKERSON

I, Mario R. Dickerson, a citizen of the United States and a resident of Willow Grove, Pennsylvania, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I serve as the Executive Director of the Catholic Medical Association ("CMA"). Given my involvement in CMA, I am familiar with the organization's history, the issues confronting it, and the views of the organization and its members concerning various emerging issues, including the deregulated use of mifepristone, or RU-486, to accomplish chemical abortions. I am also familiar with CMA members and their practices.
3. CMA is the largest association of Catholic individuals in healthcare. CMA is a national, physician-led community that includes about 2700 physicians and healthcare professionals nationwide.
4. CMA is a nonprofit organization incorporated in Virginia, and its registered agent is in Virginia.
5. CMA's mission is to inform, organize, and inspire its members, in steadfast fidelity to the teachings of the Catholic Church, to uphold the principles of the Catholic faith in the science and practice of medicine.
6. CMA seeks to pursue its mission in conformity to Christ the Divine Physician. Its members are challenged to be a voice of truth spoken in charity, to show

how Catholic teachings on the human person, human rights and the common good intersect with and improve the science and practice of medicine, and to defend the sacredness and dignity of human life at all stages.

7. CMA is a member of the Alliance for Hippocratic Medicine (AHM).

8. CMA is committed to taking a Catholic and Hippocratic approach to medicine.

9. Consistent with Catholic teaching, CMA and its members are morally and ethically opposed to all forms of abortion—chemical or surgical.

10. I have spoken with CMA members who have treated women harmed by chemical abortion drugs.

11. The FDA's unauthorized approval of mifepristone (also known as "Mifeprex" and "RU-486") and subsequent elimination of certain safeguards for the use of the dangerous chemical abortion drug regimen, including those found in the Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, has led to an increasing risk that women and girls may suffer adverse events from chemical abortion.

12. The FDA has continued to eliminate safeguards such that the chemical abortion drugs can now be administered and dispensed with no in-person examination or oversight by a physician. This leaves physicians, including CMA members, to treat the complications that women and girls suffer due to the actions of the FDA and abortionists.

13. CMA's member physicians include OB/GYNs and emergency department physicians who have treated women suffering complications from chemical abortion.

14. The FDA's actions harm CMA and its member physicians who are called away from other patients to render emergency treatment to women and/or girls who present to emergency departments with symptoms, such as heavy bleeding and severe pain, and more serious complications, including hemorrhage and sepsis caused by chemical abortion drugs. This causes CMA's member physicians much stress and grief, while impeding their ability to perform their practice of medicine in the manner that they desire.

15. Often, emergency department doctors do not have a prior relationship with these patients and lack access to the patient's medical history. Sometimes these patients were underinformed about the effects of the chemical abortion drug regimen, they may not even know what drugs they consumed, or they are told to say they are suffering a miscarriage if there is a need for them to seek emergency help following a chemical abortion. This leaves doctors at increased risk of liability and could impact their ability to render the best care possible to the patient—all because of the FDA's elimination of necessary safeguards.

16. Moreover, the FDA's removal of necessary safeguards could force CMA members to treat women and girls who present to emergency departments following an elective chemical abortion requiring those doctors to complete an

unfinished elective abortion—terminating the life of an unborn child—in violation of their conscience rights.

17. Since 2005, CMA has called upon the FDA to respond to citizens petitions calling for removal of RU-486 from the market in an urgent action. CMA renewed this resolution in 2015.

18. In 2016, CMA enacted a resolution that called for the FDA to require a central registry for all those having a chemical abortion, with mandatory reporting from every state and territory of complications and mortalities from chemical abortions; that the drug be administered only by a physician with surgical privileges at a hospital within 30 minutes of the facility where the drug is dispensed; that the dispensing physician be responsible for follow-up and handling of complications; and that the patient be informed that the process could be stopped without harm to her or the baby.

19. These resolutions are vital to ensure the safety of women and girls, and to protect doctors, including CMA members.

20. CMA has spent considerable time, effort and resources challenging the FDA's actions—at the expense of other CMA priorities. For example, to implement these resolutions, committees have had to review them, it has taken time during General Assembly meetings to discuss them, which takes our members away from their other business, and it has taken time for our Executive Director and Board to review, taking them away from other priorities such as fundraising and membership recruitment and retention.

21. Due to inadequate adverse event reporting, the true rates of risks associated with chemical abortion drugs remain unknown and undercounted. This prevents CMA from providing the public, their members, and their members' patients with accurate statistics and complete information regarding the risks associated with the use of chemical abortion drugs.

22. CMA is a leading national voice on applying the principles of the Catholic faith to medicine. CMA creates and organizes educational resources and events; advocates for members, the Church, and the medical profession in public forums; and provides guidance for bishops and other national leaders on healthcare ethics and policy. The inability to share accurate information on the risks of chemical abortion frustrates and complicates CMA's purpose to educate doctors, their patients, and the public about these dangers.

Executed this November 12, 2022.

By: Mario R. Dickerson
Mario R. Dickerson

Exhibit 4

Declaration of Dr. Donna Harrison

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. DONNA HARRISON

I, Donna Harrison, a citizen of the United States of America and a resident of Berrien Center, Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist.
3. I received my medical degree from the University of Michigan and completed my residency at a University of Michigan affiliate hospital, St. Joseph Mercy Hospital.
4. I am a diplomate of the American Board of Obstetrics and Gynecology.
5. I serve as the Chief Executive Officer of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).
6. I also serve as the President of Plaintiff Alliance for Hippocratic Medicine (AHM).
7. I am familiar with AAPLOG, its members, their fields of practice, and AAPLOG's policies and positions, including as set forth in the complaint, which I have reviewed.
8. AAPLOG is the largest organization of pro-life obstetricians and gynecologists ("OB/Gyns") in the world and is headquartered in Indiana. AAPLOG includes OB/Gyns and other physicians, with more than 7,000 medical professionals nationwide and more than 300 members in Texas.

AAPLOG members oppose elective abortion and are committed to the care and well-being of their patients including both pregnant women and their unborn children. AAPLOG members are concerned about the adverse impacts of chemical abortion on their practice of medicine.

9. AAPLOG's mission includes advocating on behalf of its members, including in litigation.

10. AAPLOG sues in this case on behalf of itself and its members.

11. I am also familiar with AHM, its members, their members' fields of practice, and AHM's policies and positions, including as set forth in the complaint, which I have reviewed.

12. AHM is a nonprofit organization that upholds and promotes the fundamental principles of Hippocratic medicine. AHM is incorporated in the State of Texas and has its registered agent in Amarillo, Texas.

13. AHM's members include the membership of the American Association of Pro-Life Obstetricians and Gynecologists, American College of Pediatricians, Catholic Medical Association, Christian Medical and Dental Associations, and Coptic Medical Association of North America. In opposing chemical abortion, AHM's members are concerned about the safety and well-being of pregnant women and girls, their preborn children, and chemical abortion's adverse impacts on the practice of medicine.

14. AHM sues in this case on behalf of itself and its members.

15. I am familiar with chemical abortion drugs, their use, and the complications that accompany chemical abortion.

16. As part of my duties and responsibilities at AAPLOG, I have authored several studies on the approval of mifepristone as an abortifacient. Among these, I co-authored two studies with other physicians and scholars examining the adverse events associated with the use of mifepristone. Our studies of the real-world use of mifepristone concluded that significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. We recommended that a pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm the gestational age of the unborn child. We concluded that the FDA's adverse event reporting system is grossly inadequate to evaluate real-world complications and significantly underestimates adverse events from mifepristone. One major reason that the FAERS database does not reflect real world complications is that FDA only required the manufacturer to report complications, and the manufacturer in turn obtains data from the abortionists. However, as our studies of the FAERs database indicate, most complications are not handled by the abortion provider, but rather by the Emergency Department, and the Emergency Department physician has no knowledge of the reporting process or obligation to report those complications to the manufacturer or to the FDA. *See* Kathi Aultman, et al., *Deaths and Severe Adverse Events After the Use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 36

Issues L. Med. 3 (2021), https://pubmed.ncbi.nlm.nih.gov/33939340/; Margaret M. Gary & Donna J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, 40 Ann. Pharmacother. 171 (2006), https://pubmed.ncbi.nlm.nih.gov/16380436/.

17. In addition, as part of my duties and responsibilities at AAPLOG, I co-authored a paper comparing the published complications after use of mifepristone from Planned Parenthood in 2009 and 2010 and compared those numbers to the complications in the FDA Adverse Event Reporting System for the same time period. We found that Cleland identified 1,530 Planned Parenthood mifepristone cases with specific adverse events (AEs) for 2009 and 2010. For this period, FAERS online dashboard includes a total (from all providers) of only 664, and the FDA released only 330 adverse event reports (AERs) through Freedom of Information Act (FOIA) requests. Cleland identified 1,158 ongoing pregnancies in 2009 and 2010. FAERS dashboard contains only 95, and only 39 were released via FOIA requests. We concluded that there are significant discrepancies in the total number of AERs and specific AEs for 2009 and 2010 mifepristone abortions reported in 1) Cleland's documentation of Planned Parenthood AEs, 2) FAERS dashboard, and 3) AERs provided through FOIA. These discrepancies render FAERS inadequate to evaluate the safety of mifepristone abortions. *See* Christina A Cirucci, et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting*

System and Those Obtained Through the Freedom of Information Act, 8 Health Servs. Rsch. & Managerial Epidemiol. 23333928211068919 (2021), https://pubmed.ncbi.nlm.nih.gov/34993274/.

18. I also co-authored a study looking at the real-world effects of the FDA Approval of Mifeprex on Emergency Room utilization after Mifeprex abortions. The massive increased utilization of Emergency Departments to manage abortion complications is a predictable consequence of the FDA's failure to require the same qualifications of Mifeprex abortion providers as were mirrored in the clinical trial for Mifeprex approval.

19. Because the FDA abandoned the post marketing requirement that abortion providers have admitting privileges to handle their own complications and allowed abortion providers who lack the ability to handle complications to dispense Mifeprex, the predictable consequence is the explosion of Mifeprex complications including hemorrhage, adding to the current shortage of blood and blood products across the United States. *See* James Studnicki, et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, 8 Health Servs. Rsch. & Managerial Epidemiol. 23333928211053965 (2021), https://pubmed.ncbi.nlm.nih.gov/34778493/.

20. I am familiar with the FDA's regulation of chemical abortion drugs, including mifepristone and misoprostol. As part of my duties and responsibilities at AAPLOG, I co-authored the original 2002 Citizen Petition and the 2019

Citizen Petition filed by AAPLOG and others to challenge the FDA's actions on chemical abortion drugs. As part of my duties and responsibilities at AAPLOG, I also co-authored a study detailing the aberrancies of the FDA Approval process as it affects real-world patients. *See* Byron C. Calhoun & Donna J. Harrison, *Challenges to the FDA Approval of Mifepristone*, 38 Ann. Pharmacother. 163 (2004), https://pubmed.ncbi.nlm.nih.gov/14742814/.

21. In a chemical abortion, women take mifepristone to terminate the pregnancy by killing the preborn child. Women then take misoprostol to expel all pregnancy tissues, including the preborn child, through contractions and cramping.

22. Women who take chemical abortion drugs experience more complications than those who have surgical abortions.

23. There are many intense side effects for women who take chemical abortion drugs, including cramping and heavy bleeding.

24. Since the FDA's 2000 Approval of Mifeprex (the chemical abortion drug regimen consisting of mifepristone and misoprostol), medical professionals have needed to treat women and girls who have suffered from chemical abortion and experienced complications.

25. Mifepristone and misoprostol are serious drugs that should not be administered without medical supervision. The FDA's actions to eliminate the necessary supervision of these drugs harm women and obstetrics professionals, including AHM, AAPLOG, and their members.

26. Since the FDA's 2016 Major Changes to eliminate safeguards for the use of Mifeprex, AAPLOG members have needed to treat an increasing rate of women and girls who suffer complications from chemical abortion.

27. The increase in the frequency of complications harms medical providers—including AHM and AAPLOG members—because they end up managing the increase in complications.

28. When women suffer complications from chemical abortions, it can overwhelm the medical system and consume crucial limited medical resources, including blood for transfusions, physician time and attention, space in hospital and medical centers, and other equipment and medicines.

29. The increased occurrence of complications related to chemical abortions also multiplies the workload of healthcare providers, including AHM and AAPLOG members, in some cases by astronomical amounts. This is especially true in maternity care "deserts" (i.e., geographic areas where there are not a large number of OB/Gyn providers for patients).

30. For OB/Gyn professionals, the increase in complications due to increased use of chemical abortion drugs means that the typical care given to patients goes from simple patient management to complicated patient management. Patients who suffer complications from chemical abortions require significantly more time and attention from providers than the typical OB/Gyn patient requires.

31. In my experience, many patients do not fully understand the nature of chemical abortion or the risks that these drugs present to them. This results in an increase in the frequency of women seeking emergency medical care for side effects such as cramping, heavy bleeding, and severe pain even if they are not suffering an adverse event.

32. I understand that the FDA has removed the requirement for abortionists to report all adverse events for mifepristone.

33. Many doctors likely do not know about the need to report adverse events related to chemical abortion to the FDA. Similarly, many doctors likely do not know how to report adverse events. This means that complications handled by practitioners other than the abortionist are rarely reported to the FDA or the manufacturer.

34. I personally know of practitioners, including AAPLOG members, who have tried to report adverse events related to chemical abortion drugs to the FDA. The process is complicated, cumbersome, and time-consuming. The adverse event reporting requirements and the FAERS submission process harm medical practices by taking away significant time from a doctor to treat and meet with patients.

35. The FDA's decision not to require abortionists to report all adverse events for mifepristone harms women and girls because this deregulatory action creates an inaccurate and false safety profile for the use of mifepristone and misoprostol.

36. Without an accurate picture of the adverse effects of widespread chemical abortion drug use, physicians cannot effectively practice evidence-based medicine. If the FDA is not collecting the vast majority of adverse events to understand the true risk, healthcare providers cannot assess the risks of a particular course of treatment and inform their patients accordingly.

37. The inability of providers to adequately inform women of the known risks associated with chemical abortion drugs precludes women and girls from giving informed consent to taking these drugs. The lack of information also harms the patient-doctor relationship with all medical care providers because the patients no longer trust that their healthcare providers are telling the truth. This even harms organizations and practitioners who do not support or practice chemical abortion, including AHM, AAPLOG, and their members.

38. Due to inadequate adverse event reporting, the true rates of risks associated with chemical abortion drugs remain unknown and undercounted. This prevents AHM and AAPLOG from providing the public, their members, and their members' patients with accurate statistics and complete information regarding potential risks associated with the use of chemical abortion drugs.

39. The inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates AHM's and AAPLOG's purpose to support women's health and to educate doctors, their patients, and the public about these dangers.

40. AHM and AAPLOG need to divert limited time, energy, and resources to compensate for this lack of information by conducting their own studies and analyses of the available data. This diversion of time, energy, and resources comes to the detriment of other advocacy and educational efforts of AHM and AAPLOG, including their efforts regarding the dangers of surgical abortion, the conscience rights of doctors, and the sanctity of life at all stages.

41. On behalf of AAPLOG and serving as the chairperson for AAPLOG's Subcommittee on Mifeprex, I submitted a Citizen Petition in 2002 challenging the FDA's approval of Mifeprex and requesting an audit of the Mifeprex clinical studies. AAPLOG, as an organization, is concerned about women's health issues and recognized that the FDA's violations of its standards and rules in approving Mifeprex put women's lives and health at risk. It took considerable time, energy, and resources to draft the 92-page petition and the 30-page response to comments letter, in addition to compiling and analyzing supporting sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

42. Similarly, AAPLOG submitted another Citizen Petition in 2019 challenging the FDA's 2016 major changes to the chemical abortion drug regimen, which I also co-authored. It also took considerable time, energy, and resources to draft the 26-page petition, in addition to compiling and analyzing supporting

sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

43. Because abortion activists continue to file their own citizen petitions and letters with the FDA asking the agency to eliminate all protections for women and girls who take chemical abortion drugs, and knowing the Biden administration's relentless, politicized efforts to push these drugs throughout the country, AHM and AAPLOG continue to expend considerable time, energy, and resources on its public advocacy and educational activities regarding chemical abortion drugs—to the detriment of other AHM and AAPLOG priorities and functions. This diversion of time, energy, and resources will not cease until the FDA's approval and deregulation of chemical abortion drugs ceases.

44. AHM and AAPLOG members are opposed to being forced to end the life of a human being in the womb for no medical reason. The objections are both ethical and medical as they stem from the purpose of medicine itself, which is to heal and not to electively kill human beings regardless of their location. The FDA's removal of REMS for safe use—which eliminates in-person evaluations and follow-up care—places our member doctors at increased risk of being forced to violate their conscience rights. The FDA's actions could force our members into a situation where they must render treatment to a woman in the emergency department suffering complications from chemical

abortion while she is still carrying a living fetus, and they must perform a D&C to treat her complications—ending the life of a human being.

Executed this November 11, 2022.

By: Donna Harrison MD
Donna Harrison, M.D.

Exhibit 5

Declaration of Dr. Jeffrey Barrows

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. JEFFREY BARROWS

I, Jeffrey Barrows, D.O. M.A. (Ethics), a citizen of the United States and a resident of Blountville, Tennessee, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist and am the Senior Vice President of Bioethics and Public Policy for Plaintiff Christian Medical & Dental Associations (CMDA).
3. I practiced obstetrics and gynecology for approximately 18 years. I practiced gynecology in an office setting for an additional ten years.
4. I am familiar with CMDA, its members, their fields of practice, and CMDA's policies and positions.
5. CMDA is a national nonprofit organization headquartered in Tennessee. Its members are more than 13,000 Christian physicians, dentists, and allied healthcare professionals. CMDA has more than 1,200 members in Texas, including more than 600 physicians and approximately 35 OBGYNs.
6. CMDA is opposed to elective abortions as contrary to sacred scripture, respect for the sanctity of human life, and traditional, historical Judeo-Christian medical ethics.
7. CMDA's mission includes advocating on behalf of its members, including in litigation.

8. CMDA brings this suit on behalf of itself and its members.

9. CMDA has members in Texas and around the country who care for pregnant women in hospitals and clinics. CMDA's members care for women who suffer complications from chemical abortions.

10. A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

11. I am familiar with the FDA's approval of chemical abortion drugs in 2000.

12. I am familiar with the FDA's regulatory changes regarding chemical abortion drugs, especially the REMS issued in 2016 and associated with the use of mifepristone and misoprostol for chemical abortions.

13. I understand that the FDA's 2016 changes expanded the gestational age for approved mifepristone use to 70 days (or 10 weeks) from 49 days (or 7 weeks), that it eliminated the in-person administration requirements for chemical abortion drugs, that it eliminated the requirement for a follow-up appointment after those drugs have been taken, and that it eliminated the prescriber reporting requirement for all adverse events except for death.

14. I also understand that the FDA subsequently eliminated the in-person dispensing requirements in 2021.

15. The FDA's actions harm women, practitioners, CMDA members, CMDA as an organization, and the medical profession generally.

16. Mifepristone and misoprostol are dangerous drugs that can potentially harm women. Relaxing the required medical supervision and oversight for patients taking these drugs puts women's health at risk.

17. By eliminating the in-person dispensing requirement and the requirement for a post-abortion follow-up, the FDA has exposed women to a higher likelihood of undetected serious complications. Specifically, the expanded use of telemedicine for chemical abortions means that some women who are beyond 70 days' gestation because they are mistaken or wrong about the gestational age of their unborn child will take these drugs outside of the appropriate window.

18. Similarly, without in-person visits and sonograms, women with ectopic pregnancies may escape diagnosis, which puts them at a greater risk of serious and life-threatening complications such as rupture of the Fallopian tube and secondary hemorrhage. Undetected ectopic pregnancies are especially dangerous for women because in some cases they can result in extreme bleeding for women.

19. By eliminating the adverse event reporting requirement for all events except death, the FDA has also undermined physicians' ability to practice evidence-based medicine. By failing to collect accurate information about the complications associated with chemical abortion, the FDA leaves doctors without accurate information about the drugs' safety for women.

20. As an organization, CMDA is harmed by the FDA's failure to require reporting of all adverse events, which prevents CMDA from providing the public, our members, and our members' patients with accurate statistics and complete information regarding potential risks associated with the use of chemical abortion drugs.

21. The inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates CMDA's purpose to provide professional healthcare and to educate doctors, their patients, and the public about the dangers of chemical abortion.

22. By removing the requirements for in-person visits, the FDA has increased the risk of malpractice claims against physicians. The best way to prevent malpractice is for physicians to establish relationships with patients who they can treat over time. By doing away with the necessary medical supervision, the FDA will cause more women to present in life-threatening circumstances into the care of hospitalists and emergency department physicians who have no prior history with these patients.

23. By putting more doctors into riskier, emergent medical situations, the FDA's regulatory actions expose physicians to increased claims of liability.

24. The increased risks of exposure to liability and malpractice claims also impacts physicians because it drives up their insurance costs, especially those who practice in the hospital.

25. The FDA's loosening of chemical abortion regulations impacts the standard of care and the demands and expectations that hospitals will put on their physicians. The FDA has radically altered the standard of care for mifepristone and misoprostol. The agency did this without the requisite evidence to support its actions.

26. I am also concerned that the FDA's actions will force CMDA members to complete an unfinished elective abortion in an emergency situation, causing immediate emotional and moral distress for our members who are opposed to elective abortion and do not want to feel complicit in an immoral, unnecessary procedure.

27. CMDA has been involved with challenging the FDA's approval of chemical abortion drugs for 20 years. In 2002, we submitted a Citizen Petition with other pro-life groups challenging the FDA's actions, diverting valuable time and effort from CMDA's routine functions in order to assist in filing the petition.

Executed this November 12, 2022.

By: BARROWS DO MA

Jeffrey Barrows, D.O. M.A.

Exhibit 6

Declaration of Dr. Quentin Van Meter

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. QUENTIN L. VAN METER

I, Quentin L. Van Meter, a citizen of the United States and resident of Atlanta, Georgia, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified pediatric endocrinologist.
3. I received my medical degree from the Medical College of Virginia in 1973.
4. I did my pediatric internship (1973-1974) and my pediatric residency (1974-1976) at the Naval Regional Medical Center in Oakland, through the University of California, San Francisco. I completed my pediatric endocrinology fellowship from 1978 to 1980 at The Johns Hopkins Hospital. I also worked as a staff pediatric endocrinologist at the Naval Hospital in San Diego (1980-1986) and was Chairman and Director of the residency training program at the Naval Hospital Oakland (1986-1991).
5. Following a 20-year career in the Navy Medical Corps, I moved to the Atlanta area and joined the Fayette Medical Clinic as a Pediatrician and Pediatric Endocrinologist. To better serve the ever-expanding population of pediatric patients with endocrine disorders, I developed my own full-time pediatric endocrine practice. Specifically, my practice helps children by treating them for disorders related to hormones and the endocrine glands that produce them.

6. I currently serve as the president of the American College of Pediatricians.

7. I am familiar with the American College of Pediatricians, its members, their fields of practice, and the organization's policies and positions, including as set forth in the complaint, which I have reviewed.

8. The American College of Pediatricians is a national organization of pediatricians and other healthcare professionals. Its membership includes more than 600 physicians and other healthcare professionals drawn from 47 different states across the nation. The American College of Pediatricians has members in the State of Texas.

9. The American College of Pediatricians brings this suit on behalf of itself and its members.

10. I am familiar with the FDA's approval of mifepristone and issuance of a risk evaluation and mitigation strategy (REMS) for the chemical abortion drug regimen, which includes both mifepristone and misoprostol.

11. I understand that prior to the 2000 approval of mifepristone, the FDA never required a clinical study evaluating the safety and effectiveness of chemical abortion drugs on pregnant girls under 18 years of age.

12. As a blocker of the hormone progesterone, mifepristone is an endocrine disruptor and, therefore, could interfere with pubertal development or adversely impact an adolescent girl's developing body and reproductive system. The FDA's failure to require pediatric clinical studies places girls at

risk from these drugs, which have the potential to dangerously adversely impact the health, safety, and welfare of the exposed adolescents.

13. To my knowledge, the FDA's 2000 approval of mifepristone for use in girls was unsupported by any scientific data showing that chemical abortion drugs are safe for girls under 18 years of age.

14. By failing to require studies, the FDA's 2000 approval placed young girls going through their reproductive development at risk.

15. Numerous studies have demonstrated that there is an increased risk from chemical abortion drugs to pregnant women and girls as compared to surgical abortion.

16. One recent study discovered that one-third of all post-abortion hospital emergency department visits in 2015 were after use of chemical abortion drugs. The FDA's elimination of REMS and loosening of restrictions increases the risk that girls will suffer complications from chemical abortion drugs.

17. I am also aware that, in 2016, the FDA eliminated the requirement that abortionists report non-fatal adverse events—preventing the agency, women and girls, their doctors, and the public from having an accurate understanding of the complications from chemical abortion drugs and the rate at which they occur.

18. Women, girls and their parents cannot give informed consent to chemical abortions drugs without this necessary information. And doctors cannot

accurately apprise their patients about the dangers of chemical abortion drugs without adequate studies elucidating these risks.

19. The American College of Pediatricians is also harmed by the FDA's failure to require reporting of all adverse events because it prevents us as an organization from providing the public, our members, and our members' patients with accurate statistics and complete information regarding potential risks associated with the use of chemical abortion drugs.

20. The inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and compromises our organization's purpose to provide professional healthcare and to educate doctors, their patients, and the public about the dangers of chemical abortion.

21. The American College of Pediatricians has challenged the FDA's continued deregulation of chemical abortion drugs. In 2019, we submitted a Citizen Petition with another pro-life group challenging FDA's 2016 major changes. It took considerable time, energy, and resources to assist in drafting the 26-page petition and compiling and analyzing supporting sources and studies. This effort caused the American College of Pediatricians to divert limited time, energy, and resources from its other priorities and routine functions.

22. The American College of Pediatricians continues to expend considerable time, energy, and resources on its public advocacy and educational activities

exposing the risk of harm to women, including pediatric girls, from the FDA's unlawful approval and deregulation of chemical abortion drugs.

Executed this November 11, 2022.

By: _____
Quentin L. Van Meter, M.D.

Exhibit 7

Declaration of Dr. Christina Francis

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. CHRISTINA FRANCIS

I, Christina Francis, a citizen of the United States of America and a resident of Indiana, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified Obstetrician and Gynecologist (OB/Gyn) in good standing and licensed to practice in Indiana. I have been in active practice for 14 years and have worked for the last six years as an OB/Gyn Hospitalist in Fort Wayne, Indiana.
3. As an OB/Gyn Hospitalist, my practice is completely hospital-based. I manage both high- and low-risk pregnancies and deliveries, obstetric critical care, gynecological emergencies presenting to our Emergency Department, and inpatient obstetric and gynecologic consultations.
4. I am a member of the Board of Directors of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG). I am also the CEO-elect of AAPLOG.
5. I am familiar with AAPLOG, its policy positions, its members, the members' interests and concerns. AAPLOG and its members oppose elective abortions, both surgical and chemical.
6. AAPLOG is the largest organization of pro-life obstetricians and gynecologists ("OB/Gyns") in the world and is headquartered in Indiana.

AAPLOG includes OB/Gyns and other physicians, with more than 7,000 medical professionals nationwide and more than 300 members in Texas. AAPLOG members oppose elective abortion and are committed to the care and well-being of their patients including both pregnant women and their unborn children. AAPLOG members are concerned about the adverse impacts of chemical abortion on their practice of medicine.

7. AAPLOG's mission includes advocating on behalf of its members, including in litigation.

8. AAPLOG sues in this case on behalf of itself and its members.

9. I am familiar with the FDA's regulation of chemical abortion drugs, including mifepristone and misoprostol.

10. I have seen first-hand the complications that can result from use of these dangerous chemical abortion drugs. Although Fort Wayne does not have an abortion facility, I have seen several women present with complications after seeking chemical abortions with mifepristone and misoprostol.

11. The frequency of these complications has increased since a federal district court first enjoined and set aside the FDA's in-person dispensing requirement for mifepristone in 2020.

12. As an example of how chemical abortion harms my patients and my medical practice, one of my patients had obtained mifepristone and misoprostol from a website, without an in-person visit. She was told that the drugs would come from India. After taking the chemical abortion drugs, she began having very

heavy bleeding followed by significant abdominal pain and a fever. When I saw her in the emergency room, she had evidence of retained pregnancy tissue along with endometritis, an infection of the uterine lining. She also had acute kidney injury, with elevated creatinine. She required a dilation and curettage (D&C) surgery to finish evacuating her uterus of the remaining pregnancy tissue and hospitalization for intravenous (IV) antibiotics, IV hydration, and a blood transfusion. I spent several hours with her the day of her surgery/hospital admission, keeping me from my primary patient responsibilities in the labor and delivery unit and requiring me to call in an additional physician to help cover those responsibilities.

13. As an additional example, a partner of mine and I cared for another patient who also suffered complications from chemical abortion. I had taken care of her when she was hospitalized for hyperemesis gravidarum at 9 weeks 5 days gestation. She was discharged home in good condition after significant improvement with medications. During that hospital stay, she had an ultrasound, which showed a healthy pregnancy with no apparent complications and a strong fetal heart rate. During her hospitalization, she expressed to me that she was considering abortion because of experiencing hyperemesis but was unsure. Approximately one week after her discharge, the patient presented back at our emergency room with heavy vaginal bleeding and unstable vital signs as a result of taking chemical abortion drugs. One of my partners was able to detect a fetal heartbeat. Due to the

amount of bleeding that she was experiencing and evidence of hemodynamic instability, however, my partner had no choice but to perform an emergency D&C. The patient needed to be hospitalized overnight for close observation after the D&C. Not only did my partner need to provide several hours of critical care for this patient, but my partner also needed to call in a back-up physician to care for another critically ill patient. And because the preborn baby still had a heartbeat when the patient presented, my partner felt as though she was forced to participate in something that she did not want to be a part of—completing the abortion.

14. As we see an increasing number of complications related to chemical abortions, it will place a greater strain on our healthcare system (especially in light of the fact that we are in the midst of a nationwide blood shortage and there are several healthcare deserts where there are no OB/Gyn's), and more physicians with ethical and medical objections to abortion will be forced to participate in completing unfinished elective chemical abortions in emergency situations, just as my partner was.

15. AAPLOG members are opposed to being forced to end the life of a human being in the womb for no medical reason, including by having to complete an incomplete elective chemical abortion. The objections are both ethical and medical as they stem from the purpose of medicine itself, which is to heal and not to electively kill human beings regardless of their location. Accordingly, AAPLOG and our members are harmed by the FDA's repeated removal of

necessary safeguards, which may force them to treat women and girls seeking the completion of an elective chemical abortion.

16. AAPLOG, its members, and their patients are also harmed by the FDA's actions that require prescribers to report only deaths and no other complications associated with chemical abortion. As a physician, I know that other complications have significant impacts on my patients as well as our healthcare system. Therefore, the FDA should require reporting of these complications too. But the system for reporting adverse events is not set up to be conducive for busy physicians to report these complications and takes a significant amount of time.

17. To report complications to the manufacturer, Danco, a form must be printed, filled out by hand, and then either mailed or scanned and emailed back. Much of the information required by this form is impossible to obtain by the physician seeing the patient if they were not the one who dispensed the chemical abortion drugs (such as lot number and dosage)—forcing me to leave several fields blank. I never received confirmation from Danco whether the complications I reported were recorded or reported to the FDA.

18. In addition to reporting to the manufacturer, the process of reporting to the FDA Adverse Event Reporting System (FAERS) is also cumbersome. The actual form to be filled out is not easy to find online—requiring several steps to get to it. It once took me two hours to get the website to accept submission of the form, taking me away from the care of my other patients. The

minimum amount of time I have spent reporting a mifepristone complication to the FAERS is thirty minutes—valuable time that should be spent in patient care.

19. The FDA's failure to require reporting of all adverse events, combined with its inadequate reporting system, prevents AAPLOG from providing the public, our members, and our members' patients with accurate statistics and complete information regarding potential risks associated with the use of chemical abortion drugs.

20. The inability to share accurate information with member physicians, their patients, and the public on the risks of chemical abortion frustrates and complicates AAPLOG's purpose to support women's health and to educate doctors, their patients, and the public about these dangers. It forces physicians to actually provide their patients with inaccurate information, leading to the lack of fully informed consent for women.

21. AAPLOG needs to divert limited time, energy, and resources to compensate for this lack of information by conducting our own studies and analyses of the available data. This diversion of time, energy, and resources comes to the detriment of other advocacy and educational efforts of AAPLOG, including our efforts regarding the dangers of surgical abortion, the conscience rights of doctors, and the sanctity of life at all stages.

22. In 2002, AAPLOG submitted a Citizen Petition challenging the FDA's approval of Mifeprex and requesting an audit of the Mifeprex clinical studies.

AAPLOG, as an organization, is concerned about women's health issues and recognized that the FDA's violations of its standards and rules in approving Mifeprex put women's lives and health at risk. It took considerable time, energy, and resources to draft the 92-page petition and the 30-page response to comments letter, in addition to compiling and analyzing supporting sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

23. Later, in 2019, AAPLOG submitted another Citizen Petition challenging the FDA's 2016 major changes to the chemical abortion drug regimen. It also took considerable time, energy, and resources to draft the 26-page petition, in addition to compiling and analyzing supporting sources and studies. This effort caused AAPLOG to divert limited time, energy, and resources from its other priorities and routine functions.

24. Because abortion activists continue to file their own citizen petitions and letters with the FDA asking the agency to eliminate all protections for women and girls who take chemical abortion drugs, and knowing the Biden administration's relentless, politicized efforts to push these drugs throughout the country, AAPLOG continues to expend considerable time, energy, and resources on its public advocacy and educational activities regarding chemical abortion drugs—to the detriment of other AAPLOG priorities and functions. This diversion of time, energy, and resources will not cease until the FDA's approval and deregulation of chemical abortion drugs ceases.

Executed this November 11, 2022.

By: _____, MD
Christina Francis, M.D.

Exhibit 8

Declaration of Dr. Ingrid Skop

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. INGRID SKOP

I, Ingrid Skop, a citizen of the United States and a resident of San Antonio, Texas, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist working for OB Hospitalist Group with privileges in the Baptist Hospital System.
3. I also serve as a Senior Fellow and Director of Medical Affairs at the Charlotte Lozier Institute.
4. I am a member of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG), where I served as a member of the board from 2018-2020. I am also a member of the Christian Medical & Dental Associations.
5. I received my medical degree from Washington University School of Medicine in 1992 and completed my residency in obstetrics and gynecology at the University of Texas Health Sciences Center at San Antonio in 1996.
6. My current practice involves delivering babies and performing surgeries in a hospital setting as an obstetric hospitalist. In my prior 25-year career in a large single-specialty OB/GYN practice, I also provided clinic-based obstetric and gynecologic care to women and girls.

7. I have provided written and oral expert testimony about chemical abortion to several state legislatures and to the United States Congress.

8. I have also published the peer-reviewed articles "Chemical Abortion: Risks Posed by Changes in Supervision" and "Medical Abortion: What Physicians Need to Know" in the Journal of American Physicians and Surgeons.

9. The articles I published reflect the research I have performed on the risks associated with unsupervised chemical abortion—a practice that is becoming more common.

10. A chemical abortion includes providing patients with a combination of two drugs. One drug—mifepristone—blocks hormonal support, killing the unborn child, while the other—misoprostol—induces uterine contractions to expel the unborn child and the pregnancy tissue.

11. The drugs mifepristone and misoprostol may cause serious complications for the women and girls who take them.

12. In my practice, I often treat patients who are admitted through the hospital's emergency department with complications from chemical abortions.

13. In my practice, I have cared for several dozen women in the emergency department who were totally unprepared for the pain and bleeding they experienced due to chemical abortion.

14. In my experience caring for women who have gone through chemical abortion, the doctors who prescribed or administered chemical abortion drugs

to these women often did not adequately prepare them for the drugs' effects, so these women could not have truly achieved informed consent.

15. At least a dozen patients have expressed significant emotional distress to me when they viewed the body of their unborn child in the toilet after the chemical abortion.

16. I have treated patients who have experienced trauma and emotional distress because of complications from chemical abortion. Those women were not anticipating that complications were possible and likely did not have sufficient informed consent to proceed with chemical abortion.

17. In my practice, I have cared for at least a dozen women who have required surgery to remove retained pregnancy tissue after a chemical abortion. Sometimes this includes the embryo or fetus, and sometimes it is placental tissue that has not been completely expelled.

18. I have cared for approximately five women who, after a chemical abortion, have required admission for a blood transfusion or intravenous antibiotics or both.

19. Complications from chemical abortion are not uncommon. In fact, chemical abortions involve more complications than surgical abortions.

20. The FDA's actions in 2016 and 2021 have increased the frequency of complications from chemical abortion.

21. Given my experience, I expect to see and treat more patients presenting with complications from chemical abortion.

22. For example, in one month while covering the emergency room, my group practice admitted three women to the hospital. Of the three women admitted in one month due to chemical abortion complications, one required admission to the intensive care unit for sepsis and intravenous antibiotics, one required a blood transfusion for hemorrhage, and one required surgical completion for the retained products of conception (*i.e.*, the doctors had to surgically finish the abortion with a suction aspiration procedure).

23. In my office, I treated one young woman who had been bleeding for six weeks after she took the chemical abortions drugs given to her by a doctor at a Planned Parenthood clinic. After two follow-ups at Planned Parenthood, during which she was given additional misoprostol but not offered surgical completion, she presented to me for help. I performed a sonogram, identified a significant amount of pregnancy tissue remaining in her uterus, and performed a suction aspiration procedure to resolve her complication.

24. I have also cared for minor women below the age of 18 who have obtained chemical abortion drugs. Although mifepristone has not been studied specifically in minor women, the FDA has negligently allowed their provision to this special age group, assuming their response will be the same as adult women.

25. The FDA's actions deregulating mifepristone and expanding access to unsupervised chemical abortion harm women and their doctors, including me. Concerns about "unsafe, back-alley abortions" were used to overturn all

state abortion restrictions in 1973 and they are being recycled today to allow the abortion industry to continue perpetuating dangerous abortion methods. Yet, a clear-eyed look at the FDA's actions allowing unsupervised "mail-order abortions" shows that they are now promoting illegal, unsafe "chemical coat hangers" to the women they falsely say they want to protect.

26. The FDA's actions harm women, including my patients, because without proper oversight, chemical abortions can become even more dangerous than when they are supervised.

27. The FDA's actions harm women, including my patients, because clinics and physicians prescribing or dispensing chemical abortion drugs, or websites that provide these drugs through mail order delivery without any physician involvement, often underprepare women for the severity and risks of chemical abortion, and they often provide insufficient or no follow-up care to those women. Many women are inadequately prepared for the effects of the drugs, the severity of the pain and bleeding they will experience, the human tissue they will expel, and some are unaware that they have complicating factors such as ectopic implantation, more advanced gestation than estimated, and Rh-negative blood type. These patients are being abandoned because in many cases there is no doctor-patient relationship, so they often present to overwhelmed emergency rooms in their distress, where they are usually cared for by physicians other than the abortion prescriber.

28. Unsupervised chemical abortion—authorized by the FDA—harms women because they may have underestimated the gestational age of their unborn child. Women who should not be a candidate for chemical abortion because they are past the FDA-approved cutoff of ten weeks gestation may consume chemical abortion drugs, which will increase their chances of complications due to the increased amount of tissue, leading to hemorrhage, infection and/or the need for surgeries or other emergency care.

29. For example, approximately 2% of pregnancies are ectopic pregnancies, implanted outside of the uterine cavity. Chemical abortion drugs will not effectually end an ectopic pregnancy because they exert their effects on the uterus, which leaves women at risk of severe harm from hemorrhage due to tubal rupture, in need of emergent surgery or potentially at risk of death. Failure to perform an ultrasound prior to prescribing abortion drugs will cause some women to remain undiagnosed and at high risk for these adverse outcomes.

30. The FDA's removal of the reporting requirement for adverse events of mifepristone harms women by creating an inaccurate safety profile, and it harms my practice because it makes it more difficult to practice evidence-based medicine. The incidence of abortion-related complications remains unknown if there is no accurate system for data collection.

31. The FDA's actions also harm women because the lack of oversight will likely exacerbate human trafficking, which happens frequently in San Antonio. In

my practice, part of my care of my patients is ensuring that they are making medical decisions free of coercion. Many trafficked women experience unintended pregnancies and alert doctors serve as an important resource to intervene on behalf of women. Removing the in-person medical interaction removes an opportunity to identify and rescue these women. It also leaves them at risk of being coerced into an abortion they may not desire.

32. Deregulated chemical abortion harms my practice because it increases the number of women who come to the emergency department with complications. When I must perform surgery to deal with complications from chemical abortions, this takes attention away from my other patients. As a hospitalist, I am often supervising multiple laboring patients on labor and delivery. When I am called to the operating room to address an emergency resulting from chemical abortion, this necessarily means I may not be immediately available if an emergency should occur with one of my laboring patients.

33. Unsupervised chemical abortion is heartbreaking to me because it causes women to suffer unnecessarily, and my patients deserve quality medical care.

34. The FDA's expansion of chemical abortion also harms my conscience rights because it could force me to have to surgically finish an incomplete elective chemical abortion. I object to abortion because it ends a human life. My moral and ethical obligation to my patients is to promote human life and health.

But the FDA's actions may force me to end the life of a human being in the womb for no medical reason.

Executed this November 11, 2022.

By: Ingrid Skop MD
Ingrid Skop, MD

Exhibit 9

Declaration of Dr. Nancy Wozniak

IN IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. NANCY WOZNIAK

I, Nancy Wozniak, M.D., a citizen of the United States and a resident of Fishers, Indiana, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist practicing in the greater Indianapolis area. My practice includes obstetrics at two Indianapolis-area hospitals.
3. I am a member of the Board of Directors of Plaintiff American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG) and serve as AAPLOG's Secretary. I am familiar with AAPLOG, its policy positions, its members, the members' interests and concerns. AAPLOG and its members oppose elective abortions, both surgical and chemical.
4. I am familiar the approval of mifepristone and misoprostol as chemical abortion drugs by the U.S. Food and Drug Administration (FDA) and with the FDA's Risk Evaluation and Mitigation Strategy (REMS) for the use of mifepristone and misoprostol for chemical abortions.
5. A REMS is a drug safety program that the FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

6. Under the REMS established by the FDA in 2016 for mifepristone and misoprostol, the agency eliminated (a) the in-person administration requirement, (b) mandatory post-abortion follow-ups, and (c) the requirement that prescribers report all adverse events except death.
7. In 2016, the FDA also expanded the gestational age for approved mifepristone use to 70 days (or 10 weeks) from 49 days (or 7 weeks).
8. The FDA's actions harm patients and practitioners like me.
9. Mifepristone and misoprostol are dangerous drugs that can harm women. Without the appropriate supervision, women taking these drugs are at risk of serious complications and even death in the worst cases.
10. I believe the FDA's expansion of the approved timeframe for mifepristone and misoprostol use to 10 weeks of gestation harms women. An abortionist should never prescribe these drugs to any woman for an abortion after 8 weeks' gestation because I have seen so many women get into trouble with bleeding past that gestational age.
11. Few people die from chemical abortions because of the excellent care they receive from OBGYN doctors, but the infrequency of deaths conceals the danger that these drugs pose to women and girls—especially when administered without proper supervision.
12. In my experience, most of the complications related to the use of mifepristone and misoprostol for chemical abortions result in "near misses" due to the timely intervention of healthcare providers.

13. Recently many states like Indiana have enacted laws to regulate abortions more carefully. To circumvent those laws, abortion providers are relying on increased access to chemical abortion drugs through mail-order schemes or telemedicine.

14. The increasing number of chemical abortions through mail-order or telemedicine methods means that more women will suffer complications from unsupervised use of mifepristone and misoprostol.

15. The risk of complications from chemical abortions is four to seven times greater than from surgical abortions.

16. Currently, many women are now being prescribed mifepristone and misoprostol without a sonogram to verify the gestational age of the unborn child or to rule out ectopic pregnancies or other potential complications.

17. Women have the potential to present to the emergency department with torrential bleeding due to taking mifepristone and misoprostol for a chemical abortion without accurate dating and appropriate supervision. This places enormous stress and pressure on physicians and OB/Gyns who work in hospitals.

18. In my observation, incidents of women presenting to emergency departments with complaints of bleeding are becoming increasingly more common.

19. Due to the FDA's elimination of the adverse event reporting requirements, however, it is impossible to know how frequently women and doctors are facing these complications.

20. The FDA's elimination of the adverse event reporting requirements for non-fatal complications harms doctors' ability to practice evidence-based medicine and to provide their patients about the risks of chemical abortion and obtain their informed consent. Doctors are only as good as the information that they receive.

21. These physicians must treat women in emergency situations without an existing relationship with the patient, without a known gestational age, and without any known medications that the patient may have been prescribed. This dynamic also increases doctors' exposure to allegations of malpractice and potential liability.

22. The FDA's loosening of regulations related to chemical abortions harms hospitalists by putting them in higher-risk situations with less critical information about patients, which increases their exposure to allegations of malpractice and potential liability.

23. In the last six months, I had an experience treating a woman that illustrates how dangerous and damaging the FDA's actions are to women and practitioners.

24. One of my patients, who was about nine weeks pregnant, had previously been treated by hospital staff for a pulmonary embolism with anti-coagulants. She was advised that she could not seek a chemical abortion because it was contraindicated due to the medications; yet the woman left the hospital and sought an abortion at Planned Parenthood of Indiana. The woman was given

mifepristone by the doctor at Planned Parenthood and took the drug. The woman called an Uber for a ride home from Planned Parenthood. The woman began to experience bleeding and other adverse side effects from the mifepristone. The woman's Uber driver did not take her home because she was so ill and instead brought her to the hospital's emergency department. At the hospital, the woman came under my care. The woman had not yet taken the second abortion drug, misoprostol. I treated the patient for the adverse effects she suffered and told her not to take the misoprostol given to her by Planned Parenthood because of the grave risk that she could bleed out and die. The woman had a subsequent ultrasound, which showed that her unborn child was still alive. I advised the internists treating this patient to avoid administering certain medications that could harm the patient and her unborn child.

25. This experience that I had illustrates one of many "near misses" where women and girls face potentially deadly situations, but they are saved by intervention at a hospital's emergency department.

26. Under the FDA's current reporting requirements, this experience need not be reported as an adverse event. I attempted to report this event to the Indiana Department of Public Health, but my report was rejected because the State said it was not a "true" adverse event because the patient ultimately recovered.

27. In my experience with the patient I just described, I spent a significant amount of time that day working to save her life from unnecessary complications due to the irresponsible administration and use of mifepristone and misoprostol. As a result of the significant time that I devoted to that patient, my time and attention was taken away from my other patients, who also need my care.

28. I also know that many women who are suffering complications from chemical abortions tell their doctors that they are experiencing miscarriages. This phenomenon—regardless of why it occurs—means that doctors cannot be certain of what their patients have taken or are experiencing. The lack of information makes it extremely difficult to provide proper treatment to these patients. This inaccurate information also means that the true number of incidences of complications from chemical abortions are significantly underreported or not fully known.

29. Given my experience, I expect to see and treat more patients presenting themselves with complications from chemical abortion.

Executed this November 11, 2022.

By: _____
Nancy Goodwine-Wozniak, M.D.

Exhibit 10

Declaration of Dr. Steven A. Foley

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. STEVEN A. FOLEY

I, Steven A. Foley, a citizen of the United States and a resident of Carmel, Indiana, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am board-certified in obstetrics and gynecology. I practice in Angola, Indiana, and Evansville, Indiana.
3. As a hospitalist, I am associated with several hospitals and cover the emergency department for hospitals. As an OB/Gyn in a hospital setting, I have treated numerous women who have suffered complications from abortions.
4. I have practiced obstetrics and gynecology in Indiana and other states for many years.
5. I am a member of Plaintiff Christian Medical and Dental Associations.
6. During my time in Colorado, I was one of the only OB/Gyn doctors available to many patients. For example, during my time working in the plains of Colorado, it was 120 miles to the next OB/Gyn doctor.
7. I believe regulatory actions of the United States Food and Drug Administration (FDA) on chemical abortion will harm my practice and my patients.

8. Women suffer more complications from chemical abortions than surgical abortions.
9. The removal of the supervision requirements before administering chemical abortion drugs harms patients because it does not allow a doctor to establish gestational age, determine whether the woman has an ectopic pregnancy, or to check the Rhesus (Rh) levels of the patients. Giving women abortifacient drugs without these simple screening steps is simply against the standard of care and will cause more complications.
10. The FDA's actions will especially harm my practice in Indiana since the state's ban on abortions after 15 weeks took effect on September 15, 2022. This means more women will turn to chemical abortion drugs that they are able to obtain online and through the mail because they will seek to use these drugs to obtain surreptitious abortions after the gestational age limit. The increase in number of women taking chemical abortion drugs, especially later in gestational age, will lead to an increased demand in the emergency department.
11. Under the current practice by those who prescribe and dispense chemical abortion drugs like mifepristone and misoprostol, there is no follow-up or additional care provided to patients. Instead, with no established relationship with a physician, patients are simply left to report to the emergency room when they experience adverse effects.

12. Many women are underinformed on the severity of the effects associated with chemical abortions, including the duration and severity of bleeding, the pain associated with the process, and the emotional trauma that they experience.

13. When chemical abortion drugs work as intended, a woman will effectively deliver her unborn child and the placental and any other pregnancy tissues.

14. Many women who report to the emergency department do not disclose that they have taken abortifacient drugs. In some instances, women will tell medical providers that they are suffering a miscarriage. The lack of information or misinformation received by doctors by their patients impacts the course of treatment and the care that doctors can provide.

15. Because abortionists do not adequately inform a woman or a girl about what happens during a chemical abortion and give these drugs to her to take outside of the abortion facility, I have needed to treat and care for many women who have presented to the emergency department with intense bleeding and other effects of the chemical abortion drugs—although not considered complications from the regimen.

16. I have also treated several women for abortion-pill reversal, where women seek to stop a chemical abortion from occurring after they have taken mifepristone. I prescribe the drug progesterone for these patients in an attempt to save their pregnancy. These women experience mental anguish

over the experience of having chosen chemical abortion, and some of them do not feel like they were properly advised as to what they were choosing.

17. The FDA's removal of the adverse event reporting requirement for all adverse events except death harms my ability to perform evidence-based medicine. I am unable to assess the risks present to women because the FDA's removal of reporting requirements undermines the legitimacy of risk data.

Executed this November 13, 2022.

By: _____
Steven A. Foley, M.D.

Exhibit 11

Byron Calhoun, *The maternal mortality myth in the context of legalized abortion*, 80 The Linacre Quarterly 264 (2013)

The Linacre Quarterly 80 (3) 2013, 264–276

Systematic Review

The maternal mortality myth in the context of legalized abortion

Byron Calhoun

West Virginia University-Charleston, Charleston, WV, USA

It was quoted recently in the literature that "The risk of death associated with childbirth is approximately 14 times higher than with abortion." This statement is unsupported by the literature and there is no credible scientific basis to support it. A reasonable woman would find any discussion about the risk of dying from a procedure as material, i.e., important and significant. In order for the physician–patient informed consent dialogue to address this critical issue, the physician must rely upon objective and accurate information concerning abortion. There are numerous and complicated methodological factors that make a valid scientific assessment of abortion mortality extremely difficult. Among the many factors responsible are incomplete reporting, definitional incompatibilities, voluntary data collection, research bias, reliance upon estimations, political correctness, inaccurate and/or incomplete death certificate completion, incomparability with maternal mortality statistics, and failing to include other causes of death such as suicides. Given the importance of this disclosure about abortion mortality, the lack of credible and reliable scientific evidence supporting this representation requires substantial discussion.

Keywords: Maternal mortality, Childbirth, Elective abortion

Abortion Mortality: Mythology and Methodology

It was quoted recently in the literature that "The risk of death associated with childbirth is approximately 14 times higher than with abortion" (Raymond and Grimes 2012). This statement is unsupported by the literature and there is no credible scientific basis to support it.

A reasonable woman would find any discussion about the risk of dying from a procedure as material, i.e. important and significant. In order for the physician–patient informed consent dialogue to address this critical issue, the physician must rely upon objective and accurate information concerning abortion. There are numerous and complicated methodological factors that make a valid scientific assessment of abortion mortality extremely difficult. Among the many factors responsible are incomplete reporting, definitional incompatibilities, voluntary data collection, research bias, reliance upon estimations, political correctness, inaccurate and/or incomplete death certificate completion, incomparability with maternal mortality statistics, and failing to include other causes of death such as suicides.

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Given the importance of this disclosure about abortion mortality, the lack of credible and reliable scientific evidence supporting this representation requires substantial discussion.

Abortion data are unreliable

For any assessment of the health risks of abortion, it is necessary to obtain complete statistics on the incidence and prevalence of abortion as well as its mortality and morbidity in the USA. But, there is no federal reporting requirement and thus, only *estimates* are available (see, for example, Grimes 2006; Raymond and Grimes 2012). Only 26 states require providers to report abortion complications to the Centers for Disease Control (CDC) (Saul 1998; Guttmacher Institute 2009). States that do report incidence data are plagued by incomplete and inconsistent reporting, underreporting, and the lack of a national legal mandate to report.[1] Abortion data are simply not complete and those provided are merely *estimates* with huge variance, and are subject to considerable error. Current incidence *estimates* by the CDC exclude abortions in California, District of Columbia, New Hampshire, and New Jersey. The CDC data are unreliable because they base their *estimates* on voluntary submissions by state health departments, whose accuracy is widely acknowledged to be inconsistent and unreliable. "Many state health departments are able to obtain only incomplete data from abortion providers, and in some states, only 40–50 percent of abortions are reported" (Jones et al. 2008). Furthermore, CDC data regarding maternal mortality are collected by two different agencies using two different definitions and data sources: the National Vital Statistics System (NVSS) and the Pregnancy Mortality Surveillance System (PMSS). For the years 1995–1997, the NVSS reported 898 maternal deaths and the PMSS system reported 1,387 pregnancy related deaths. Therefore the total number of pregnancy related deaths for the time period was the 1,387 documented in the PMSS system. However, only 54 percent of pregnancy related deaths were reported in both systems (MacKay et al. 2005). This disparity in reporting demonstrates that even within the CDC, there is lack of comparability of data regarding pregnancy related deaths. It is from this inaccurate data that abortion mortality data is derived, and, as a result, the CDC has cautioned medical professionals to not make comparative statements based upon CDC data.

The only other institution which collects abortion data is the Guttmacher Institute (GI).

The abortion reporting by GI is based on voluntary submissions in their periodic polling of abortion providers who are simply asked to guesstimate the number of procedures performed, by trimester, proximity to provider, etc. The scientific validity and utility of this unconventional data gathering method is minimal since it does not capture all providers, who in turn are simply estimating annual data. It cannot be relied upon in identifying national incidence. Despite this, in this case, GI submitted a sworn affidavit that the only data they rely upon is that provided by the CDC, which is inherently unreliable. GI is a special affiliate of Planned Parenthood Federation of America, the largest single provider of abortions in this country. GI is an advocacy center whose expressed purpose is to broadly support abortion rights and to limit abortion regulation: "The Institute works to protect, expand and equalize access to information, services and rights that will enable women and men to…exercise the right to choose abortion…" (http://www.guttmacher.org/about/mission.html).

Because GI seeks to protect abortion rights, it would be disinclined to provide data which could interfere with unrestricted abortion. Also, in GI's periodic survey of abortion providers, physicians performing abortions face an obvious conflict of interest: disclosure of abortion complications may fuel state laws restricting access if GI publishes all data gathered. In short, GI data are not credible as it is incomplete and inherently biased. Even GI's own publications confirm this: "Without question, reputable published science should tell readers about potential conflicts of interest" (Sonfield 2005), which it obviously does not do.

There are other methodological problems with abortion data that make it largely unreliable:

(a) It is widely acknowledged that abortion is underreported in the U.S. with less than half of all abortions reported by women in face-to-face interviews (Jones and Kost 2007). The most likely effect of this systematic underreporting across studies is an overly favorable assessment of health risks due to abortion since women often do no report their abortion history (Jones and Kost 2007).
(b) There are no fetal death certificates issued when an abortion occurs. Abortions are often underreported by women and thus do not appear in their medical records. As a result, disease state or complications are not linked to abortion since it is largely not reported and thus, invisible in epidemiological research. When the patient's medical records are incomplete, any aggregated abortion mortality or morbidity reporting and analyses reflect this systematic bias.
(c) Most women do not return to the abortion clinic for follow-up care and assessment. Many abortion providers do not have after hours contact numbers or merely send patients with problems post-abortion to local emergency rooms to be seen by other healthcare providers. It has been estimated that more than two out of three women do not return for follow-up appointments at the abortion clinic (Picker Institute 1999).

Definitional issues regarding maternal mortality are problematic and not comparable

The numbers of women who die from abortion are largely unknown due to poor quality reporting and definitional issues. Abortion-related deaths are captured in some standardized definitions but not in others where they are undifferentiated from spontaneous abortions (Chang et al. 2003; Harrison 2009). The World Health Organization (WHO) has acknowledged: "…all existing estimates of maternal mortality are subject to greater or lesser degrees of uncertainty" (World Health Organization 2004). Because the data are so incomplete, the WHO has used seven different methods to estimate maternal death (World Health Organization 2004, 2007). Maternal mortality is difficult to measure precisely because routine recording of deaths tend not to be complete within civil registration systems. Even if such deaths were recorded, the woman's pregnancy status may not have been known and the death would therefore not have been reported as a maternal death even if the woman had been pregnant. Horon (2005) estimated that physicians completing death certificates after a maternal death fail to report that the woman was pregnant or had a recent pregnancy in 50 percent or more of the cases. In most developing-country settings where medical certification of cause of death does not exist, accurate attribution of female deaths as maternal death is difficult to impossible. Even in developed countries

where routine registration of deaths is in place, maternal deaths may be considerably underreported (World Health Organization 2007). Additionally, reliance upon death certificates in maternal mortality assessments has been shown to be considerably unreliable and underestimates abortion related mortality (Reardon et al. 2004a).

Abortion-related deaths are not easily or accurately identified. Among the definitions used to capture abortion mortality are:

- *Maternal deaths* are defined by the WHO as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Suicide, unintentional injuries, or homicide are not included as causes of death in this definition (Deneux-Tharaux et al. 2005). In WHO's International Classification of Diseases, coding criteria obfuscated deaths by requiring only complications be reported versus the treatment itself. According to the WHO (2004, 4) "all existing estimates of maternal mortality are subject to greater or lesser degrees of uncertainty."
- *Late maternal deaths* are defined as "the deaths of a woman from direct or indirect obstetric causes more than 42 days but less than one year after termination of pregnancy."
- *Pregnancy-related deaths*, including from direct and indirect obstetric causes, are defined as "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death." *Direct obstetric deaths*: "those resulting from obstetric complications of the pregnant state (pregnancy, labor, and puerperium), from interventions, omissions, incorrect treatment, or from a chain of events resulting from any of the above." *Indirect obstetric deaths*: "…those resulting from previous existing disease or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by physiologic effects of pregnancy" (Hoyert 2007). In the U.S. Abortion Mortality Surveillance System, Elam-Evans et al. (2003) concluded that existing methods and systems for capturing abortion related deaths are inadequate and underreported.
- *Pregnancy-associated deaths*, developed by the Centers for Disease Control and Prevention, and with the Maternal Mortality Special Interest Group of the American College of Obstetricians and Gynecologists, define a death from any cause during pregnancy or within 1 calendar year of delivery or pregnancy termination, regardless of the duration or anatomical site of the pregnancy (Wilcox and Marks 1995). Pregnancy-associated deaths include not only deaths commonly associated with pregnancy such as hemorrhage, pregnancy-induced hypertension, and embolism—which are captured in the WHO definition—but also deaths not traditionally considered to be related to pregnancy such as accidents, homicide, and suicide. Pregnancy associated death also includes deaths occurring 43–365 days following termination of pregnancy. Because cause-of-death information on death certificates cannot identify deaths from non-maternal causes or deaths occurring 43 or more days following termination of pregnancy as associated with pregnancy, additional sources of data must be used for complete assessment of all pregnancy-associated deaths (Horon and Cheng 2001). Even with pregnancy-associated deaths there is considerable differentiation between states as to case definition and comparability to

CDC estimates of pregnancy associated maternal mortality ratios (Mascola et al. 2004; Horon 2005).

Yet another way of examining abortion related mortality is calculating a national case-fatality rate: the number of known legal induced abortion-related deaths per 100,000 reported legal induced abortions. This would assume that all abortion deaths are identified from direct and indirect causes, as well as immediate and delayed causes up to 1 year after termination of pregnancy. Even if this were possible, which it is not at this time, this rate could not be calculated because a substantial number of abortions occur in non-reporting states. Thus, the denominator (total number of abortions in the United States) is unknown.

The above definitions indicate that there are only two criteria used in indentifying maternal deaths: (1) medical causes of death and (2) timing of pregnancy-related death. By excluding all other categories that are not due to physical complications, other deaths are simply not captured, including suicide and other indirect deaths which result from physical, psychological, interpersonal, or behavioral problems linked to abortion as the marker event. Causes of deaths resulting directly from abortion are identified. However, abortion may also worsen or initiate physical, psychological, interpersonal, and maladaptive behavioral pathways which can lead to diminished mental or physical health and eventuate in death. These cumulative risk factors which can substantially contribute to abortion mortality are identified. Research by Gissler et al. (2005), Reardon et al. (2004a), Christiansen et al. (2006), and Kavanaugh et al. (2009) support such a broadened assessment of pregnancy associated deaths. The impact of substance abuse, depression, anxiety, and suicide resulting from abortion is considerable. As a result, indirect abortion-associated deaths are likely to be many times higher than those deaths directly caused by obstetric complications.

Measurement issues of maternal mortality are problematic

The computation of maternal mortality is most commonly a ratio of the number of maternal deaths during a given period per 100,000 live births during the same period. But other measures are also in use: maternal mortality rate (number of maternal deaths in a given period per 100,000 women of reproductive age during the same time period) and lifetime risk of maternal death (risk of death once a woman has become pregnant). The difficulty and complexity of measuring maternal mortality are evident in the following areas:

(a) There are gross difficulties inherent in measuring maternal mortality and definitions regarding precisely what constitutes a death due to pregnancy/birth are evolving.
(b) There is a lack of consensus regarding how long after pregnancy resolution a death is appropriately linked with the pregnancy.
(c) The two national sources of abortion statistics (CDC and the Guttmacher Institute) are plagued by significant levels of underreporting. Further, discrepancies exist between the two national sources, a minimum 12 percent discrepancy was reported (Strauss et al. 2007).
(d) For various reasons (incomplete medical records, lack of fetal death records), deaths due to abortion are often not recorded as resulting from the procedure, with only the immediate cause of death (e.g., embolism, sepsis, and hemorrhage) provided.

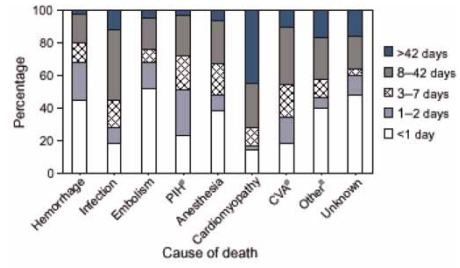
(e) Women, who experience serious, life-threatening health complications as a result of abortion usually go to a hospital emergency room and are not seen by their abortion providers. Their deaths will therefore not be counted.

(f) Abortion-related deaths (from physical complications of the procedure) are reported as maternal deaths.

(g) The death statistics tabulated for abortion focus on "uncomplicated abortion"; whereas the statistics for childbirth incorporate complicated delivery (e.g., caesarian delivery). If "uncomplicated delivery" is compared to "uncomplicated abortion," the risk of dying from abortion is twice as high. Maternal mortality caused by abortion is *twice* as high compared to women with vaginal deliveries, when caesarean deliveries are excluded (Lanska et al. 1983). Further, analyses do not control for co-morbidities in relation to abortion and pregnancy.

(h) The available statistics do not address long-term and less direct causes of death associated with abortion and childbirth. Over time the risk of death associated with abortion increases due to enhanced likelihood of substance abuse, cancer, future pregnancy complications, and suicide ideation, whereas with the risk of dying from these causes are lessened dramatically after completion of a term pregnancy without abortion.

The contemporary definition of pregnancy-related deaths that restricts inclusion of a maternal death to within 42 days of delivery is likely to capture the majority of deaths associated with a full-term pregnancy (see Figure 1 adopted from Chang et al. 2003). However, many of the most serious health risks associated with abortion noted above are more



*Number of days between the end of pregnancy and maternal death.
†Pregnancy-induced hypertension.
§Cerebrovascular accident.
¶The majority of the other medical conditions were cardiovascular, pulmonary, and neurologic problems.

Figure 1. *Distribution of pregnancy-related deaths, by cause of death and time interval—United States, 1991–1999.*

insidious and occur over a much less compressed time period.

National data compare deaths associated with term pregnancies to deaths associated with abortion at any point in pregnancy. This is a flawed technique that has produced an over-estimation of maternal mortality and an under-estimation of abortion mortality. The two central issues are detailed below:

(a) Maternal mortality is determined by dividing maternal deaths by live births as opposed to pregnancies. Deaths due to ectopic pregnancies (the leading cause of death in the first trimester), molar pregnancies, miscarriage, and stillbirth are represented in the numerator, but not in the denominator. According to the CDC only 60 percent of pregnancy-related deaths occur in conjunction with a live birth. This means that 40 percent of the deaths are never represented in the denominator, resulting in a dramatically over-inflated maternal mortality rate. Moreover, the majority of women who survive ectopic pregnancies, molar pregnancies, miscarriage, and stillbirth will not be in the data at all since their pregnancies do not result in live births.

(b) Maternal mortality and abortion mortality statistics are not analogous because maternal mortality statistics do not take into consideration the stage of gestation, whereas abortion mortality statistics are predominantly based on first trimester losses. Appropriate comparisons would be prospective in nature with same gestational point comparisons related to the risk of death associated with the two reproductive outcomes. Existing statistics compare maternal deaths at any point in pregnancy and the post-partum period to abortion deaths, which primarily occur in the second and third months of pregnancy since most abortions are in the first trimester. Bartlett et al. (2004) examined national U.S. data from 1988 to 1997 and found: the relative risk of abortion-related mortality increased dramatically with gestational age of the procedure increasing from 14.7/100,000 procedures at 13–15 weeks gestation, to 29.5/100,000 procedures at 16–20 weeks gestation, and to an astounding 76.6/100,000 procedures at/or after 21 weeks gestation.

Comparisons conducted with no regard for the gestational stage in which the death occurs are flawed for several reasons:

(a) Deaths occurring during the first 6 weeks of pregnancy (when maternal morbidity and mortality are highest) are classified as maternal deaths and are lumped together with deaths associated with birth and delivery. This is inappropriate in that the intended outcome of these early pregnancies is unknown.
(b) Women who reach the common point of awareness that they are pregnant and make the decision to abort (2 weeks late on the menstrual period or 6 weeks pregnant) have already survived beyond the period of the pregnancy's greatest risk.
(c) Abortions do not typically occur very early and are impossible beyond 9 months of gestation when most maternal deaths comprising the maternal mortality statistics occur. Therefore, valid gestational period comparisons can only logically be made in the latter half of the first trimester through the end of the third trimester. During the second and third trimesters, abortion-related mortality is equal to and then exceeds that of childbirth (Bartlett et al. 2004).

Gestational period comparisons would only be valid with sophisticated controls for a variety of socio-demographic factors (age, income, education, marital status) based on sound evidence that women belonging to particular socio-demographic groups (e.g., very young and older women) are more at risk for adverse pregnancy events occurring during pregnancy and the post-partum period.

As indicated earlier in this report, maternal mortality and morbidity are largely based on incomplete data and estimates. In the case of WHO and maternal mortality, definitional issues together with rampant statistical manipulation generate even more inaccurate estimates. In an attempt to identify abortion-related mortality, WHO researchers advocated combining the incidence of spontaneous and induced abortion together, and then correcting for the incidence of spontaneous abortion. According to Harrison (2009), one of the WHO researchers acknowledged: "We make huge adjustments to make the numbers turn out right. More than fifty percent of some numbers are 'adjusted'" (Harrison 2009, 4).

There are powerful financial, socio-political, and interpersonal forces potentially

driving the concealment of abortion-related deaths. The same facilities that report the data run the risk of being more closely scrutinized or even closed if there are deaths at their facilities. Deaths associated with abortion are likely to become highly publicized and could result in legal restrictions. Finally, abortion-related deaths may be concealed, because the family is unaware there was a termination or if the family is privy to the information there is likely to be a strong motivation to hide it in order to protect the family from further grief or shame.

Abortion Mortality Compared to Childbirth: Rresearch Evidence

According to Kaunitz (1985), induced abortion is the fifth leading cause of maternal mortality in the U.S. Even so, this finding is likely to be an underestimation as most abortion-related deaths are either not reported, or not captured in the existing definitions and national data collection from state health departments. Other deaths resulting from abortion remain excluded: suicide, avoidable deaths due to injuries, accidents, substance abuse, and cumulative and contributory disease states.

A number of factors enter into the relative risks of dying from abortion compared to childbirth, in addition to the methodological issues identified above. These include patient age, operator skill and experience, race, gestational age, type of procedure employed, pre-existing physical and mental health, etc.

In a growing body of literature, childbirth is protective against death from non-obstetric causes, including breast cancer and suicide in both the immediate and long term (Gissler et al. 1996, 2005; Marzuk et al. 1997; Thorp et al. 2003; Carroll 2007). In a large, health record-linked U.S. study spanning 8 years, women who aborted compared to those who delivered, were 62 percent more likely to die from any cause. Suicide carried a 154 percent increased risk (Reardon et al. 2002). In Finland, using a comprehensive health data linkage system, Gissler et al. (1997) examined death rates up to 1 year after abortion and found a 4 times higher risk among women who aborted versus those who carried to term. Similar adverse findings were reported in subsequent studies: mortality was lower after a birth (28.2/100,000) than after an induced abortion (83.1/100,000)—a 3 times higher mortality risk for abortion compared to childbirth (Gissler et al. 2004b); abortion was associated with a 6 times higher risk for suicide compared to birth (Gissler et al. 2005). Without such record-linkage, 73 percent of all pregnancy-associated deaths would have been missed if they were based only upon death certificates. The percentage of deaths due to abortion would have been even higher (Gissler et al. 2004a). In the U.K., Morgan et al. (1997) reported a similar increased risk of suicide for women electing abortion versus delivery: 8.1 suicide attempts per thousand among those who had abortions compared to only 1.9 suicide attempts per thousand among those who had given birth. Both Hoyer and Lund (1993) and Appleby (1991) found childbirth overall to be risk protective against suicide.

Most striking are the findings by Gissler et al. (2005) that the age group from 15 to 24 years is significantly prone to suicide in the context of an abortion with an increase of almost 50 percent in the suicide rate compared to non-pregnant women (Christiansen et al. 2006). For U.S. women aged 15–19 years, suicide is the third leading cause of death corresponding to 7.5 percent of deaths.

According to Chang et al. (2003), the literature commonly reports three main causes of abortion-related death: infection

(33.9%), hemorrhage (21.8%), and embolism (13.9%); additional abortion-related causes of death include ectopic pregnancy, perforation or rupture of the uterus, and anesthesia complications among others. Hemorrhage and infection deaths from abortion are nearly 8 times and 9 times greater when compared to the percentage of maternal deaths attributed to these causes in live-birth.

Gissler et al. (2004a) compared the pregnancy-associated mortality ratio for the different pregnancy outcomes (live births and stillbirths, spontaneous abortions and ectopic pregnancies, and induced abortions) for all childbearing Finnish women. They reported: "The pregnancy associated mortality ratio per 100,000 pregnancies increased only slightly for live births and stillbirths, but became sevenfold for spontaneous abortions and ectopic pregnancies, and 5.5-fold for induced abortions. The outcome-specific denominator also revealed that the crude risk of a pregnancy-associated death was more than twice as high after a spontaneous abortion or an ectopic pregnancy and more than three times as high after an induced abortion than after a live birth or stillbirth" (Gissler et al. 2004a, 453). Pregnancy-associated deaths have usually been calculated using the number of live births as the denominator. Gissler et al. (2004a) demonstrated that calculating pregnancy-associated deaths per 100,000 pregnancies with a specific pregnancy outcome gives a very different and improved picture (Gissler et al. 2004a).

Reardon et al. (2004b) estimated that there were between 2,132 and 7,036 excess deaths per year among women who abort and 766 to 4,021 deaths due to violent causes. These researchers further reported that abortion-related increases in smoking are likely to result in 3,740 more lung cancer deaths in the lifetimes of the 1.4 million women who abort each year in the U.S. (Reardon et al. 2004b). Available evidence points to numerous unexamined pathways where abortion can increase a woman's chance of dying from either direct and immediate complications or after prolonged exposure to adverse disease and dysfunctional coping in the future.

The true number of deaths related to pregnancy might increase from 30 to 150 percent with active surveillance (Chang et al. 2003; Deneux-Tharaux et al. 2005). Until more robust research is undertaken accounting for multiple confounders in national prospective studies, statements about abortion being many times safer than childbirth are unreliable and false. Existing research does not support this allegedly factual assertion. A reasonable patient would want to be informed of the risks of death related to abortion *from all causes*.

Abortion Mortality: Most Recent Research Evidence

In a carefully done study using 42 years of United Kingdom National Health data comparing England, Wales, and Scotland with Northern Ireland and parallel national data from the Republic of Ireland found that countries with legal abortion actually had a higher maternal mortality rate per 100,000 live births (Ireland's Gain 2011). In fact, Carroll's maternal mortality rates of 8/100,000 and 10/100,000 live births in England, Wales, and Scotland are eerily familiar to the maternal mortality rate of 8.8/100,000 quoted for the U.S. in Raymond and Grimes (2012). The Raymond and Grimes (2012) mortality rate of 0.6/100,000 for abortion is simply not supported by good data (i.e., real data from a national database not estimates) and the present literature. In fact such assertions about abortion mortality seem

to represent a biased misuse of statistics and maternal mortality calculations.

Koch et al. (2012a, b) demonstrated in their study of Mexico and abortion the problem of significant overestimation of maternal mortality when not utilizing actual data from a national database (Coleman et al. 2012). Koch et al. (2012a, b) accessed the national database to compare the Federal District of Mexico (Mexico City) with the remainder of Mexico and found a *10-fold* overestimation of abortion mortality in the Federal District of Mexico. Previously, maternal mortality in Mexico had been thought to be linked to lack of access to legal abortion. However, maternal deaths fell 30 percent in Mexico in spite of the lack of access to legal abortion. Koch et al. (2012a, b) noted that abortion legalization in the Federal District of Mexico did nothing to lower maternal mortality in the Federal District of Mexico City. In fact, the maternal mortality ratio of maternal deaths compared to abortion deaths per 100,000 live-births decreased from 1.48 to 1.14 in Mexico during the interval from 2007 to 2012 (Koch et al. 2012a, b). Koch's conclusion was that maternal health in Mexico would be better served with better access to emergency and specialized obstetrical care not abortion (Koch et al. 2012a, b).

Coleman et al. (2012) review mortality rates in Denmark's linked data base for the 25-year interval from 1962 to 1993, which included over 1 million women with complete reproductive outcomes including abortions, live births, and spontaneous miscarriages. They found that the risk of death was 6 times greater among women who had never been pregnant compared to women who delivered. There was increased risk of death was 45, 114, and 191 percent for 1, 2, and 3 abortions, respectively, compared to women who had ever given birth during the same time period (Coleman et al. 2012). Maternal death rates compared to abortions were reduced by 108 percent for 2 births and reduced by 63 percent for 3 or more births (Coleman et al. 2012). This significant study with linked, database data overturns previous assertions based on limited and incomplete data demonstrating increased death rates with abortion compared to live births. Further, it shows the dose-related effects of multiple abortions on increasing maternal death rates compared to giving birth.

Abortion laws have been liberalized in countries where there have been large numbers of deaths attributable to clandestine abortions. Those who favor liberalizing abortion laws assume that the health of women is better served by providing abortion. Koch et al. (2012a, b) challenged this assertion recently in their paper covering 50 years of maternal deaths in Chile. Koch et al. (2012a, b) found by utilizing national birth registry statistics over two separate epochs: one with legal abortion covering 1957–1988 and one with prohibition of abortion covering 1989–2007. They found by careful analysis that the legal status of abortion had no relationship to the reduction in maternal mortality. Rather, the reduction in maternal deaths during pregnancy was related to the better education and obstetrical care for women available in the different time periods (Koch et al. 2012a, b).

Certainly critically important issue of maternal mortality in women's health requires the use of accurate data that is only available with the collection of data at a national level in a comprehensive national health database that includes all of women's reproductive outcomes linked to abortion and all other health variables. Such a database must also provide open access to all researchers to evaluate this critical women's health issue. We urge the

establishment and financial support of a national healthcare database for the United States with the inclusion of *all* reproductive outcome variables and associations: including elective abortions.

Endnote

1. See, for example, the Guttmacher Institute's critique of CDC incidence data: "The estimates presented in this report are subject to some limitations and should be considered provisional. First, not all states are included; the estimates assume that changes in abortion incidence in the excluded states are similar to the overall trend seen in the reporting states. Second, the completeness of abortion reporting to state health departments can vary from year to year. We attempted to exclude all states that had inconsistent reporting, but if (for example) reporting improved in some states we included, it would mean that earlier state reports were too low and that the percentage decline we calculated was too small. In such cases, our new estimates of the number of abortions would be too high" (Finer and Henshaw 2006, 3).

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Exhibit 12

The FDA and RU-486: Lowering the Standard for Women's Health: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform, 109th Cong. 4 (2006)

UNITED STATES HOUSE OF REPRESENTATIVES
GOVERNMENT REFORM COMMITTEE

OCTOBER 2006

THE FDA AND RU-486: LOWERING THE STANDARD FOR WOMEN'S HEALTH

STAFF REPORT

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I. EXECUTIVE SUMMARY

This report explores the Food and Drug Administration's activities as they relate to RU-486 – the abortion pill – including the highly unusual process by which the drug was approved, the failures to ensure that the drug is dispensed as the Food and Drug Administration (FDA) requires, the subsequent illnesses, hospitalizations and deaths known to be associated with the drug and the failure to provide any meaningful restrictions despite evidence of its association with a 100% fatal septic infection.

On May 17, 2006, Congressman Mark Souder, Chairman of the Subcommittee on Criminal Justice, Drug Policy and Human Resources ("Subcommittee"), House Committee on Government Reform, convened a hearing to inquire into the safety of the FDA-approved drug Mifeprex (the trade name for mifepristone) commonly known as RU-486. The hearing was entitled, "RU-486 - Demonstrating a Low Standard for Women's Health?" The Subcommittee's hearing followed several months of investigative inquiries with the FDA after the Agency's July 2005 disclosure that four women had died of a septic infection after taking RU-486 to induce an abortion.[1]

This Subcommittee Staff Report ("Report") provides background information about RU-486, including the reasons the drug was brought to market. It also explores the allegation that FDA disregarded various statutes and rules in the RU-486 approval process, and it examines RU-486's safety record in the United States. The accumulation of safety data from "real world" use of the drug in America has allowed Subcommittee investigators to more completely grasp FDA's understanding of the risks posed by RU-486 when it approved the drug on September 28, 2000.

Based on the significant demonstrated danger this drug poses to women, the Report examines options for withdrawing this drug from the market.

II. BACKGROUND

RU-486 is the common name for mifepristone, which in the United States is marketed under the trade name Mifeprex. Shanghai HuaLian Pharmaceutical Co., Ltd.[2] of China produces the drug, which is imported and distributed by Danco Laboratories, [3] a corporate entity located in the Caribbean nation of the Cayman Islands. RU-486, Danco's sole product, [4] is approved for the

[1] FDA Public Health Advisory: Sepsis and Medical Abortion, July 19, 2005. Available at http://www.fda.gov/cder/drug/advisory/mifeprex.htm (last visited October 14, 2006).

[2] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Senator Jim DeMint (August 11, 2006) (on file with Subcommittee).

[3] *See, Foes criticize Chinese manufacture of abortion pill for U.S.*, CNN.com, (Oct. 13, 2000) at http://archives.cnn.com/2000/HEALTH/women/10/13/abortionpill.plant.ap/index.html (last visited October 10, 2006).

[4] Unlike other drug companies with multiple products that are approved by or in application before the FDA--and which therefore cooperate with the FDA to withdraw drug products when recognizable problems arise--Danco has

termination of an established pregnancy through 49 days development (LMP),[5] when used in conjunction with the prostaglandin, misoprostol.[6]

RU-486 terminates pregnancy by blocking progesterone receptors in the uterus, a hormone necessary for the maintenance of pregnancy.[7] This leads to degeneration of the uterine lining, blocking nutrition to the prenate, thus resulting in its death.[8] Mifeprex is used in combination with a prostaglandin called misoprostol, which causes contractions that expel the contents of the uterus.[9] This is an off-label use for misoprostol, which contains an FDA-mandated black-box warning against using the drug during pregnancy.[10]

Under the protocol approved by the FDA – one considerably less stringent than the agency's proposed protocol leaked to the public a few months prior to approval – if the patient is

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no other products for which it must be answerable to the FDA. *See also,* Rogoff, Natasha L, *Haven or Havoc?,* PBS Frontline, February 19, 2004 at http://www.pbs.org/wgbh/pages/frontline/shows/tax/schemes/cayman.html.

[5] FDA Approval Memo (September 28, 2000); "LMP" refers to the first day of the last menstrual period, and is the customary measure of gestational age, from approximately 14 days pre-fertilization of the conceptus.

[6] The FDA examined misoprostol to see if the deadly *Clostridium Sordellii* bacteria that killed four California women after taking RU-486 was associated with misoprostol, rather than the Mifeprex: "An FDA Public Health Advisory in mifepristone dated July 22, 2005 reported 4 cases of septic death in California following the use of mifepristone and intravaginal misoprostol for medical abortion. For this reason, DRUP [Division of Reproductive and Urologic Products] and DDRE [Division of Drug Risk Evaluation] met on July 19, 2005, to discuss searches of the AWRS database to further investigate this cluster of repo0rts. At this meeting, DDRE agreed to provide 3 consults to examine this issue… The proposed consults were as follows:

- Consult #1: Review of all reports of serious infections with misoprostol in women of childbearing age
- Consult #2: Review of all reports for suspected intravaginal products with a fatal outcome
- Consult #3: Review of all serious, unusual infections with intravaginal products."

"This review did not identify any new safety signal associated with intravaginal product administration, especially in regards to infection or pregnancy status." FDA Office of Drug Safety Postmarketing Safety Review, December 8, 2005 (on file with the Subcommittee).

The FDA also tested the manufacturing lots from which the misoprostol was distributed and eliminated that drug product as a source of contamination that would have caused the fatal *C. Sordellii* infections. *See* Marc Fischer, M.D., M.P.H., CDC, *Clostridium sordelli Toxic Shock Syndrome Following Medical Abortion*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/fisher.pdf (last visited October 20, 2006).

[7] See., e.g., University of Chicago Department of Obstetrics and Gynecology, Information on Hormonal Imbalance, available at http://babies.bsd.uchicago.edu/endo/hormoneImbalance.htm (last visited October 10, 2006).

[8] Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn*. 262:13; 1808-1814 (October 6, 1989).

[9] Pfizer (along with their generic subsidiary) and Teva Pharmaceuticals, the makers of misoprostol, have never filed a New Drug Application to seek approval from the FDA for its use in abortion. It was approved for use with ulcers, and is contraindicated for pregnancy. Pfizer's German affiliate recently pulled the drug from the market.

[10] Cytotec (misoprostol) Full Revised Label, April 17, 2002, available at www.fda.gov/cder/foi/label/2002/19268slr037.pdf (last visited October 10, 2006).

found to be a candidate for a chemical abortion (according to criteria such as gestational age of 49 days or less, absence of ectopic pregnancy and a host of health contraindications), she is given 600 mg of Mifeprex to consume at once and instructed to return two days later to consume orally 400 mcg of misoprostol. Patients are further instructed to return in 14 days for a follow-up, which could include a surgical abortion in the three percent to 7.9% of cases in which the chemical abortion fails.[11]

Many providers, however, deviate from the FDA protocol, extending the RU-486 abortion cut-off to 56 and even 63 days' gestation,[12] cutting the dose of Mifeprex by two-thirds, and handing the patient misoprostol pills to insert vaginally at home two days later.[13] Failure rates at these gestational ages are approximately 17% and 23% respectively.

In the decade preceding FDA approval of RU-486 for use in the United States, advocates of RU-486 promoted the drug as a private, easy, safe and effective method of pregnancy termination,[14] offering women the choice of ending pregnancy at an earlier stage and in a less "invasive," instrumented manner, when compared to surgical and suction abortion methods.[15] In sum, the public was told that access to RU-486 had everything to do with women's privacy and choices.

Cited as justification for RU-486 approval and use were the following goals: "defusing the abortion conflict,"[16] putting abortion "into the medical mainstream and out of this ghettoized place it's been in,"[17] making "abortion … more socially acceptable,"[18] "expanding the number

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[11] See Mifeprex Label ("Medical abortion failures should be managed with surgical termination." Also, "Each patient must understand…that medical abortion treatment failures are managed by surgical termination.") at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited October 10, 2006).

[12] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al*., "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

[13] Evidence of this method deviation can be found in many Adverse Event Reports, including those reporting on the deaths of four California women from toxic shock related to *C. Sordellii.*

[14] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26.

[15] Planned Parenthood of New York City Press Release, December 4, 2000: "Women will now have access to this option of a very safe, early abortion without undergoing an invasive procedure. … By allowing women to take part in their own care, mifepristone offers women more privacy in their decisions and control over their bodies."

[16] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[17] *Ibid*, quoting Carole Joffe, professor of sociology, University of California-Davis.

[18] *Ibid*.

of abortion providers"[19] and even advancing the U.S. aim of "population control"[20] in the developing world. One vocal advocate explained: "Abortion in the U.S. is this degraded, shameful, violence-surrounded thing. …It's not like that in Europe. So that makes our context for medical [e.g., RU-486] abortion unique."[21] Safety and efficacy questions were brushed aside with assurances that several hundred thousand women in France and China had already used RU-486 to induce abortion.[22]

One might reasonably wonder why, when the surgical option is readily available and exponentially safer,[23] the FDA would approve, or the abortion industry would support, a chemical procedure that subjects women to increased pain and risk. To answer this question, it is helpful to understand abortion industry fears concerning the dwindling number of providers, and to assess the industry's leverage and access within the FDA.

The National Abortion Federation reported in May 2004 that the "number of abortion providers has declined by 37% since 1982."[24] In 1997, 36% of ob/gyns reported ever performing elective abortions.[25] Among them, 57% were fifty years of age or older and another 30% were 40 or older.[26] In other words, the abortion industry perceived that—unless drastic measures were taken—it was in danger of losing nearly 57% of its doctors by 2012 and 87% of its doctors by 2022, significantly reducing the availability of abortion in the United States.[27]

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[19] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Seattle abortion provider Suzanne Poppema, M.D.

[20] Nathanson, Bernard, "Drugs for the Production of Abortion: A Review," Obstet & Gyn Survey 25:8; 727-731 (1970); Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 59: "It is a further misconception to believe that this [RU-486] research took place in order to expand or improve women's 'choices' to control their reproduction. Quite unmistakenly, the concept evolved as a means of population control. More than 20 years ago, the Center of Population Research of the U.S. National Institutes of Health became interested in the corpus luteum and called for research to determine whether to find 'means to inhibit corpus luteum function is a desirable goal'. The specific intention of such research was to restrict population growth in countries that were judged to be 'under-developed.' If successful, the method(s) could be extended to groups in the United States, Black, Hispanic and Native American Women (Department of Health, Education and Welfare, NIH, USA, 1969)."

[21] Margaret Talbot, "The Little White Pill," *New York Times Magazine*, July 11, 1999, quoting Carole Joffe, professor of sociology, University of California-Davis.

[22] Lawrence Lader. A Private Matter: RU-486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 115-117.

[23] The Alan Guttmacher Institute, an affiliate of Planned Parenthood, reports that the mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318.

[24] Abortion Access Project, Fact Sheet: The Shortage of Abortion Providers, May 6, 2004, available at www.abortionaccess.org/AAP/publica_resources/fact_sheets/shortage_provider.htm (last visited October 10, 2006).

[25] Kaiser Family Foundation, *Abortion*, Issue update, Menlo Park, CA: Kaiser Family Foundation, May 1999.

[26] *Ibid.*

[27] Lawrence B. Finer and Stanley K. Henshaw, "Abortion Incidence and Services In the United States in 2000," Perspectives on Sexual and Reproductive Health, 2003, 35(1):6-15.

The industry, then, out of concern for its own preservation, pinned its hopes on chemical abortion. A Kaiser Family Foundation survey, for example, noted: "Many reproductive health groups in the U.S. have looked to widespread availability and marketing of mifepristone … to expand access to abortion in this country."[28] Pediatrician Eric Schaff, who oversaw at least one RU-486 trial, put the matter somewhat more crudely. Objecting to an FDA proposal (never formally adopted) that any doctor dispensing RU-486 would have to be trained in surgical abortion, Dr. Schaff explained, "The whole idea of [RU-486] was to increase access. … [The FDA proposal] kills the drug if it can't be used by primary care providers."[29]

Despite the problems associated with RU-486 (discussed in depth in Section III, below), it looked like a panacea for the abortion industry. Advocates predicted that the number of providers would increase. The Kaiser Family Foundation stated that one-third of all ob/gyns who did not perform abortions said they would be "very" or "somewhat" likely to prescribe mifepristone for abortions if approved by the FDA.[30] Furthermore, rather than limiting abortion procedures to medical doctors alone, advocates saw an opportunity for nurse practitioners, nurses, and others to administer abortions to women.[31]

In June 1989, one year after its introduction into the French market, the FDA issued an import alert on RU-486. The concern was that women would obtain the drug themselves and use it without support from a physician. The wisdom of this policy is supported by the fact that, as the RU-486 label states, nearly *all* users of RU-486 will experience adverse events.[32] But it wasn't long before Democrats, led by then-Representative Ron Wyden of Oregon, seized this opportunity to politicize the approval process.

Under the auspices of the Committee on Small Business's Subcommittee on Regulation, Business Opportunities and Energy, as early as September 18, 1990, Representative Wyden was investigating the FDA's import alert on RU-486, alleging that the FDA's overriding concerns for the alert were political, rather than medical, and that the actions of the FDA were preventing cures for several diseases, including breast and brain cancer, Cushing's disease, glaucoma and

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[28] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[29] Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times*, June 8, 2000.

[30] Kaiser Family Foundation, News Release, June 8, 2000, available at www.kff.org/womenshealth/20000613a-PressRelease2.cfm (last visited October 10, 2006).

[31] Press release, Ibis Reproductive Health, the National Abortion Federation, and the Abortion Access Project, May 9, 2006, available at www.prochoice.org/news/releases/20060509.html (last visited October 10, 2006).

[32] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006): "Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction."

diabetes. Two hearings in his committee followed, one in November of 1990[33] and another in December, 1991.[34]

Following these hearings, Representative Wyden introduced legislation to prohibit the FDA from taking any action to bar the import of RU-486 unless the FDA finds that it is being imported for an illegal use.[35]

It is interesting to contrast the interests of Representative Wyden and the abortion industry with the concerns of the American Medical Association (AMA), which offered this view about the health and safety of women who might obtain and use RU-486 without a physician's supervision:

> "[I]t is the AMA's understanding that RU-486 poses a severe risk to patients unless the drug is administered as part of a complete treatment plan under the supervision of a physician…Rumors exist that the FDA, due to political pressure, is standing in the way of research on RU-486. We do not believe this to be true. On the contrary, it is the FDA's responsibility to ban a drug that has not met legal and regulatory requirements for importation into the United States. Because RU-486 has not met these requirements, the FDA complied with its charge and acted well within its authority in issuing its June 9, 1989, automatic detention import alert concerning the drug."[36]

In the meantime, women's groups orchestrated an offensive consisting of media stunts to exert political pressure on the FDA. Lawrence Lader, founding chairman of the then-National Abortion Rights Action League (NARAL), and Ms. Leona Benton, who volunteered to serve as a "test case," traveled to Europe to acquire RU-486 with the specific purpose of being apprehended by Customs agents when they returned on July 1, 1992.[37] Agents seized the pills, and 45 members of the press showed up to publicize her "plight."

Ms. Benton immediately filed suit against the FDA in federal district court (Brooklyn), and Judge Charles Sifton ruled in her favor on July 14. Before she could physically recover the confiscated pills, however, government attorneys filed an appeal with the U.S. Court of Appeals for the Second Circuit, where a three-judge panel reversed Judge Sifton's order. The U.S. Supreme Court accepted an expedited appeal and, on July 17, ruled 7-2 against releasing the

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[33] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990).

[34] *Safety and Effectiveness of the Abortifacient RU-486 in Foreign Markets: Opportunities and Obstacles to U.S. Commercialization: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Dec. 5, 1991).

[35] H.R. 875 "RU-486 Regulatory Fairness Act of 1991," introduced February 6, 1991.

[36] *RU-486: The Import Ban and its Effect on Medical Research: Hearing before the House Subcommittee on Regulation, Business Opportunities and Energy, Committee on Small Business*, 101st Cong. (Nov. 19, 1990) (statement of Dr. John P. Seward, Board Member, American Medical Association).

[37] Lawrence Lader, A Private Matter: RU 486 and the Abortion Crisis. Amherst, N.Y.: Prometheus Books, 1995, 135-136.

pills.[38] In the interim, she and Lawrence Lader gained widespread publicity concerning RU-486 in the media. She had a surgical abortion.[39]

In that same month, Public Media Video released a documentary financed by the Chicago abortion advocacy group, Women's Issues Network, entitled, "Science Held Hostage: RU-486 and the Politics of Abortion," hosted by Cybil Shepard. They held a screening on Capitol Hill.

In the six years since approval, mounting evidence points unavoidably to one conclusion: the political motivations for bringing RU-486 to the U.S. market overwhelmed considerations of women's health and safety.

In a September 28, 2000 interview following the announcement of the FDA's approval of RU-486, then-FDA Commissioner Dr. Jane E. Henney stated: "Politics had no role in this decision."[40] That assurance has been called into question by documents made public this year which reveal the Clinton Administration's vigorous role from 1993 forward[41] in facilitating the abortion drug's entry and approval. The actors behind these documents approached approval as a matter of logistics rather than as involving an open-minded scientific inquiry. One memorandum goes so far as to advise the Administration on how to contextualize the anticipated FDA approval of the drug in terms of "promoting women's health and maintaining the close relationship of the Administration to these [pro-choice women's] groups."[42]

However, had the FDA undertaken a thorough review of the scientific literature evaluating RU-486/prostaglandin abortions before approving RU-486, the agency would have been alerted to paramount safety concerns. Certainly, the FDA Medical Officer's Review, discussed in detail below, falls short of endorsing the safety of RU-486. Even so, only two additional studies are referenced in the Medical Officer's Review[43] apart from discussion of the U.S. clinical trials and the two so-called "pivotal French trials" conducted by the manufacturer. In light of this omission, and more significantly, in light of the FDA's approval of RU-486, one wonders why numerous studies demonstrating the inherent risks to women who undergo RU-486 abortions did not appear to influence the FDA's decision to approve RU-486.

And, in fact, such a thorough review of medical and scientific literature on RU-486 had already been published in 1991 by three women who describe themselves as pro-choice

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[38] *Benten v. Kessler*, 505 U.S. 1084 (1992).

[39] *Ibid*., at 139.

[40] Gina Kolata, "U.S. Approves Abortion Pill; Drug Offers More Privacy, and Could Reshape Debate," *The New York Times*, September 29, 2000.

[41] See, various documents compiled by Judicial Watch, Inc.. and appended to "A Judicial Watch Special Report: The Clinton RU-486 Files," April 26, 2006, available at http://JudicialWatch.org/archive/2006/jw-ru486-report.pdf.

[42] HHS Chief of Staff Kevin Thurm, Memorandum to White House Director of Public Policy Carol Rasco, Subject: RU-486, dated May 11, 1994.

[43] Beverly Winikoff *et al*., "The Acceptability of Medical Abortion In China, Cuba and India," *Int Fam Plan Perspect*. (1997) 23:73-78 & 89; and J.T. Jensen *et al*., "Outcomes of Suction Curettage and Mifepristone Abortion in the United States," *Contraception* (1999): 153-159.

feminists. A brief synopsis of some of the studies they review will help set the context for the discussion of the FDA's approval process, which follows in Part II (below).

Renate Klein,[44] Janice G. Raymond[45] and Dr. Lynette J. Dumble[46] co-authored a "comprehensive literature review and analysis of hundreds of medical and scientific articles on RU 486/PG [prostaglandin], a large percentage of which have a connection with Roussel Uclaf,"[47] the pharmaceutical company that developed RU-486 in the 1980s.

The first clinical trial of RU-486 in humans took place in October 1981 in Geneva, Switzerland after only 17 months of animal research with rats, rabbits and monkeys,[48] although the results of animal trials were not such a resounding success that they justified the rush to human trials. "RU 486 caused the death in two out of three monkeys in toxicity tests,"[49] for example. None of the eleven women in Geneva who were given 200 mg of RU-486 per day for three consecutive days died, but only nine pregnancies were terminated (eight after five days and the ninth at nine days). Furthermore, one woman claimed initially as a "success" later required uterine evacuation, and another woman needed emergency surgery and a blood transfusion due to heavy bleeding.[50] Klein *et al.* describe how the Parisian newspaper *Liberation* reported on the Geneva trial: "Liberation commented that, given these associated complications and risks, RU 486 was no 'abortion miracle.' *Liberation* also reported that RU 486 is not only an anti-progesterone but an anti-glucocorticosteroid which can take the place of cortisone in the adrenal glands, and that contraindications emanating from this double action of the drug could be a problem,"[51] as it turned out to be for two out of three monkeys.

Roussel Uclaf staff proceeded next to clinical trials on small groups of women in France, Sweden, Australia, Holland, the United States of America, England, Finland and China. The manufacturer supplied RU-486 for these trials, and its staff and consultants co-authored articles reporting on the results.[52] The success rates (defined as "a complete termination of pregnancy

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[44] Ms. Klein is a biologist, professor of sociology and women's studies and author/editor of numerous books on reproductive technologies.

[45] Then Professor, University of Massachusetts and associate director of MIT's Institute on Women and Technology.

[46] Then visiting professor of surgery at the University of Texas and senior research fellow in the University of Melbourne's Department of Surgery, Royal Melbourne Hospital.

[47] Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 4.,.

[48] *Ibid*., at 9-10.

[49] Lawrence Lader. RU486: The Pill that Could End the Abortion Wars and Why American Women Don't Have It. Reading, Mass.: Addison-Wesley Publ. Co., 1991, 17-26, at 48.

[50] Renate Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 10, citing Etienne-Emile Baulieu, "RU-486 as an Antiprogesterone Steroid: From Receptor to Contragestion and Beyond," *Journal of the American Medical Assn*. 262:13; 1808-1814 (October 6, 1989)..

[51] *Ibid*., at 10.

[52] *Ibid*.

without the need for further medical intervention") using RU-486 alone ranged from 54%[53] and 61%[54] to a high of 85%[55] and 90%[56] -- at best substantially below the 99% success rate for surgical abortion.

The Kovacs *et al*. trial, finding a 61% average efficacy, illustrates some of the risks encountered in RU-486 use. A total of 37 women "with amenorrhea of 42 days or less" were given RU-486 twice daily for four days at several different levels of dosage. All patients attended three follow-up visits at one, two and five-to-six weeks after the "therapy" began. In three patients (8%) pregnancy was unaffected by the drug. Two patients required blood transfusion and curettage due to heavy bleeding, and another was found at the second follow-up visit to have an extra-uterine pregnancy. Kovacs *et al*. concluded that "treatment with RU 486 may provide a novel therapy for 'menstrual regulation' but the efficacy of the treatment needs to be improved to compete with alternatives such as vacuum aspiration."[57]

In 1984, researchers in Sweden began using a prostaglandin in conjunction with RU-486 to improve efficacy rates (achieving complete abortions in 32 of 34 women subjects, or 94%), without, however, having first undertaken basic research into the potential adverse effects arising from interactions between these drugs.[58]

In late 1988, the French Minister of Health issued approval for the marketing of RU-486 in France.[59] A distinguished committee of scientific and medical experts, which included the president of France's National Academy of Medicine, the head of Nephrology Department, Necker Hospital (Paris), research directors at the (French) National Institute for Health and Medical Research and National Center for Scientific Research, began reviewing data on 30,000 women who by then had used RU-486. In April 1990, this committee issued its scathing "Report of the International Inquiry Commission on RU 486", which faults the approval of RU-486 on several grounds and which warns of the inherent and well-documented risks of RU-

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[53] Herrmann, W.L., Wyss, Rolf, Riondel, A., Philibert, Daniel, Teutsch, Georges, Sakiz, Eduoard and Baulieu, Etienne-Emile. (1982). Effet d'un stéroide antiprogesterone chez la femme: interruption du cycle menstruel et de la grossesse au début. *C R Acad Sci Paris* 294.933-938.[The effect of an anti-progesterone steroid on women: interruption of the menstrual cycle and early pregnancy. Reports of Proceedings of the Academy of Sciences, Paris].

[54] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[55] Couzinet, Béatrice, Le Strat, Nelly, Ulmann, André, Baulieu, Etienne-Emile and Schaison, Gilbert. (1986). Termination of early pregnancy by the progesterone antagonist RU 486 (Mifepristone). *New England Journal of Medicine* 315.1565-1570.

[56] Grimes, David A., Mishell, Daniel R., Shoupe, Donna and Lacarra, Maria. (1988). Early abortion with a single dose of the antiprogestin RU-486. *American Journal of Obstetrics and Gynecology* 158: 1307-1312.

[57] Kovacs, L., Sas, M., Resch, B.A, Ugocsai, G. Swahn, Marja-Lisa, Bygdeman, Marc and Rowe, PJ. (1984). Termination of early pregnancy by RU 486 - an antiprogestational compound. *Contracep* 29.399-410.

[58] Bygdeman, Marc and Swahn, Marja-Liisa. (1985). Progesterone receptor blockage: Effect on uterine contractility and early pregnancy. *Contraception* 32; 45-51, cited in Klein *et al*., RU 486: Misconceptions, Myths and Morals. Melbourne, Aus.: Spinifex Press, 1991 The book is out of print, but the full text is available at http://www.spinifexpress.com.au/non-fict/ru486.htm (last visited October 20, 2006) at 11.

[59] Report of the International Inquiry Commission on RU 486, April 1990, available at http://www.trdd.org/RU486/RUCIEE.HTM (last visited Oct. 18, 2006).

486/prostaglandin abortions. They note cardiovascular and respiratory risks – a full year before the first such fatality, but already evident from the report of one woman who lapsed into a 36-hour-long coma during an RU-486 abortion.[60]

Among the many serious issues raised by the International Inquiry Commission on RU 486 are these:

- the "very strong anti-glucocorticoid" effect of RU-486 (with which the FDA is now familiar, following the deaths from septic shock of four California women)
- the continued uncertainty surrounding RU-486's mode of action
- the necessity of using a prostaglandin to achieve marginally acceptable effectiveness, in light of the known serious side effects of prostaglandin
- metrorrhagia in over 90% of cases, lasting from 1 to 35 days (in "many cases an emergency 'Revision Uterine' [uterine evacuation] was necessary to contain the hemorrhaging. In certain cases, the only recourse was an emergency blood transfusion, with all the risks this involves.")
- "Beyond far heavier risks [compared to] the surgical method … there is – with the medicinal method – an uncertainty about the result during 5 to 12 days," as well as
  - "failure for 5% of the women who will therefore undergo surgery,
  - "around 5 to 10% persistent hemorrhages will need medicinal or surgical treatment,
  - "absolute necessity, some days after abortion, to [perform] an ultrasound examination and a HCG dosage, to be completely sure there [are] no traces of the fetus."
- the risks to women who do not return for follow-up treatment
- recently published studies demonstrating "a strong stimulating effect by RU 486 on the growth of a breast cancerous cellular line"[61] and immune system inhibition.[62]

On immune system inhibition, one wonders how the FDA could have failed to take note of the World Health Organization's 1991 study,[63] in which "9 of the 341 women (2.6%) with complete abortion and … 5 of the 17 subjects (29.4%) with incomplete abortion" had to be given "antibiotic therapy to prevent or cure suspected genitourinary infection" during the six-week follow-up period.[64] Nearly *thirty percent* of incomplete abortions involved infection.

A last example of facts the FDA should have taken into account in the agency's review of RU-486 is the personal story of Tamara Keta Hodgson, a nurse who took part in the RU-486

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[60] *Ibid*.

[61] The referenced report cites RT Bowden, JR Hissom, MR Moore. (1989) "Growth stimulation of T47D human breast cancer cells by the anti-progestin RU-486," *Endocrinology* 124; 2642-2644.

[62] BJ Van Voorhis, DJ Anderson, and JA Hill (1989), "The effects of RU 486 on immune function and steroid-induced immunosuppression in vitro," *J Clin Endocrinol Metab* 69:1195-1199.

[63] World Health Organization. (1991) "Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertil Steril* 56: 32-40.

[64] *Id*., at 37.

trials conducted by Dr. David Grimes in Los Angeles. In a letter published in the *Los Angeles Times* under the heading "Pros and Cons of 'Dr. Grimes' bitter pill,' " Ms. Hodgson writes:

> I took RU-486 in December, 1986, when I was three weeks pregnant. Twenty-four hours later I began to have severe cramping and started vomiting. When this had gone on for 10 to 12 hours, a friend took me to the County-USC Emergency Room. After an excruciating pelvic exam, I was given a shot of Demerol, which did nothing, and a prescription for a prostaglandin inhibitor to slow down the process, which did relieve the pain. I had mild bleeding for a few days and then six days after taking the drug, I began to hemorrhage. I continued to bleed or spot until mid-March, 1987.
>
> I'm not sure why I had such an extreme response. I chose to take the drug rather than have a surgical abortion because it had been presented to me as a relatively benign experience. I also thought it might help advance the causes of both science and women.
>
> Do I think RU-486 should be licensed in the United States? I'm not sure. I had access to many resources not available to the general population of women who might take this drug. I am a registered nurse who works at one of the most sophisticated hospitals in the world. I was cared for by the research team investigating the drug. I had no children who needed to be cared for.
>
> The same cannot be said for women of the Third World. It also cannot be said for women in the United States who do not have access to adequate health care.[65]

Despite all this, what many abortion advocates promoted as a "miracle pill"[66] has turned out to be anything but. Even before its approval, the medical community knew what American women would soon learn by experience:

- mifepristone interferes with the body's immune response[67]

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[65] *Los Angeles Times*, May 6, 1990, at E-20.

[66] David Van Biema, "But Will It End the Abortion Debate?" *Time*, June 14, 1993; available at http://www.time.com/time/magazine/article/0,9171,978680,00.html (last visited October 20, 2006).

[67] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of

- it is more inconvenient than surgical abortion[68]
- it is more painful[69]
- it is less effective[70]
- it is associated with more adverse events[71]
- it causes more frequent and more severe hemorrhage than its surgical counterpart[72]

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the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[68] *See* FDA Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006):

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion…[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients… On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients…

[69] *See, e.g.,* B. Elul, et.al, *Side Effects of Mifepristone-Misoprostol Abortion Versus Surgical Abortion, Data From a Trial in China, Cuba, and India*, Contraception 59:107-114, 111 (1999): China—60.3% chemical, 36.0% surgical patients experienced pain / cramps; Cuba—89.2 % chemical, 65.4% surgical; India—61.9% chemical, 36.8% surgical.

[70] *See, e.g.,* Beverly Winikoff, et. al., *Safety, efficacy and acceptability of medical abortion in China, Cuba, and India: A comparative trial of Mifepristone-misoprostol versus surgical abortion*, Am. J. Obstet. Gynecol. 431, 434 (Feb. 1997). Failure Rates: China—chemical 8.6%, surgical .4%; Cuba—chemical 16.0%, surgical 4.0%; India—chemical 5.2%, surgical 0%.

[71] *See, e.g.,* E. Cabezas, *Medical versus surgical abortion,* 63 Internat. J Gynecol. & Obstet. Supp. 1, S141, S144 (1999). Cramping: chemical 60.0%, surgical 48.3%; Nausea: chemical 30.6%, surgical 8.9%; Vomiting: chemical 15.1%, surgical 2.0%.

[72] *See Ibid.*, chemical abortion patients experienced 2.3 days of heavy bleeding, 4.8 days of normal bleeding, and 4.9 days of light bleeding compared to 0.3, 1.8, and 3.3 days for surgical, respectively. Furthermore, 50.8% of chemical abortion patients bled more than expected, compared to 7.3% for surgical patients; and 64.1% of chemical abortion patients bled longer than expected, compared to 18.7% of surgical abortion patients. *See also,* Y.F. Chan, et.al.,

The safety issues associated with RU-486 are discussed in depth in Section III, below.

III. RU-486 APPROVAL IRREGULARITIES

Since FDA approved RU-486 in September 2000, a number of criticisms have been lodged against FDA alleging procedural irregularities in the approval process.[73] The Subcommittee investigators were aware of these criticisms and requested information from FDA regarding the issues raised by opponents of the approval. This section assesses the claims made and FDA's responses to the following allegations: 1) that FDA's approval was based solely on data from uncontrolled trials; 2) that FDA used Subpart H unlawfully when it approved the drug and, furthermore, that the clinical data used in support of the application was insufficient to satisfy Subpart H requirements; and, 3) that FDA unlawfully mandated the unapproved use of a drug, misoprostol, as part of the RU-486 abortion regimen.

A. The Approval was Unlawfully Based Solely on Data from Uncontrolled Trials

FDA's reputation as the world's foremost regulator of drug products is based largely on the rigor which it demands for data submitted in support of drug applications. The law requires, in Section 505(d)(5) of the Food, Drug and Cosmetic Act, that FDA shall not approve a drug when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[74] "Substantial evidence" means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[75]

Over the years, FDA's high standard in supervising the production of clinical trial data has been referred to as its "gold standard." Typically, FDA requires data from two clinical trials that are randomized, blinded and controlled against a "comparator" – often a placebo but more typically an alternative therapy.[76] FDA's Section 314.126(e) indicates that "[u]ncontrolled

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Blood Loss in Termination of Early Pregnancy by Vacuum Aspiration and by Combination of Mifepristone and Gemeprost, Contraception 47:85-95, 90 (1993): Groups receiving 200mg, 400mg, and 600mg of mifepristone experienced an average loss of 84.1ml, 99.9ml, and 101.4ml of blood respectively (ranges were 16.8 - 371.3ml, 16.7 - 524.3ml, and 20.8 - 472.4ml, respectively) compared to an average blood loss of 53.2ml for patients undergoing a vacuum aspiration abortion (range of 29.3ml - 226.0ml).

[73] For example several groups have filed a "citizen petition" with FDA regarding RU-486's approval. *See* Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) ("Mifeprex Citizen Petition"). On October 10, 2003, these groups filed a response to the Danco Laboratories and the Population Council's Opposition to the Citizen Petition which was filed in March 2003. These documents are available in FDA Docket No. 02P-0377.

[74] 21 U.S.C. § 355(d)(5).

[75] 21 U.S.C. § 355(d).

[76] FDA issued a guidance document in 1998 ("Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," May 1998)("FDA Clinical Evidence Guidance") that outlines the

studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness."[77] The question of whether the RU-486 trial data was produced solely by uncontrolled clinical trials was examined by the Subcommittee investigators.

The French and American trial data were generated by trials in which the participants were given mifepristone and misoprostol to chemically end pregnancies. The RU-486 regimen was judged to have been effective, "defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[78] The studies measured the rate at which RU-486/misoprostol abortions succeeded or failed at different gestational ages.

However, neither the French nor American RU-486 trials randomized trial participants concurrently against either a placebo or the most similar RU-486 alternative, first-trimester surgical abortion.[79] Neither the French trials,[80] nor the American trial was concurrently controlled.[81] Furthermore, no discussion of controls can be found in FDA analyses of the French trials[82] or in the Spitz Study[83] that reported the results of the U.S. trial. Thus, the question arose as to whether the RU-486 trials were in fact uncontrolled.

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requirements of its drug trial policies with respect to proving effectiveness. Additionally, FDA has signed on to the principles enunciated in documents produced by the International Conference on Harmonization on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH").

[77] 21 C.F.R. § 314.126(e).

[78] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[79] Blinding would have been very difficult to achieve with respect to the medical personnel performing the surgical abortion or dispensing the drugs to the patient, but blinding of abortion evaluators might have been achievable. In any event, scientifically rigorous randomized and concurrently controlled trials could have been performed with limited or no blinding.

[80] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone), at 2-4 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[81] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[82] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[83] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

At the Subcommittee's May 17, 2006 hearing, *RU-486: Demonstrating a Low Standard for Women's Health?,* Dr. Woodcock, Deputy Commissioner for Operations for the Food and Drug Administration, asserted in her written testimony for the Subcommittee that "[FDA's] finding of drug effectiveness was based on a comparison to a historical control of the expected rate of continued pregnancy."[84]

In response to a post-hearing Subcommittee question, FDA noted that the historical control, used in the RU-486 clinical trials, comprised of "the well-established data and pool of medical knowledge concerning both the natural course of pregnancy itself, including the well-documented rate of spontaneous abortion or miscarriage (less than 20%), and surgical abortion."[85] We take this to mean that the spontaneous abortion rate and the rate of induced abortion were together subtracted from the expected rate of ongoing pregnancy. It is important, then, to examine the FDA's claim that the French and U.S. trials were historically controlled.

First, FDA's assertion that the French and U.S. trials were historically controlled appears to be a *post hoc* assertion. There is no mention of any control group in the Spitz Study;[86] the word "control" does not appear in the article. Moreover, an FDA statistician reviewing the French trial data asserted that "[i]n the *absence of a concurrent control group* in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy"[87] (emphasis added). The reviewer made no mention of a historical control to which mifepristone would be compared, and it is well known that controls have to be specified *before* trials are performed. The lack of a prior delineation of the controls demonstrates that FDA's claims are not supported by the record.

Second, the U.S. RU-486 trials were conducted with specific groups of persons excluded. The Spitz Study[88] lists those disqualified from participation as follows:

> "Women with liver, respiratory, renal, adrenal, or cardiovascular disease, thromboembolism, hypertension, anemia, insulin-dependent diabetes mellitus, coagulopathy, or known allergy to prostaglandins were excluded, as were women less than 18 years of age or those more than 35 years of age who smoked more

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[84] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[85] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[86] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

[87] Center for Drug Evaluation and Research, Food and Drug Administration, Statistical Review and Evaluation for NDA 2-687 (Mifepristone) at 7-8 (May 21, 1996). The French trial is referred to as FFR/91/486/14. Available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_statr.pdf.

[88] Spitz, Bardin, Benton, and Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," 338 *New England Journal of Medicine* (1998), 1241-47.

> than 10 cigarettes per day and had another cardiovascular risk factor. Women were also excluded if they had in situ intrauterine devices, were breast-feeding, were receiving anticoagulation or long-term glucocorticoid therapy, had adnexal masses, had ectopic pregnancies, or had signs or symptoms suggesting they might abort spontaneously.[89]

Yet when FDA was asked what populations were excluded from its control group, the Subcommittee was told that "[a] historical control group does not include specific individuals, but rather is based on experience historically derived from the adequately documented natural history of the condition."[90] FDA made this additional point: "Thus, historical control populations usually cannot be assessed with respect to certain variables, such as the inclusion or exclusion of specific sub-populations."[91] This answer is methodologically insufficient, and it underscores the conclusion that, regardless of FDA's statement to the contrary, these trials were uncontrolled. The trial and control groups must be matched to each other in almost all possible ways if there is to be a meaningful control. If it was not possible to match the populations with the historical data set, then a concurrent control should have been used.

Finally, FDA allowed the use of uncontrolled trials for medical abortion because it defined the clinical endpoint too restrictively.[92] Neither spontaneous nor medical abortions produce only simple zero or one outcomes – that is, one-dimensional instances of success or failure. Not all abortions, whether spontaneous or medical, pass by themselves. Many require surgical intervention to be completed, or serious complications may ensue. FDA's cramped definition of RU-486 "effectiveness" ignores this.[93] A control should have been used in the RU-486 trial that compared different methods of producing the experimental outcome – first-trimester pregnancy termination – while assessing each method's ability to manage highly predictable, regular complications of medical abortion (*i.e.*, hemorrhage, incomplete abortion). As the International Conference on Harmonization[94] has noted, "non-defined" external controls

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[89] *Ibid*, at 1241-2.

[90] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17, 2006) (on file with Subcommittee).

[91] *Ibid*.

[92] *Ibid*.

[93] *Ibid*. ("In the case of medical abortion, determining the effectivness of the drug is straightforward, because it is relatively easy to determine whether the pregnancy has been terminated. Therefore, it is unnecessary to utilize a randomized clinical trial design.").

[94] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The International Conference on Harmonization "is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health." *See* www.ich.org (last visited October 10, 2006).

– those in which "a comparator group [is] based on general medical knowledge of outcome" – are "particularly dangerous" and "such trials are generally considered uncontrolled."[95] Such a characterization pertains in instances like this in which the study's dependent variable (i.e., the termination of pregnancy) has been defined so narrowly as to give the false impression of complete knowledge of a simple medical outcome.

B. FDA's Abuse of Subpart H

RU-486 was approved through an important part of FDA's drug approval rules called "Subpart H."[96] In the Subcommittee's May 17 hearing, Dr. Woodcock told the Subcommittee, "FDA approved the Mifeprex NDA [new drug application] under Subpart H at the sponsor's request because the Agency determined that post-marketing distribution restrictions on the product were necessary to ensure its safe use."[97]

These rules were promulgated by FDA in 1992 as part of an attempt to correct perceived deficiencies in FDA's approval process made apparent by the need to quickly develop drugs for HIV/AIDS patients. However, in order to benefit from the provisions contained in Subpart H (*e.g.*, its restricted distribution provisions in the case of RU-486) certain conditions must be satisfied, and in the RU-486 instance, Subpart H was unlawfully used for its approval.

Inducing Medical Abortion Does Not Qualify for Subpart H

Supbart H can only be applied to drug products "that have been studied for their safety and effectiveness in treating *serious or life-threatening illnesses*…."[98] (emphasis added). FDA was aware of this requirement, and FDA asserted in its approval memo to the Population Council "that the termination of an unwanted pregnancy is a *serious condition* within the scope of Subpart H…."[99] (emphasis added).

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[95] *FDA Guidance (ICH E10): Choice of Control Group* at 5 (§ 1.3.5). Section 2.5.4 adds the following point to this discussion: "An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs."

[96] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).. The Subpart H rules are found at 21 C.F.R. § 314.500ff.

[97] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf. We note that the Mifeprex Citizen Petition references a letter from Sandra Arnold of the Population Council to FDA, dated Sept. 6, 2000, in which she vociferously protests Mifeprex's approval under Subpart H. Mifeprex Citizen Petition at 20 (". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider.").

[98] 21 C.F.R. § 314.500.

[99] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4

Linguistic gymnastics notwithstanding, pregnancy or the termination of pregnancy is not a "serious or life-threatening illness," and therefore does not fall within the defined reach of Subpart H; the term "serious condition" is not found in the Subpart H rule. Subpart H is intended for the treatment of "serious or life-threatening illnesses," not conditions. There are situations in which pregnancies become serious or life-threatening, but the underlying condition is not "serious or life-threatening." Moreover, pregnancy itself is not an illness. There are situations in which serious or life-threatening complications may arise, but these are atypical events.

It is difficult to find a credible counter-argument from FDA or any private party defending the use of Subpart H to approve RU-486. This is not a mere technicality. If the condition being treated did not qualify for Subpart H approval, then the various restrictions that could be imposed pursuant to Subpart H to ensure the safe distribution of the drug would not have been available to the agency.

The FDA imposed several such restrictions on the distribution of Mifeprex.[100] (These restrictions, however, are less rigorous than what was initially proposed prior to approval.[101])

Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
- Has read and understood the prescribing information of Mifeprex
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going

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Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[100] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[101] FDA "Division Director Memo to File" on Mifepristone NDA, September 17, 1996 (on file with the Subcommittee): "The applicant has appropriately proposed that drug distribution be limited to licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and in the performanceof surgical abortion) who will attend educational seminars on the safe use of this regimen." The final restrictions allow for distribution under the supervision of a physician, rather than limiting it to licensed physicians, and do not require educational training on the safe use of the regimen.

pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
- Must record the Mifeprex package serial number in each patient's record

With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:

- Secure manufacturing, receiving, and holding areas for the drug
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
- Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
- Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

In addition, the Population Council agreed to two post-marketing studies on the effects of RU-486 on women[102] (though earlier reviews considered six post-marketing studies, four of them were dropped when the drug was approved[103]). In the six years since the approval of RU-486, these studies have not been completed.[104]

The RU-486 Trials Did Not Establish a "Substantial Benefit" for Subpart H

In addition to being intended for drug products studied for their safety and effectiveness in treating serious or life-threatening illnesses, Subpart H is intended only for those products that "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[105] FDA's Approval Memo stated that, for RU-486, "….[t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[106] The French and American clinical trial data did not satisfy the requirements established in the

[102] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[103] Center for Drug Evaluation and Research, Food and Drug Administration, Office Memo to Population Council (documenting the approval action for RU-486) September 28, 2000. Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

[104] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[105] 21 C.F.R. § 314.500.

[106] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000). Available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited October 15, 2006).

Subpart H rules for establishing a meaningful therapeutic benefit to patients over existing treatments.

First, RU-486 was not approved for a medical indication intended for only the treatment of patients who were intolerant of surgical abortion. It was approved to treat the general population of women seeking first-trimester abortions. FDA baldly asserted that there was a clinical benefit for chemical abortion, and made no effort to produce statistical evidence of an actual benefit.

Second, surgery is an integral part of the RU-486 abortion process, because a substantial proportion of women require D&C's after beginning the mifepristone regimen. Therefore, women who have RU-486 abortions must be able to tolerate the surgical procedure. This fact alone makes it all the more difficult to accept FDA's bald assertion of a meaningful therapeutic benefit above that presented by surgical abortion. While such a benefit may exist, the law requires FDA to make its judgments based on scientific evidence. Subpart H requires that both safety and effectiveness be established for the Subpart H drug above the existing standard of care. At the very least, FDA should have required the drug sponsor to conduct non-inferiority trials to generate data for the drug application.

Third, even though some women may prefer RU-486 abortions over surgical abortions, that fact does not establish the existence of a therapeutic benefit in and of itself. One can imagine numerous ways of delivering therapies that are more desirable for the patient – for example, pills rather than injection – but FDA must establish this fact statistically.

Fourth, it appears that no concurrently-controlled trials comparing medical and surgical abortion were required by FDA, because the Agency already knew that medical abortion—i.e., abortion by RU-486—is unambiguously inferior to surgical abortion with respect to safety and effectiveness. Prior to the approval of the RU-486 NDA, the FDA medical officer made the following observations about studies that had compared medical and surgical abortion:

> [In a study comparing medical and surgical abortion in India, Cuba, and China (n = 1373)], [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical abortion (8.6% versus 0.4% in China, 16.0% versus 4.0% in Cuba, and 5.2% versus 0% in India)…. Three patients (all medical abortions) received blood transfusions. This is a serious potential disadvantage of the medical method. On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients….[107]
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> [In another non-concurrent study of 377 patients comparing mifepristone to surgical abortion in the U.S patients], [f]our mifepristone patients required curettage for acute bleeding while no surgical patients did. Nine mifepristone

[107] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

> patients required curettage to manage ongoing pregnancy while no surgical patients did. Five mifepristone patients required suction curettage because of incomplete abortion while no surgical patients did. Fourteen mifepristone and eight surgical patients required suction curettage for persistent bleeding. The median time delay for therapeutic curettage was significantly longer in the mifepristone group than in the surgical group (35 days versus 8 days). Mifepristone patients experienced significantly longer postprocedure bleeding than did surgical patients. The mean difference in bleeding days between cohorts was 9.6 days (95% CI, 6.8, 12.4)…. Overall, mifepristone abortion patients reported significantly higher levels of pain, nausea, vomiting, and diarrhea during the actual abortion than did surgical patients… Mifepristone patients reported more problems during the follow-up interval than did surgical patients. Post-abortion pain occurred in 77.1% of mifepristone patients compared with only 10.5% of surgical patients…. Nausea or vomiting in the follow-up interval was common in the mifepristone group (68.6%), but rare among surgical patients."[108]

Given these comments, it is impossible to conclude that RU-486 medical abortions provide a meaningful therapeutic benefit over surgical abortion. Consequently, FDA's approval of the RU-486 NDA using Subpart H was unjustified and unlawful.

C. The Highly Unusual Placement of Misoprostol on the Mifeprex Label

When FDA approved the Population Council's RU-486 application it also mandated the use of another drug, misoprostol, as part of a two-drug abortion regimen. The use of misoprostol was not only an unapproved or off-label use – it was actually contraindicated at that time.[109] This aspect of the approval highlights another irregular component of FDA's approach to reviewing the RU-486 NDA. Shortly after FDA's approval of mifepristone, Peter Barton Hutt, a former FDA general counsel and noted commenter on food and drug law, told the Wall Street Journal that FDA appeared to have created "an extraordinary precedent", because FDA was "seemingly encouraging a drug's unapproved use."[110] He added that the agency is in an "embarrassing and uncomfortable position."[111]

The Subcommittee's questions to FDA on this matter have produced some information but no clear sense as to what FDA's policy is with respect to placing off-label or contraindicated drug uses on another drug's label.[112]

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[108] *Ibid*.

[109] On April 17, 2002, the misoprostol label was amended to remove "the contraindication and precaution that Cytotec should not be used in women who are pregnant."

[110] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[111] *Ibid*.

[112] In addition to questioning the FDA on this matter, the Subcommittee has looked for, and failed, to find any FDA Guidance documents on this topic.

Attention is drawn to two problems. First, it is well known that the NDA-holder for misoprostol (Searle) did not want to have its product used or labeled to reflect off-label uses as an abortifacient. [113] Thus, FDA mandated misoprostol's use in this abortion regimen and placed information about Searle's product on the Mifeprex label. Second, the entire edifice of FDA's regulation of drugs rests on the principle that only indications whose effectiveness has been demonstrated with "substantial evidence" may be placed on the label. FDA has procedures by which new indications can be approved using the supplementary new drug applications. No supplementary drug application was ever filed for misoprostol's use as an abortifacient.

In her prepared testimony before the Subcommittee, Dr. Woodcock noted that the FDA was "aware that questions ha[d] been raised about the use of misoprostol, a drug indicated for the prevention of NSAID-induced gastric ulcers, in the medical abortion regimen with mifepristone, without a separate approval and labeling of misoprostol for this use."[114] She then observed that numerous cases existed "where the labeling of one drug recommends its use with a second drug without the approval of the sponsor of the second drug."[115]

This statement is troubling and warrants further investigation. First, Woodcock's use of "recommends" is grossly inaccurate. In the Mifeprex regimen, the use of misoprostol is mandated. A physician might use an off-label variant of the regimen and, therefore, use another prostaglandin, but the Mifeprex label gives very specific directives to use misoprostol.[116] The non-optional nature of the regimen is carried forward into the language of the Patient Agreement Form which states: "I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3)."[117] Second, Subcommittee investigators finds it problematic that FDA can dictate that a drug – under the proprietary control of a firm whose NDA has been approved – can be approved for a use to which it objects.

In a letter to Chairman Souder, FDA provided two examples in which non-approved uses appear on FDA-approved labels.[118] The examples relate to coronary heart disease and metastatic

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[113] See letter from Searle warning against the use of misoprostol in abortion: http://www.fda.gov/medwatch/safety/2000/cytote.htm (last visited October 20, 2006).

[114] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

[115] *Ibid*.

[116] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[117] Mifeprex Patient Agreement, Item # 6, available at http://www.fda.gov/cder/drug/infopage/mifepristone/patientAgreement20050719.pdf (last visited October 20, 2006).

[118] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee). *See also*, See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Janet Woodcock, M.D., Deputy Commissioner for Operations, FDA) Available at http://reform.house.gov/UploadedFiles/Woodcock%20Testimony.pdf.

breast cancer, and the relevant labels should be read to understand the comments that follow.[119] Some comments are in order. First, there is no *mandated* use of the second/off-label drug in either example. Second, in the coronary disease case, the drugs were designed and approved to work on aspects of cardiovascular system-blood pressure regulation. There is nothing unusual in this use of drugs intended to manage cardiac failure.

These facts provide a qualitative difference with the Mifeprex regimen in which misoprostol was *not* designed to work to produce abortions – or uterine contractions for that matter. Rather, misoprostol was a medication intended to protect the gastro-intestinal tract from adverse events related to the use of non-steroidal anti-inflammatory medication – an indication far removed from misoprostol's novel application as an abortifacient.

Finally, FDA's Herceptin/Taxol example is somewhat disingenuous. After reading each drug's label, one recognizes that Taxol is approved for metastatic breast cancer treatment as a single agent, and so is Herceptin, but neither is specifically indicated for metastatic breast cancer treatment where no prior chemotherapy has been given. The combination use is approved (but not MANDATED) for patients with metastatic breast cancer overexpressing HER2 protein who have not received any prior chemotherapy.

Both drugs are approved for use in metastatic breast cancer. Herceptin's indication is more specifically tied to use when there is overexpression of HER2 protein. If there has been no other chemotherapy given then both may be used together. FDA seems to be splitting hairs when it claims that the use of Taxol in such cases is off-label. That characterization depends upon a fine distinction having to do with a specific tumor marker and whether or not other chemotherapy had been used.

The tenuousness of FDA's examples leads the Subcommittee to conclude that FDA is having difficulty finding examples that parallel the mandated, dissimilar off-label use of misoprostol in the Mifeprex regimen.

IV. SAFETY

Since the introduction of RU-486 to the U.S. market, the FDA has acknowledged, as of May 2, 2006, the deaths of six women associated with the drug, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 cases of infection.[120] These and other cases have added up to a total of 1070 adverse event reports (AERs) as of April 2006.[121]

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[119] The relevant information can be found using the website: <www.rxlist.com>.

[120] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[121] Numbers do not convey the full story. More telling are the first-hand accounts of women who have lived these events. Below are some examples from the Individual Safety Reports (ISRs) which describe in detail the type of experience RU-486 chemical abortion has turned out to be (mistakes are as they appear in the originals):

Event of January 1, 2000, reported September 27, 2000, one day before the approval of Mifeprex: "I was issued RU-486 in effort of obtaining an abortion. I followed directions exactly, and after taking the ru-486, I was in

excrutiating physical pain, for at least 12 hours straight and I was bleeding extremely excessively. I was bleeding through my pants but was in so much pain I couldn't even clean myself. It was the worst physical pain I've ever experienced in my life. This extreme pain was constant the whole 12 hours, it did not let up at all the whole time. I vomited continuously but couldn't even hold my head up. I had unbelievable abdominal pains, I can't even put in words. I couldn't speak, eat, drink, sit up, and had difficulty breathing. The only thing I could do was lie on the floor and pull my hair to deal with the pain. I couldn't clean myself or go to the bathroom, I thought I was going to die. After about 7 hours of this, I really wanted to die because I couldn't take the pain anymore. I wanted to call the hospital but I was hours from any hospital because I went to our cabin in a remote area to have privacy during this time. The administering clinic was closed since it was the weekend…. I was not informed of the extent of these side effects, I was told it would be just like a menstrual period. I never would have taken this had I been properly informed, even of the possibility of those effects…I was not told that this drug was experimental and not approved by the FDA…I believe they outright lied to me…when I returned to the clinic after the abortion was complete, they were not very attentive or interested in me, I explained to them my pains even though they didn't ask me any questions. I filled out a questionairre that they gave me before I took the drug and they said I have to do the questionnaire ever couple hours during the abortion, but when I offered it to them upon return, they didn't even want the questionaire, they didn't take it."

Event of July 26, 2002, reported September 28, 2002: "28 year old Gr5. Para 2 Ab 2 at 6 weeks 5 days gestation received 200 mg Mifeprex on [redacted] and inserted 800 mcg misoprostol vaginally on [redacted] at 11:00 a.m. The bleeding was 'normal' until 3:30 p.m. when it became heavier. That evening she stated 'it was like water coming out of me' and she felt dizzy. That evening she reported that she briefly 'passed out' twice. She went to an emergency room and received [missing] litres of IV fluid and had a D&C. Her hemoglobin on arrival was 8.7 gm/dl and was [missing] gm/dl after the D&C. She was started on iron supplementation. On [redacted] her hematocrit was 28% at the clinic and she reported that she was resting, on limited to light activity and doing well."

Event of August 15, 2004, reported July 25, 2005: "I took RU-486 last year and it caused me serious problems. After 15 days after taking it I hemorrhaged while at work requiring subsequent D&C, then had an infection that would not go away despite multiple antibiotics. I ended up being hospitalized and having multiple tests due to the infection and pain. I was hospitalized for four days in september of last year. Even after being hospitalized I was very ill for quite some time. I believe it took me until December to fully recover, during this time I lost quiet a bit of weight and had to enter counseling as a result of all the problems after using RU486."

Event of October 31, 2002, reported August 13, 2005: "Previous to 2002 I had two pregnancies and two live births…In 2002, 2003, and 2004, I had a three abortions at a very early stage, using the 'French' pill—RU-486—with each being almost exactly a year apart. I had the same experience each time. I developed a very bad case of bacterial vaginosis…I also was told to insert the final pill vaginally in all three cases. I had no idea it could even be taken orally."

Event of September 8, 2004, reported August 17, 2005: "I was given 2-step Abortion Pill. In the middle of the night I was awoken by severe abdominal pains. Having had endometriosis has built my pain tolerance quite high, but this pain was excruciating. Between the pain and diarrhea, I wanted to pass-out. I laid on the cold tile of the bathroom floor for 4 hours to keep me from fainting and because I couldn't get up. I thought it would eventually taper off, but after 4 hours I was exhausted and couldn't tolerate the pain. I yelled until my sister woke up to help me and asked her to call 911. She knew that I never go to the hospital, much less ask for 911, she immediately called. At the hospital, blood tests –b-hcg- kept coming back positive and I was still in alot of pain. They sent me for ultrasounds, blood tests again, and pelvic exams. I asked for more morphine, but they told my sister that they gave me the maximum dose and were surprised that I was still moaning of pain. The doctor said that my body was going through labor over and over, but wasn't ridding of anything. After the 3rd pelvic exam and blood test, the HCG count started coming down."

Event of December 14, 2005, reported December 27, 2005: "Approximately 2 1/2 weeks after taking Mifeprex and Cytotec to end a pregnancy, I began having very heavy bleeding. This was after I had not bled for a week, and after a 2 week follow up at a clinic—in which was told I was fine—I began hemorraging on the evening of the 14th, passing clots approximately 3 inches in size. I went through approximately 7 pads in 2 hours. The clinic wanted me to wait until the morning to get care from their facility, but when we called the local ER, they told me I needed to come in right away to get examined. I was cold, weak, and fatigued during the 2 hours my bleeding was excessively heavy. Unfortunately I was not able to make it into the ER because I am a single mother of 4, and had noone to care

A. Adverse Events for RU-486

These reports are based on the FDA's Adverse Event Reporting System (AERS), a voluntary system, with inherent underreporting. Common estimates of the proportion of adverse events actually captured by FDA in AERS are from one to ten percent. FDA acknowledges that it does not capture all adverse events associated with a drug: "When evaluating reports from the AERS system, it is important to recognize several caveats. First, *accumulated case reports cannot be used to calculate actual incidences of adverse events or estimates of risk for a product, as the reporting of adverse events is a voluntary process with inherent underreporting*"[122] (emphasis added).

The Government Accountability Office (GAO) has also commented on the underreporting of Adverse Events: "FDA cannot establish the true frequency of adverse events in the population with AERS data. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and it makes comparisons of risks across similar drugs difficult."[123]

FDA nonetheless claims that it is capturing most adverse events associated with RU-486: "Because healthcare professionals who prescribe Mifeprex have agreed in writing" (with the manufacturer, Danco, *not* the FDA) "to report 'any hospitalizations, transfusions or other serious events' to the manufacturer, FDA believes that there are unlikely to be significant numbers of serious adverse events, including deaths, associated with Mifeprex that have not been reported to the Agency."[124]

During the Subcommittee staff's review of the 1070 Adverse Event Reports that had been reported through April 2006, ISRs were found that had been submitted through MedWatch, the voluntary reporting mechanism for AERS, rather than through Danco. FDA acknowledged that these reports were not matched by reports submitted through Danco,[125] undermining the Agency's claim that it is capturing most adverse events.

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for my children. Luckily for me, the bleeding lessened. I was told it was 'normal' to bleed for up to 4 weeks, but I am NOW at day 32 and still bleeding."

[122] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[123] Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process GAO-06-402 March 31, 2006.

[124] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (July 31, 2006) (on file with Subcommittee).

[125] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (June 30, 2006) (on file with Subcommittee).

In light of FDA's repeated claim that it captures most RU-486-related adverse events—despite the Agency's own acknowledgement of underreporting and experience to the contrary—it is important to note that there is no true enforcement mechanism, either by Danco or the FDA, for ensuring that doctors report all adverse events, and there is little incentive on the part of the prescribing physician to do so.[126]

Even Danco has noted that the FDA's "obligatory" reporting system is of little value. In 2003, Dr. Richard Hausknecht, Medical Director for Danco, wrote that "[t]he obligatory reporting of adverse events is limited to transfusions, hospitalizations, ongoing pregnancies or 'other serious adverse events,' which allows considerable subjective judgment on the part of the providers. In addition, the reporting of other common adverse events may not be reported at all."[127]

Moreover, emergency room personnel and medical professionals who do not prescribe RU-486, but who may likely treat the infected or hemorrhaging patient, or provide surgical intervention, *have no obligation whatsoever to report adverse events for RU-486*, even assuming that the healthcare worker is aware the patient took the RU-486 drug regimen.[128] In such scenarios, prescribing physicians may remain unaware of adverse events that take place after they administer RU-486, alleviating them of reporting requirements. This underscores the fact that there is not an accurate picture of the total adverse events that are being experienced with this drug.

In addition to the fact that there is no accurate number of adverse events to serve as a realistic "numerator" for evaluating the rate of adverse events actually being experienced in the population, the FDA does not use an accurate figure for the true number of patients who have taken RU-486 as a "denominator." Rather, FDA accepts and reports "estimates" proposed by Danco. The most recent estimate is that 612,000 women in the U.S. have used RU-486 as of July 24, 2006.[129]

This estimate is likely inflated, since Danco arrives at its estimate by basing it on the number of packages sold (in three-pill packages of 200 mg pills) and multiplying that number by three to account for the number of doses that are given at the off-label 200 mg dose (rather than

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[126] Although RU-486 is approved for use through 49 days of pregnancy, it is commonly prescribed in the United States up to 63 days of pregnancy. Physicians also commonly prescribe a dosing regimen that is different from that approved by the FDA. Therefore, it has been suggested that in fact there is a *dis*incentive on the part of prescribing physicians to report adverse events that may be attributed to a physician's negligence or willingness to prescribe a regimen that is outside the FDA-approved regimen for RU-486.

[127] Hausknecht, R., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003) 463-465.

[128] Treating personnel might never know that a woman has taken RU-486; Women who seek medical treatment for adverse reactions after RU-486 may be too sick to disclose, may fail to disclose, or may simply refuse to disclose (because she does not want it in her medical record) that she has taken the RU-486 drug regimen.

[129] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (August 17. 2006) (on file with Subcommittee).

the FDA approved 600 mg dose).[130] That Danco is allowed to provide a loosely-figured *estimate* flouts the restricted approval provision for RU-486, which requires Danco to distribute the drug with a tracking system allowing the company to track packages "to the patient level while maintaining patient confidentiality."[131]

For FDA to rely upon guesses as a basis for understanding safety problems with RU-486 is highly problematic. Danco's estimate is used as the denominator for determining the rate of adverse events associated with the drug. The larger the denominator, the lower the percentage of adverse events. This inaccuracy of using Danco's estimate is inexcusable in light of the way the estimate is relied upon to determine and discuss the rate of adverse events associated with RU-486.

B. RU-486 Safety Issues Known Prior to Approval

Prior to FDA's approval of RU-486, the Agency's own medical experts recognized that any benefits that could be gained from the use of this drug for a "medical abortion" were limited at best and that significant dangers were inherent in its use. These dangers are especially acute when compared to surgical abortion. According to the FDA's medical reviewer, writing before the drug's approval:

> This method of pregnancy termination is of limited value because of the relatively short window of opportunity, [sic] in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. This means that most women would not suspect that they are pregnant and have a confirmatory pregnancy test until at least four weeks after the beginning of their last menses. This, then, leaves only a three week period for the women to secure this method of abortion.
>
> Another disadvantage of this method of pregnancy termination is the need for at least three visits to the medical facility [sic] including at least a four hours [sic] stay after the administration of the misoprostol.
>
> In addition, medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)...
>
> [In a comparison of medical termination of pregnancy with surgical termination,] [t]he medical regimen had more adverse events, particularly bleeding, than did surgical abortion. Failure rates for medical abortion exceeded those for surgical

[130] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators… were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), …[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices…[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

[131] CDER Office Memo to Population Council, September 28, 2006. At http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf (last visited September 28, 2006).

> abortion…[and] increased with gestational age. Specific symptoms and adverse events, including cramping, nausea, and vomiting, were far more frequent among the medical than the surgical abortion patients… On the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients….[132]

The negative physical experience of RU-486 was explained this way by Dr. Tom Tvedten, an abortion provider in Little Rock, Arkansas: "With medical termination, the discomfort is significant because they have to go through mini-labor…There's a lot of hard cramps and usually significant bleeding. It's cheaper, safer and less painful to have a surgical termination."[133]

In fact, as explained in the RU-486 label, "nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction,"[134] including: abdominal pain; uterine cramping; nausea; headache; vomiting; diarrhea; dizziness; fatigue; back pain; uterine hemorrhage; fever; viral infections; vaginitis; rigors (chills/shaking); dyspepsia; insomnia; asthenia; leg pain; anxiety; anemia; leucorrhea; sinusitis; syncope; endrometritis / salpingitis / pelvic inflammatory disease; decrease in hemoglobin greater than 2 g/dL; pelvic pain; and fainting.[135]

The FDA's Medical Officer's review notes that, "[m]ore than one adverse event was reported for most patients…Approximately 23% of the adverse events in each gestational age group were judged to be severe."[136]

In addition to these known, startling adverse effects, of which the FDA was aware during the RU-486 NDA review process, the incredibly high failure rate of the drug was also known, averaging 14.6% in the U.S. trial testing the drug through 63 days gestation.

The FDA's Medical Officer's review noted that in the U.S. trial of 2015 women, "[a] total of 295 patients were classified as having failed medical abortion."[137] This represents a

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[132] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[133] John Leland, *Under Din of Abortion Debate, an Experience Shared Quietly*, N.Y. TIMES, Sept. 18, 2005, *at* http://www.nytimes.com/glogin?URI=http://www.nytimes.com/2005/09/18/national/18abortion.html&OQ=_rQ3D1&OP=41647c1fQ2FQ2AQ7EklQ2AbBG)ABB7FQ2AFqqjQ2AqQ2FQ2A42Q2A-_7VB-_YQ2A42_lBA7VB-vC7KY. (Quoting Dr. Tom Tvedten of Little Rock, Arkansas).

[134] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[135] *Ibid.*

[136] Medical Officer's Review of Amendments 024 and 033, Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments, Finalized November 22, 1999 (dated January 27, 2000), available at http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (last visited September 28, 2006).

[137] *Ibid*.

failure in 14.6% of total patients. "Of these patients, 79 (27%) had ongoing pregnancies, 126 (43%) had incomplete abortions, 30 (10%) requested and had surgical terminations, and the remaining 60 (20%) patients had surgical terminations performed because of medical indications directly related to the medical procedure."[138]

The "best" outcome was in the patient group consisting of women whose pregnancies were less than or equal to 49 days. In this group, 7.9% of patients required surgical intervention after taking RU-486. As the gestational age increases, the failure rate of RU-486 increases rapidly, to 17% in the 50-56 days gestation group, and 23% in the 57-63 days gestation group.

By any objective standard, a failure rate approaching eight percent and requiring subsequent surgical intervention as the "best" outcome is a dismal result. Nonetheless, the Medical Officer stated that "[t]he 92% success rate in the ≤ 49 days group is an acceptable one."[139] This failure rate, along with the anticipated adverse events that patients would experience, is explicit in the FDA Medical Officer's review, and also part of the RU-486 label.[140]

Despite these known problems with adverse events and high failure rates, the FDA recommended and gave approval for distributing this drug to women.

B. Post-Approval Hemorrhage, Infections and Deaths

As stated above, the FDA has acknowledged the deaths of six U.S. women associated with RU-486, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions and 88 cases of infection. [141] A quarter all the patients were hospitalized.[142] These and other cases add up to a total of 1070 adverse event reports (AERs) as of April 2006.

A review[143] of only a portion of all the reported AERs demonstrates in real world experience how women have suffered after taking dangerous drug. Out of only 607 unique adverse events submitted to the FDA, the high number of serious and life-threatening events is startling:

> The most frequent [adverse event reports] were hemorrhage (n=237) and infection (66). Hemorrhages included 1 fatal, 42 life threatening, and 168 serious case; 68 required transfusions. Infections included 7 cases of septic shock (3 fatal, 4 life-threatening) and

[138] *Ibid*.

[139] *Ibid*.

[140] Mifeprex Label, available at http://www.fda.gov/cder/foi/label/2005/020687s013lbl.pdf (last visited September 28, 2006).

[141] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[142] *Ibid*.

[143] M. M. Gary, D. J. Harrison, *Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient*, The Annals of Pharmacotherapy, February 2006, 40.

> 43 cases requiring parenteral antibiotics. Surgical interventions were required in 513 cases (235 emergent, 278 nonemergent). Emergent cases included 17 ectopic pregnancies (11 ruptured). Second trimester viability was documented in 22 cases (9 lost to follow-up, 13 documented fetal outcome). Of the 13 documented cases, 9 were terminated without comment on fetal morphology, 1 was enrolled in fetal registry, and 3 fetuses were diagnosed with serious malformations, suggesting a malformation rate of 23%.[144]

Since this review by Gary and Harrison, there have been hundreds more adverse event reports and two additional reported septic infection deaths. Nearly all among the afflicted and dead who experienced these serious adverse events following RU-486 were healthy women of child-bearing age. (This is in sharp contrast to other drugs with inherent risks—Viagra, for example—which result in adverse events often after repeated use over long intervals of time, in patients with other risk factors associated with age or disease.) Without access to emergency room services, women who suffered severe hemorrhage would have died.

In total, there are eight known deaths following RU-486: four Californians and one Canadian from *C. Sordellii* septic infection; a Tennessee woman with ruptured ectopic pregnancy; a Swedish teen, from massive hemorrhage; and a British female, from "unknown etiology," (but her clinical presentation of shock and an autopsy revealing one liter of blood in her stomach makes sepsis a plausible etiology).[145]

Five of the eight known deaths following the use of RU-486 have been the result of a toxic shock-like syndrome initiated by the bacteria *C. Sordellii.* This bacteria is thought to exist in low numbers in the reproductive tracts of many women and is normally contained by the immune system.[146] Experts in immunology,[147] pharmacology[148] and maternal-fetal medicine[149]

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[144] *Ibid*.

[145] *Ibid*.

[146] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[147] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486.")

[148] *See,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

have suggested that because RU-486 interferes with the immune response, the bacteria, if present, are then able to flourish, causing a widespread, multi-organ infection in the woman.

The infections are *not* accompanied by a fever, and symptoms match those that are expected after taking the RU-486 regimen (cramping, pain, bleeding, nausea, vomiting), making detection of the fast-spreading infection difficult. Each of the women infected with *C. Sordellii* after RU-486 were dead within five to seven days.

The FDA describes the clinical presentation of *C. Sordellii* infection the following way:

- Rapid onset of influenza like symptoms (nausea, vomiting, and weakness)
- Hypothermia or *absence* of fever
- *Absence* of purulent discharge
- Localized pelvic tenderness may be *absent*
- Elevated hematocrit and marked leukemoid reaction
- Progressive refractory hypotension
- Marked edema with peritoneal and pleural effusions
- Rapidly fatal despite aggressive treatment[150] (emphasis added).

To investigate the nature of the *C. Sordellii* bacteria, the FDA and CDC held the "Emerging Clostridial Disease" workshop on May 11, 2006.[151] Workshop presenters – experts in the fields of pharmacology, immunology, and maternal-fetal medicine – noted that the rapid growth of the *C. Sordellii* bacteria likely forecloses effective treatment;[152] that there is no currently identifiable "window of opportunity" for treatment once a woman is infected, even with major interventions such as hysterectomy;[153] and that antibiotic prophylaxis was unlikely to provide any protection in the RU-486 / *C. Sordellii* context.[154] The fatality rate has been 100% for the women who contracted *C. Sordellii* infection after RU-486.

In an effort to dismiss any association between RU-486 and the *C. Sordellii* deaths, some have promoted the idea that *C. Sordellii* is linked to pregnancy and childbirth, not the abortion pill. However, in five years, five women have died from this infection after taking RU-486. In contrast, the FDA has noted that there were "only five additional cases not associated with

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[149] *See*, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[150] Food and Drug Administration "Center Director Briefing" June 27, 2005 (on file with the Subcommittee).

[151] A full transcript for the meeting is available at: http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[152] Letter to the Editor, James A. McGregor and Ozlem Equiles, *Risks of Mifepristone Abortion in Context*, Contraception 2005, 71: 161.

[153] Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Transcript available at http://www.fda.gov/cder/meeting/clostridial/transcript.pdf (last visited October 13, 2006).

[154] *Ibid*.

mifepristone/misoprostol retrieved with a text search of the entire AERS database"[155] of 3.5 million records.[156]

Distinguishing the 100% fatality rate with this infection following RU-486 among women who were otherwise healthy, the FDA noted, "[t]he patients in these 5 [non-RU-486 related] cases had weakened or altered immune function due to chemotherapy and age (neonatal & elderly patients), and use of multiple antibiotics. None of these five cases involved intravaginal product administration and 3 cases had a fatal outcome. *In contrast to these 5 additional cases in [3.5 million] AERS, the 4 U.S. confirmed cases of Clostridium Sordellii infection with medical abortion involved healthy patients and all cases had fatal outcome*"[157] (emphasis added).

A more extensive database search for any reported *C. Sordellii* infections since 1925 found a total of eleven fatal cases related to post-partum/ob-gyn infection or to spontaneous abortion.[158] In contrast with this small number of cases (11 since 1925) five women in five years are known to have died from *C. Sordellii* following RU-486.

Experts studying the immune suppression properties of RU-486 have found that it has the ability to block innate immune response.[159] Lazar had published information as early as 1992

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[155] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[156] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[157] Memorandum, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, April 12, 2006, From [redacted], Division of Drug Risk Evaluation, Through: [redacted] Division of Drug Risk Evaluation, TO: [redacted] Division of Reproductive and Urologic Products. Subject: Supplementary investigations related to reports of fatal infections associated with mifepristone and misoprostol use for medical abortion. [handwritten note: DFS 4/17/06 Consult #3]

[158] Dennis L. Stevens, M.D., PhD., *Clostridium sordellii: Clinical Settings, Diagnostic Clues and Pathogenic Mechanisms*, Public Workshop on Emerging Clostridial Disease," (CDC Conference Center: Atlanta, Georgia, May 11, 2006). Available at http://www.fda.gov/cder/meeting/clostridial/stevens.pdf (last visited October 13, 2006).

[159] *See,* Jeanette I. Webster and Esther M. Sternberg, *Role of the Hypothalamic-Pituitary-Adrenal Axis, Glucocorticoids and Glucocorticoid Receptors in Toxic Sequelae of Exposure to Bacterial and Viral Products*, Journal of Endocrinology 2004, 181:207-221 ("Natural and synthetic glucocorticoids protect against the lethal effects of many bacterial and viral components...agents that block the hypothalamic-pituitary-adrenal axis, as in…mifepristone…enhance lipopolysaccharide (LPS) and endotoxin lethality and LPS-induced fever. Even the normally endotoxin-nonresponsive C3H/HeJ mice could be made endotoxin sensitive by RU-486."). *See also,* Ralph P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, The Annals of Pharmacotherapy, September 2005, 39:

> "Mifepristone is a potent progesterone antagonist that, in addition to its ability to block glucocorticoid receptors, blocks progesterone receptors...Blockade of progesterone receptors…results in rejection of the developing placenta and death of the embryo. Prolonged ischemia of the decidua and the embryonic placenta causes necrosis [death] of these tissues. Mifepristone also [causes] cervical dilation and liquefaction of the cervical mucus plug. The

about the increase in fatal septic infection in mice after receiving RU-486, which caused the survival rate to drop dramatically from the control level of 71% to only 15%.[160] Nonetheless, the theory that RU-486 suppresses the immune system was only noted by the FDA as late as 2003,[161] and it wasn't until 2004 that the Agency conducted the minimal inquiry of a literature review to examine the immune suppression properties of RU-486:.

> "The Division of Anti-Infective Drug Products (DAIDP) reviewed the medical literature to examine the potential impact that either or both mifepristone and misoprostol might have on human immune function. They concluded, 'Systemic levels of mifepristone and misoprostol may both influence the host response to infection via their anti-inflammatory effects, respectively. In theory, *these effects may predispose an individual to infection or may predispose an infected individual to a worse outcome*. Such roles are apparently dependent on dose, timing, and rates of uptake and intracellular degradation in different target tissues'"[162] (emphasis added).

Beyond this, there is little more in the thousands of pages of documents provided to the Subcommittee to indicate an extensive FDA examination of the immune suppression properties of RU-486.

In the meantime, women who take RU-486 are exposing themselves to an exponentially greater risk of infection or death as compared to the alternative of surgical abortion. The risk of death from infection is at least ten times greater than surgical abortion during the first eight weeks of pregnancy.[163] In addition to *C. Sordellii* infection, women taking RU-486 have developed other infections following the abortion pill regimen. The FDA has acknowledged 88 reported cases of infection following RU-486.

The most frequent serious adverse event is hemorrhage, where women who lost enough blood as to require transfusions. These cases of massive hemorrhage comprise 12% of the RU-

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> combined loss of a closed cervix and the protective cervical mucus plug permits contamination of the decidua and the intrauterine necrotic cells with aerobic and anaerobic bacteria from the normal vaginal flora."

See also, Sharon Worchester, *Mifepristone Deaths Raise Unanswered Questions*, Ob. Gyn. News, (October 1, 2005) at 13. (Quoting Dr. James A. McGregor)("Mifepristone has multiple pharmacologic properties that may interfere with innate immune responses to infection, toxin exposures, and inflammatory stimuli.").

[160] G. Lazar, *et al.*, *Modification of septic shock in mice by the antiglucocorticoid RU 38486*, 36 Circulatory Shock 180 (1992).

[161] FDA Division of Anti-Infective Drug Products, Report of Medical Officer Consultation (Intravaginal Misoprostol), November 19, 2003, at 4 (on file with the Subcommittee)..

[162] FDA Mifeprex plus Misoprostol Postmarketing Safety Review, November 15, 2004, at 24 (on file with the Subcommittee).

[163] *See,* Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353;22 *at* 2318. The mortality rate for women who procure a surgical abortion is 0.1 in 100,000 during the first eight weeks of pregnancy, the period for which RU-486 is available for women. Dr. Michael Green, based on usage rates of 460,000 and 4 deaths, suggested that the risk of death from chemical abortion is ten times greater. The rate could be higher, if an accurate numerator is used for the true number of patients who have taken RU-486.

486 AERS.[164] A review of the AERS through September 2005 finds that fifteen women suffered hemorrhages so serious that they lost over half of their entire blood volume and would have died without rapid access to emergency room services.[165]

According to Dr. Donna Harrison, who testified before the Subcommittee at the May 17 hearing *RU-486: Demonstrating a Low Standard for Women's Health?*, "In my experience as an ob-gyn, the volume of blood loss seen in the life-threatening cases is comparable to that observed in major surgical trauma cases like motor-vehicle accidents. This volume of blood loss is rarely seen in early surgical abortion without perforation of the uterus, and it is rarely seen in spontaneous abortion."[166]

As with other adverse events associated with RU-486, no risk factors for hemorrhage have been identified. Rather, they are unpredictable and sporadic.[167]

The proven health risks and demonstrated association with fatal septic infections necessarily prompt urgent consideration of this drug's immediate withdrawal from the market.

V. RECOMMENDATIONS

The high incidence of adverse events has prompted Danco, in cooperation with the FDA, to take steps to alert women and the medical community to the dangers of the drug:[168]

- "Dear Health Care Provider" Letter, April 19, 2002 (warning of danger of ruptured ectopic pregnancies).[169]
- "Dear Emergency Room Director" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[170]
- "Dear Health Care Professional" Letter, November 12, 2004 (warning of infection, heavy bleeding and ruptured ectopic pregnancy).[171]
- Updated label, December 22, 2004 (reflecting danger of infection, heavy bleeding and ruptured ectopic pregnancy).[172]

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[164] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources (May 2, 2006) (on file with Subcommittee).

[165] See *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of Donna Harrison, M.D.) Available at http://reform.house.gov/UploadedFiles/Harrison%20Testimony%20-%20scan%20test.%20w%20attchmts.pdf.

[166] *Ibid*.

[167] *Ibid*.

[168] See Danco's website, http://www.earlyoptionpill.com/.

[169] Available at http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf (last visited October 14, 2006).

[170] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf (last visited October 14, 2006).

[171] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

- "Dear Health Care Provider" Letter, July 19, 2005 (warning of the cases of fatal septic shock).[173]
- Updated label, July 19, 2005 (warning of danger of fatal *C. Sordellii* infections).[174]

In light of the significant health risks posed by this drug, the current restrictions, and the letters and label changes subsequent to approval are demonstrably insufficient to protect women from the dangers of RU-486. Rather, the FDA possesses the authority to suspend or withdraw approval of the drug under various provisions. The most important, and perhaps necessary and justified for removing RU-486 from the market, is the Imminent Hazard authority possessed by the Secretary of Health and Human Services.

"Imminent Hazard" is defined and the criteria to be considered are set forth in 21 CFR 2.5:

> (a) Within the meaning of the Federal Food, Drug and Cosmetic Act an imminent hazard to the public health is considered to exist when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation (1) that should be corrected immediately to prevent injury and (2) that should not be permitted to continue while a hearing or other formal proceeding is being held. The imminent hazard may be declared at any point in the chain of events which may ultimately result in harm to the public health. The occurrence of the final anticipated injury is not essential to establish that an imminent hazard of such occurrence exists.
>
> (b) In exercising his judgment on whether an imminent hazard exists, the Commissioner will consider the number of injuries anticipated and the nature, severity, and duration of the anticipated injury.

Under this provision, the Secretary's decision is subject to judicial review, but the courts are deferential to the Secretary's conclusions.[175] Within the context of RU-486, the unpredictability and frequency of serious adverse event and death (discussed in Section III above) warrants withdrawal of this dangerous drug from the market.

The FDA also possesses the authority to unilaterally withdraw approval of a drug under 21 CFR 314.530. RU-486 falls into the withdrawal categories of this provision:

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[172] Available at http://www.fda.gov/cder/foi/label/2004/020687lbl_Revised.pdf (last visited October 14, 2006).

[173] Available at http://www.fda.gov/medwatch/safety/2005/mifeprex_deardoc_071905.pdf (last visited October 14, 2006).

[174] Available at http://www.fda.gov/cder/drug/infopage/mifepristone/DearHCP.pdf (last visited October 14, 2006).

[175] See *Forsham v. Califano*, 442 F. Supp. 203 (D. D.C. 1977)(this case appears to be the only instance in which the "imminent hazard" authority of the HHS Secretary has invoked). See also *RU-486: Demonstrating a Low Standard for Women's Health? Hearing before the House Subcommittee on Criminal Justice, Drug Policy and Human Res., Committee on Government Reform*, 109th Cong. (May 17, 2006) (statement of O. Carter Snead, Assoc. Professor, University of Notre Dame Law School). Available at http://reform.house.gov/UploadedFiles/Snead%20Testimony.pdf.

(a)(1) A post-marketing clinical study fails to verify clinical benefit

Since its approval, RU-486 has been associated with six known U.S. deaths of healthy women.[176] The safety problems associated with RU-486 are discussed above. Additionally, because women who visit the emergency room arrive with symptoms virtually identical to those associated with miscarriage,[177] deaths within the U.S. following the use of RU-486 may be higher, but unreported.

Moreover, as discussed above, the mortality rate for surgical abortion for the first eight weeks of pregnancy is 0.1 per 100,000.[178] The makers of RU-486 report that 575,000 women have used the drug (based on units shipped, not units prescribed, and based on the assumption that one tablet—rather than the FDA-approved three—is administered to the patient;[179] the actual number of women who have taken the drug may be much lower). Using the figure of 575,000 women having taken RU-486, this works out to a known death rate of approximately 1.39 per 100,000, nearly *14 times* greater than surgical abortion. As noted above, Subpart H drug approval is conditioned on "meaningful therapeutic benefit." The statistics demonstrate that medical abortion is far more dangerous than the existing treatment of surgical abortion, which is proof of a lack of clinical benefit.

(a)(3) Use after marketing demonstrates that post-marketing restrictions are inadequate to assure safe use of the drug product

Experience shows that post-marketing restrictions on RU-486 are inadequate to assure the safe use of the product, because the medical community has ignored them on a widespread basis. As noted earlier in this report, abortion providers routinely use RU-486 beyond the time periods approved by the FDA[180] and with dosing regimens that stray from the FDA's approved

[176] Letter from David W. Boyer, Assistant Commissioner for Legislation, Food and Drug Administration, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee).

[177] "Dear Emergency Room Director" Letter from Danco Laboratories to emergency room directors, (Nov. 12, 2004), *at* http://www.fda.gov/cder/drug/infopage/mifepristone/DearER.pdf.

[178] Michael F. Green, M.D., *Fatal Infections Associated with Mifepristone-Induced Abortion*, Dec. 1, 2005, N. ENGL. J. MED 353:22 *at* 2318.

[179] *Ibid.*

[180] Some abortion providers (e.g., Planned Parenthood of New York City at www.ppnyc.org/services/factsheets/mifep.htm, Capital Care Women's Center at www.capitalcarewomenscenter.com/services.php, and Camelback Family Planning at www.camelbackfamilyplanning.com/abortionpill.html.), even advertise the availability of RU-486 through 63 days LMP, by which time the rate of incomplete abortion, infection, and other complications rises sharply. In U.S. clinical trials, the failure rate for RU-486 abortions jumps to 17% at 50-56 days LMP, and to 23% at 57-63 days LMP, from 8% at 49 days or less. Irving Spitz *et al*., "Early pregnancy termination with mifepristone and misoprostol in the United States," *New England Journal of Medicine* 1998, 338:1241-47.

regimen.[181] While off-label use of drugs is common, it runs contrary to the entire purpose of the regulatory regime approved for RU-486 under Subpart H.

The FDA is aware of the medical community's refusal to heed the regulations it instated on RU-486. In its own words, the FDA "is aware that…some [physicians] may have chosen to use a modified version of the Patient Agreement form. However, these decisions are made by physicians exercising their own judgment about what is best for their patients**.**"[182]

This is contrary to the detailed Risk Management Program, explained in the FDA memo detailing the drug's approval, which states: "the signed agreement form will be given to the patient for her reference and another kept in the medical records," and "[the prescribing physician] must provide each patient…with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well."[183] The FDA determined that these restrictions were critical to the safe use of the drug, and in spite of this, physicians have refused to heed them.

(a)(4) The applicant fails to adhere to the post-marketing restrictions agreed upon

Although the FDA stipulated that the manufacturer have systems in place to track the distribution of RU-486 "to the patient level," and that require physicians to "record the Mifeprex package serial number in each patient's record,"[184] Danco has not provided reliable patient numbers, but rather estimates.[185]

In addition to the FDA requiring patients to sign a Patient Agreement form, the Population Council agreed, as part of the approval process, to "auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms." It is unclear whether the Population Council, Danco, or any other entity associated with the production of RU-486 has adhered to this requirement.

(a)(5) The promotional materials are false or misleading

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[181] R. Hausknecht, "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65: "Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg)."

[182] Letter from Patrick Ronan, Associate Commissioner for Legislation Department of Health and Human Services FDA to Hon. Mark E. Souder, (March 16, 2006) (on file with Govt. Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources).

[183] Memorandum from FDA Center for Drug Evaluation and Research to Population Council 6, (Sept. 28, 2000) (available at http://www.fda.gov/cder/drug/infopage/mifepristone/memo.pdf).

[184] *Ibid.*

[185] Richard Hausknecht, Medical Director for Danco, described how Danco estimates the usage figures for RU-486: "Denominators… were estimated from sales figures. Although the FDA-approved regimen specified a single oral dose of mifepristone 600 mg, many physicians are using a lower dose (200 mg), …[an] estimated range was based upon Planned Parenthood practices and National Abortion Federation (NAF) polling of their membership practices…[and by] [a]djusting for utilization patterns of providers." *Contraception* 67 (2003): 463-65.

The FDA conditioned approval of RU-486 on tracking its use "to the patient level." In spite of this, the manufacturer estimates the usage of its drug for its promotional materials.[186] This affects the perceived safety of the drug, as the manufacturer may be overstating its actual usage in comparison with the adverse events reported.

Both the "Imminent Hazard" provision and the regulatory provision for approval withdrawal under Subpart H provide sufficient authority for the Administration to remove this dangerous drug from the market.

VI. CONCLUSION

The integrity of the FDA in the approval and monitoring of RU-486 has been substandard and necessitates the withdrawal of this dangerous and fatal product before more women suffer the known and anticipated consequences or fatalities. RU-486 is a hazardous drug for women, its unusual approval demonstrates a lower standard of care for women, and its withdrawal from the market is justified and necessary to protect the public's health.

[186] *Ibid*. *See also*, Letter from David W. Boyer, Assistant Commissioner for Legislation, to Hon. Mark E. Souder, Chairman, Subcommittee on Criminal Justice, Drug Policy, and Human Resources, (May 2, 2006) (on file with Subcommittee); *FDA Announces Mifeprex Not Cause of One of Two Recent Abortion-Related Deaths*, KAISER NETWORK DAILY REPORTS, (April 11, 2006) *at* http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=36534. ("We stand behind the safety profile of the drug, which has been used by approximately 575,000 women in this country since FDA approval in 2000," quoting Cynthia Summers, director of marketing and public affairs at Danco Laboratories, originally in Wall Street Journal, April 11, 2006.)

Exhibit 13

2002 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to U.S. Food & Drug Admin. (FDA) (Aug. 20, 2002)

BEFORE THE DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

5536 '02 AUG 20 P1:55

Citizen Petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation

CITIZEN PETITION AND REQUEST FOR ADMINISTRATIVE STAY

The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"), the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA") (collectively, "the Petitioners") submit this Petition pursuant to 21 C.F.R. §§ 10.30 and 10.35; 21 C.F.R. Part 314, Subpart H (§§ 314.500-314.560); and Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355).[1] The Petitioners urge the Commissioner of Food and Drugs to impose an immediate stay of the approval by the Food and Drug Administration ("FDA" or "agency") of Mifeprex™ (mifepristone; also, "RU-486"),[2] thereby halting all distribution and marketing of the drug, pending final action on this Petition. In addition the Petitioners urge the Commissioner to revoke FDA's approval of Mifeprex and request a full FDA audit of the Mifeprex clinical studies.[3]

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[1] Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

[2] The New Drug Application for Mifeprex, which was filed by the Population Council, was approved on September 28, 2000. Mifeprex is distributed by Danco Laboratories, a licensee of the Population Council.

[3] The Petitioners will, at times, cite to documents contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <http://www.fda.gov/cder/archives/mifepristone/default.htm>. Since the initial release FDA has edited some of the 94 files. However, the stamped page numbers have not changed. Additionally, many footnotes refer to Appendix A to this Petition, which contains a selected bibliography.

02P-0377

CP 1

I. ACTION REQUESTED

The Petitioners respectfully request that the Commissioner immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on this Petition. They urge the Commissioner to revoke market approval for Mifeprex in light of the legal violations and important safety concerns explained below. In addition, they request a full FDA audit of all records from the French and American clinical trials offered in support of the Mifeprex NDA.

II. INTEREST OF THE PETITIONERS

While it is true that the Petitioners have consistently opposed abortion and continue to do so, a careful examination of the claims made in this petition should alert people of conscience on either side of this issue that women are being harmed. Regardless of one's position on abortion, FDA's violations of its standards and rules have put women's health and lives at risk. The Petitioners are non-profit organizations that share a great concern about women's health issues. The American Association of Pro-Life Obstetricians and Gynecologists ("AAPLOG") is a recognized interest group of the American College of Obstetricians and Gynecologists ("ACOG"), currently representing over 2,000 obstetricians and gynecologists throughout the United States of America. The Christian Medical Association, founded in 1931, is a professional organization with thousands of physician members representing every medical specialty. Concerned Women for America ("CWA"), founded in 1979, is the largest public policy women's organization in the United States with members in every State and a total membership exceeding 500,000.

III. STATEMENT OF GROUNDS

A. SUMMARY OF THE PETITIONERS' ARGUMENTS

Good cause exists to grant an immediate stay of the agency's September 28, 2000 Mifeprex approval.[4] Good cause also exists for the subsequent revocation of that approval.[5] As established herein, (1) the approval of Mifeprex violated the Administrative Procedure Act's prohibition on agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;[6] (2) FDA's approval of Mifeprex violated 21 U.S.C. § 355 because the drug does not satisfy the safety and labeling requirements of that section; and (3) the agency approved Mifeprex despite the presence of substantial risks to women's health.

This Petition represents the latest attempt by members of the medical community and other concerned observers to warn FDA of the dangers posed by Mifeprex abortions to the health of women.[7] Women undergoing Mifeprex abortions risk, among other problems, uncontrolled fatal hemorrhage and serious bacterial infections. Mifeprex abortions particularly endanger women with ectopic pregnancies and those whose pregnancies have progressed beyond 49 days.[8]

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[4] When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Petition, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

[5] *See* 21 C.F.R. § 314.530 ("Withdrawal Procedures").

[6] 5 U.S.C. § 706(2)(A).

[7] On February 28, 1995, Americans United for Life and other groups and individuals filed a Citizen Petition with FDA requesting it to "refuse to approve any NDA for RU 486 for use as a pharmaceutical abortifacient that does not contain adequate evidence that the drug has undergone nonclinical and clinical safety and effectiveness trials." The petitioners also set forth a number of factors for the agency to consider. Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995)[FDA FOIA Release: MIF 006144-6248]; *see also*, Letter, Ronald G. Chesemore, Associate Commissioner for Regulatory Affairs, FDA, to Gary L. Yingling, McKenna & Cuneo (March 20, 1995) (one-page letter suggesting that the petition was prematurely filed and claiming to be a "full response")[FDA FOIA Release: MIF 006250].

[8] The gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy. On Day 49, a woman is deemed to be seven weeks pregnant, which means she has experienced 49 days of amenorrhea (time elapsed since the beginning of her last menstrual period).

Warnings about these dangers, together with FDA's own concerns about the safety of the abortion regimen, went unheeded. On September 28, 2000, FDA approved the new drug application ("NDA") for Mifeprex.[9] The initial reports of life-threatening and fatal adverse events appear to bear out the safety concerns underlying the pre-approval warnings. The Petition highlights a number of agency actions that were arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with the law. These serious departures from standard agency practice allowed the NDA for Mifeprex, a drug that is not safe for its intended use, to be approved by FDA.[10]

First, the approval of Mifeprex violated the legal requirements of FDA's Accelerated Approval Regulations found in Subpart H.[11] Mifeprex is not a drug for the treatment of a serious or life-threatening illness. It does not demonstrate the potential to address an unmet medical need because a less dangerous and more effective alternative for performing abortions already exists. It appears that FDA's decision to use Subpart H was motivated by its concern that, without restrictions, the drug could not be used safely. Rather than attempting to compensate for

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Ovulation for the small percentage of woman with a perfect 28 day cycle typically takes place between Days 12 and 14 and fertilization typically takes place 24 to 48 hours later.

[9] *See* U.S. Department of Health and Human Services, *HHS News*, Press Release P00-19, "FDA Approves Mifepristone for the Termination of Early Pregnancy," September 28, 2000. A selection of FDA documents relevant to its approval of Mifeprex may found at: <http://www.fda.gov/cder/drug/infopage/mifepristone>; and on a second page: <http://www.fda.gov/cder/foi/nda/2000/20687_mifepristone.htm>.

[10] FDA's unlawful approval of Mifeprex may not be unprecedented. The medical-scientific community and the mainstream press have called attention to a number of other instances in which one could question whether drugs and medical devices have been improperly approved. *See, e.g.*, Richard Horton, "Lotronex and the FDA: A Fatal Erosion of Integrity," *Lancet* 357 (May 19, 2001): 1544-1545; David Willman, "How a New Policy Led to Seven Deadly Drugs," *Los Angeles Times* (Dec. 20, 2000): at A1; Kit R. Roane, "Replacement Parts: How the FDA Allows Faulty, and Sometimes Dangerous, Medical Devices onto the Market," *U.S. News & World Report* (July 29, 2002): 54-59 (discussing FDA's recent approval policies regarding medical devices).

[11] 21 C.F.R. §§ 314.500-314.560. FDA's Accelerated Approval Regulations are set forth at 21 C.F.R. Part 314, Subpart H ("Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses") ("Accelerated Approval Regulations" or "Subpart H"). The Accelerated Approval Regulations were promulgated by FDA after notice and comment: New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234 (April 15, 1992) ("*Subpart H Proposed Rule*") and New Drug, Antibiotic, and Biological

the inherent dangerousness of Mifeprex by inappropriately resorting to the Subpart H approval mechanism, FDA should simply have refused to approve Mifeprex. (*See* Section III.D., *infra*.)

Second, Mifeprex was not proven to be "safe and effective" as required by law.[12] The scientific quality of the trials used to support the NDA was undeniably deficient according to Congress's statutory requirements and FDA's well-established standards.[13] The trials were not blinded, randomized, or concurrently controlled. FDA failed to explicitly waive its rules or offer a reasoned explanation for defying its own standards. (*See* Section III.E., *infra*.)

Third, the Mifeprex Regimen requires that Mifeprex be used in conjunction with another drug, misoprostol. FDA, however, has never approved misoprostol as an abortifacient. Although FDA normally opposes the promotion of off-label uses, in connection with the Mifeprex NDA, the agency sanctioned and itself participated in the promotion of the off-label use of misoprostol. Mifeprex, the label of which creates the false impression that misoprostol is approved for use as an abortifacient, is misbranded. (*See* Section III.F., *infra*.)

Fourth, and most critically, the Mifeprex Regimen is dangerous. FDA sought, without success, to convince the drug sponsor to place safety restrictions on Mifeprex. When that failed, on June 1, 2000, FDA itself proposed restrictions intended to reduce the unacceptable health risks associated with mifepristone abortions. Nevertheless, the agency, under concerted pressure from abortion advocates and politicians, ultimately approved mifepristone for use in a deregulated regimen that lacks key safeguards. For example, the regimen does not include a requirement that transvaginal ultrasound be used to date pregnancies and rule out ectopic

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Product Regulations; Accelerated Approval, *Final Rule*, 57 Fed. Reg. 58942 (Dec. 11, 1992) ("*Subpart H Final Rule*") (available at: <http://www.fda.gov/cder/fedreg/fr19921211.txt>).

[12] *See* 21 U.S.C. § 355.

[13] *See* 21 C.F.R. § 314.126.

pregnancies, which cannot be treated with the Mifeprex Regimen. In addition, FDA failed to restrict access to mifepristone to physicians trained in the provision of Mifeprex and surgical abortions and capable of treating complications arising from abortions. Concerns about the dangers of Mifeprex were confirmed when Danco and FDA announced publicly on April 17, 2002, a number of serious adverse events, including two deaths. (*See* Section III.G., *infra*.)

Fifth, the drug's sponsor has neglected to require Mifeprex providers to adhere to the limited restrictions contained in the approved regimen. The sponsor's inaction is surprising in light of the fact that these restrictions are being flouted openly. Section 314.530 authorizes FDA to withdraw the approval of a Subpart H drug if a drug's sponsor does not fulfill its responsibility of ensuring compliance with the restrictions on the use of the drug. (*See* Section III.H., *infra*.)

Sixth, the safeguards employed in the U.S. Clinical Trial are not mirrored in the regimen that FDA approved. Transvaginal ultrasounds, for example, although employed in the U.S. Clinical Trial, are not required under FDA's approved regimen. Nor are the trial requirements governing emergency care reproduced in the approved regimen. (*See* Section III.I., *infra*.)

Seventh, FDA's waiver of its rule, 21 C.F.R. § 314.55, requiring the testing of all new drugs for their potential effects on children, has jeopardized the health and safety of American teenage girls who may have abortions. FDA expressly contemplated the pediatric use of Mifeprex, but waived, without an adequately reasoned justification, the requirement that the drug undergo pediatric testing. (*See* Section III.J., *infra*.)

Eighth, FDA did not require the sponsor of Mifeprex to honor its commitments for Phase IV studies, which provide the opportunity to study in-depth the drug's safety and effectiveness after approval. When FDA approved Mifeprex, the agency permitted the Population Council to replace the six Phase IV study commitments it had made in 1996 with two much narrower

commitments. The modified studies will not adequately address outstanding questions, such as the effects of mifepristone abortions on women outside the tested age range of 18 to 35 years. (*See* Section III.K., *infra*.)

In sum, FDA, in approving Mifeprex, acted in a manner inconsistent with its statutory authorization, regulations, and well-established policies. FDA did not provide a contemporaneous explanation of its numerous departures from past practice.[14] Its aberrant actions coupled with the absence of explanations violated a fundamental principle of administrative law; an agency must either adhere to prior policies or fully explain why it is not doing so.[15] The approval of Mifeprex was, therefore, arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. It must be reversed.

B. FDA APPROVAL OF THE MIFEPREX REGIMEN

1. The Introduction of Mifepristone into the United States

Roussel Uclaf, a French pharmaceutical firm, first developed and tested mifepristone ("RU-486") as an abortifacient. By April 1990 the drug had become permanently available in

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[14] An agency must explain its reasons for acting in a particular manner. *See, e.g., Securities & Exchange Commission v. Chenery Corp.*, 332 U.S. 194, 196-97 (1947) (noting that a court should not "be compelled to guess at the theory underlying the agency's action," but rather "[i]f the administrative action is to be tested by the basis upon which it purports to rest, that basis must be set forth with such clarity as to be understandable."). *Post hoc* rationalizations cannot salvage the agency's action with respect to Mifeprex. *See, e.g., Martin v. Occupational Safety and Health Review Commission*, 499 U.S. 144, 156-57 (1991) (*post hoc* rationalizations of counsel "do not constitute an exercise of the agency's delegated lawmaking powers"); *Investment Company Institute v. Camp*, 401 U.S. 617, 628 (1971) ("Congress has delegated to the administrative official and not to appellate counsel the responsibility for elaborating and enforcing statutory commands.").

[15] *See, e.g., Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970) ("[A]n agency changing its course must supply a reasoned analysis indicating that prior policies and standards are being deliberately changed, not casually ignored, and if an agency glosses over or swerves from prior precedents without discussion it may cross the line from the tolerably terse to the intolerably mute.") (footnote omitted) (citing approvingly *Motor Vehicle Manufacturers Ass'n v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 57 (1983)); *JSG Trading Corp. v. USDA*, 176 F.3d 535, 544 and 545 (D.C. Cir. 1999) (remanding agency action where "the agency manifestly failed to explain its abrupt departure from prior precedent" and noting that the agency "was obligated to articulate a principled rationale for departing from [its prior] test") (citations omitted); *Gilbert v. National Labor Relations Board*, 56 F.3d 1438, 1445 (D.C. Cir. 1995) ("It is, of course, elementary that an agency must conform to its prior decisions or explain the reason for its departure from such precedent.").

France. According to Dr. André Ulmann, the Roussel project manager for the development of RU-486, Roussel prohibited the commencement of any new studies in the United States and took the position that "under no circumstance[s]" would it permit a new drug application to be filed with FDA.[16] In fact, "the chairman of Hoechst [the parent company to Roussel] had officially declared that mifepristone was not compatible with the ethics of the company."[17]

Undeterred by Hoechst's reluctance to bring the drug to the United States, on January 22, 1993, President Clinton directed Department of Health and Human Services ("HHS") Secretary Donna Shalala to assess initiatives to promote the testing and licensing of mifepristone or other antiprogestins in the United States.[18] Further signaling that approval of mifepristone by FDA was a top priority of his Administration, President Clinton reportedly "wrote to Hoechst asking the company to file a new drug application with the FDA (an unprecedented situation in the pharmaceutical industry!), which Hoechst intransigently refused to do."[19]

In early 1993, Secretary Shalala and FDA Commissioner David Kessler "communicated with senior Roussel Uclaf officials to begin efforts to pave the way for bringing RU-486 into the American marketplace."[20] On May 16, 1994, the Population Council reached an agreement with Roussel Uclaf, pursuant to which the European drug maker transferred "without remuneration,

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[16] *See* André Ulmann, M.D., "The Development of Mifepristone: A Pharmaceutical Drama in Three Acts," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 117-20, at 119. In 1994 Roussel Uclaf joined with the German pharmaceutical firm, Hoechst AG, to form Hoechst Roussel Ltd. In 1995, this entity merged with a third firm, Marion Merrell Dow, to form Hoechst Marion Roussel. In December 1999 Hoechst and Rhône-Poulenc combined to form Aventis, S.A., headquartered in Strasbourg, France.

[17] Ulmann, *infra* Appendix A, at 120.

[18] *See* Memorandum for the Secretary of Health and Human Services, "Importation of RU-486," *Public Papers of the Presidents: Administration of William J. Clinton, 1993* (Jan. 22, 1993) at 11.

[19] Ulmann, *infra* Appendix A, at 120 (emphasis in original).

[20] HHS Fact Sheet, "Mifepristone (RU-486): Brief Overview," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

its United States patent rights for mifepristone (RU-486) to the Population Council . . . ."[21] Secretary Shalala was instrumental in bringing about the transfer of the patent rights to the Population Council[22] and even set a deadline – May 15, 1994 – for the transfer.[23]

After obtaining the American patent rights to mifepristone, the Population Council conducted clinical trials in the United States and filed a new drug application in 1996. The Population Council established a non-profit corporation, American Health Technologies ("AHT"), to assist in the effort to bring the drug to the market.[24] The Population Council ultimately granted Danco Laboratories, LLC ("Danco"), which was incorporated in the Cayman Islands in 1995, "an exclusive license to manufacture, market, and distribute Mifeprex in the United States."[25] Danco, after a difficult search,[26] selected the Chinese drug manufacturer,

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[21] HHS Press Release, "Roussel Uclaf Donates U.S. Patent Rights for RU-486 to Population Council," (rel. May 16, 1994). Available at: <http://www.hhs.gov/news/press/pre1995pres/940516.txt>.

[22] *Id.* ("Shalala commended Roussel Uclaf and the Population Council for coming to closure after months of complex negotiations amid repeated urging from the Clinton administration.")

[23] *See* William J. Eaton, "Path Cleared for Abortion Pill Use Medicine: French Maker of RU-486 Gives Patent Rights to a Nonprofit Group," *Los Angeles Times*, May 17, 1994, at A1 ("Negotiations between the French manufacturer and the Population Council dragged on for more than a year until Shalala set a May 15 deadline, producing the agreement . . . .").

[24] Dr. Susan Allen, who once served as president and CEO of American Health Technologies, joined the staff of the Reproductive and Urologic Drug Products Division in FDA's Center for Drug Evaluation and Research in 1998 as a medical officer and was promoted to team leader for reproductive drugs in January 1999. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14. Dr. Allen became acting director of the Division in January 2000 and permanent director on June 18, 2000. *See id. The Pink Sheet* also commented, "Allen is presumably recused from the mifepristone review as a result of her prior experience with the product." *Id.*

[25] Danco, "The History of Mifeprex,"available at <http://www.earlyoptionpill.com/history.php3>. (Danco has dubbed mifepristone "the Early Option Pill" for marketing purposes.) Little information about Danco is available. *See* Robert O'Harrow, "RU-486 Marketer Remains Elusive," *Washington Post* (Oct. 12, 2000): at A18 ("Secretive and obscure, Danco is one of the most enigmatic companies in the pharmaceutical industry."). Danco is apparently a successor entity to Advanced Health Technology. *See* "RU-486 Action Date Is Sept. 30; Allen Named Reproductive Division Director," *The Pink Sheet* 62 (June 12, 2000): at 14 (reporting that Advanced Health Technologies had become Neogen, which, in turn, had become Danco, according to the Population Council and Danco, "with some management and investor changes").

[26] In 1995 Danco contracted with a Hungarian pharmaceutical firm, Gideon Richter, to manufacture mifepristone for American distribution. After Gideon Richter reneged on the contract in February 1997, Danco sued Gideon Richter for breach of contract and began searching for a new producer. *See* "Ru-486: U.S. Partners Sue European Manufacturer," *Kaiser Daily Reproductive Health Report* (June 12, 1997) (available at: <http://www.kaisernetwork.org/reports/1997/06/a970612.1.html>). This was one of a number of lawsuits stemming

Shanghai Hua Lin Pharmaceutical Company, to manufacture the drug.[27] Abortion advocates eagerly awaited the approval of mifepristone in the United States because, among other reasons, they anticipated that it would enhance women's access to abortion.[28]

2. FDA Approval of Mifepristone

The Population Council filed a new drug application for "mifepristone 200 mg tablets" on March 18, 1996.[29] FDA initially accorded the drug standard review, but in a letter dated May 7, 1996, FDA's Center for Drug Evaluation and Research notified the Population Council that mifepristone would receive priority review.[30] On September 18, 1996, FDA issued a letter

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from attempts to bring mifepristone to the United States. *See* "Ru-486: Litigation Could Cause Delay For U.S. Introduction," *Kaiser Daily Reproductive Health Report* (Dec. 17, 1996) (available at: <http://www.kaisernetwork.org/reports/1996/12/a961217.9.html>) (describing some of the legal problems encountered by the Population Council in bringing the drug to market).

[27] Pamela Wiley, "Chinese Plant to Make RU-486 for U.S.," (Oct. 15, 2000) (available at: <http://www.nurseweek.com/news/00-10/1015-486.asp>).

[28] *See* Margaret Talbot, "The Little White Bombshell," *New York Times Magazine* (July 11, 1999): at 39-43 ("'One of my real, and I think realistic, hopes for this method,' says Carolyn Westhoff, an OB-GYN at Columbia University medical school who offers medical abortion as part of a clinical trial, 'is that it will help get abortion back into the medical mainstream and out of this ghettoized place it's been in.' And if that is indeed the scenario we're looking at – a scenario in which abortion is folded far more seamlessly into regular medical practice – then it has implications not only for women's experience of abortion but for the politics of abortion as well."); *id.* ("Not only are mifepristone abortions, by nature, more discreet than their surgical equivalents (like vacuum aspiration), but the practitioners who prescribe them will almost certainly constitute a larger and a more varied group than the dwindling corps of OB-GYNs willing to do surgical abortions.") In fact, access to medical abortion, will continue to depend on the availability of surgical abortion, which serves as a back-up in FDA's approved Mifeprex regimen. Thus, it is spurious to suggest that Mifprex abortions can safely be made available in places in which surgical abortion is not offered.

[29] The application was dated March 14, 1996 and received by FDA on March 18, 1996. *See* Letter, FDA/CDER to Ann Robbins, Population Council (Sept. 18, 1996): at 1 ("1996 Mifepristone Approvable Letter").

[30] *See* Letter, FDA/CDER to Ann Robins, Population Council (May 7, 1996)[FDA FOIA Release: MIF 006431]. The Population Council filed its complete response on March 30, 2000, which gave FDA until September 30, 2000 to act on the application. In fiscal year 2000 a "standard" designation would have given FDA at least ten months to consider the application. FDA accorded mifepristone "priority review," which typically required FDA to act within six months. *See* FDA/CDER, "PDUFA Reauthorization Performance Goals and Procedures" (Nov. 16, 1997) (available at: <http://www.fda.gov/cder/news/pdufagoals.htm>) ("Fiscal Year 2000"). Of 98 approvals in 2000, only 20 were Priority Review drugs. *See* FDA/CDER, *Report to the Nation* (2000): at 6. FDA's use of priority review appears inappropriate when considered in light of the agency's current guidance on the issue, which states that priority review is appropriate when "[t]he drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease." *See* FDA/CDER, "Review Management: Priority Review Policy," Manual of Policies and Procedures (MAPP) 6020.3, at 1 (Apr. 22, 1996) (text bracketed as in original).

stating that the application was approvable and requested more information from the sponsor.[31] FDA issued a second approvable letter for mifepristone, dated February 18, 2000, setting forth the remaining prerequisites for approval.[32] The 2000 Mifepristone Approvable Letter announced that FDA had "considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and [had] concluded that restrictions as per [21] CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[33]

On September 28, 2000, FDA approved mifepristone ("Mifeprex™") "for the medical termination of intrauterine pregnancies through 49 days' pregnancy."[34] Mifeprex was approved under Subpart H, which, FDA explained, "applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with certain skills or experience."[35] The approved regimen requires at least three office visits.[36] FDA required the Population Council to include, on the Mifeprex Label, a "black box warning for special problems, particularly those that may lead to death or serious injury."[37]

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[31] 1996 Mifepristone Approvable Letter at 1.

[32] 2000 Mifepristone Approvable Letter at 1.

[33] 2000 Mifepristone Approvable Letter at 5.

[34] Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 1 ("Mifeprex Approval Letter"). In conjunction with the Mifeprex Approval Letter, FDA issued a memorandum that expanded upon the basis for and the restrictions on the approval of Mifeprex. *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 6 ("Mifeprex Approval Memo").

[35] Mifeprex Approval Memo at 6.

[36] Pursuant to the approved regimen, on "Day One: Mifeprex Administration" the patient reads the Medication Guide, signs the Patient Agreement, and ingests 600 mg of Mifeprex; on "Day Three: Misoprostol Administration" the patient ingests 400 micrograms of misoprostol orally (unless abortion has occurred and been confirmed by clinical examination or ultrasonographic scan); and, on or about "Day 14: Post-Treatment Examination" the patient returns to the practitioner for verification through a clinical examination or ultrasound that the pregnancy has been successfully terminated. *See* Mifeprex Label ("Dosage and Administration")(available at: <http://www.fda.gov/cder/foi/label/2000/20687lbl.pdf>).

[37] Mifeprex Approval Memo at 2 (citing 21 CFR 201.57(e), which authorizes FDA to require such a warning). The terms "label," "labeling," and "package insert" are often used interchangeably in food and drug law literature. In this Petition, "Label" describes the fine-print "package insert" that accompanies a drug when it is purchased. However, the FD&C Act defines "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." 21 U.S.C. § 321(k). The term "labeling," which will also appears in this Petition,

FDA also outlined the Population Council's post-approval, Phase IV study commitments[38] and waived, without explanation, FDA's regulations providing that all new drugs must be tested for safety and effectiveness in children.[39]

C. BACKGROUND ON FDA'S DRUG APPROVAL PROCESS

1. FDA's Default Rules for Establishing Drug Safety and Effectiveness

FDA's regulations state that "[t]he purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation."[40] FDA's default criteria for establishing safety and effectiveness are commonly referred to as the agency's "gold standard."[41] At the core of this default standard is FDA's recognition, reflecting the development of the scientific method and its application to pharmacology, that human bias and misperceptions are pervasive and that every precaution must be taken to avoid them. "The history of experimental medicine and research psychology," Michael Greenberg writes, "had demonstrated that uncontrolled, unblinded clinical trials were systematically vulnerable to experimenter bias, placebo effects, and the like."[42] Consequently, rigorous policies have been set forth by FDA and,

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encompasses "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m). "Labeling" may even describe promotional materials used by the drug manufacturer including "[b]rochures, booklets, mailing pieces, . . . price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, . . . and reprints and similar pieces of printed, audio or visual matter descriptive of a drug and references published (for example, the Physician's Desk Reference) for use by medical practitioners, pharmacists, or nurses . . . ." 21 C.F.R. § 202.1(l)(2). FDA has provided more information on this terminology at: <http://www.fda.gov/cder/handbook/adverdef.htm>.

[38] *See* Mifeprex Approval Memo at 7.

[39] *See* FDA Mifeprex Approval Letter at 3.

[40] 21 C.F.R. § 314.126(a).

[41] *See* Jennifer Kulynych, "Will FDA Relinquish the 'Gold Standard' for New Drug Approval? Redefining 'Substantial Evidence' in the FDA Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 127-149, at 129. We will refer to these criteria as the "default standard."

[42] Michael D. Greenberg, "AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process," *Legislation and Public Policy* 3 (2000): 295-350, at 308.

more recently, by the International Conference on Harmonisation ("ICH") to eliminate bias from the evaluation of drug safety and effectiveness.[43]

FDA has been criticized for its zealous implementation of this policy,[44] but there is widespread recognition of the value of the default standard. The 1962 statutory amendments to the FD&C Act "authorized the agency to review all NDAs, not only to assess drug safety, but also to determine whether a manufacturer has provided 'substantial evidence' from 'adequate and well-controlled investigations' that a drug is effective for its intended use."[45] In implementing regulations, FDA "required that the evidence include at least one (and usually two) well-controlled (preferably 'blind') trials showing statistically significant results for treatment of humans with the new drug."[46] "[B]arring unusual circumstances, the agency ordinarily requires two successful and well-controlled clinical trials for new drug approval."[47] FDA's mandate for clinical trials "has two very important elements:"

> (1) a "controlled" trial, in which an experimental drug is compared to a placebo, or a known effective treatment in order to establish the comparative efficacy of the drug, and (2) a "double-blind" trial, which involves random assignment of research subjects to the

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[43] FDA, "International Conference on Harmonisation; Guidance on General Considerations for Clinical Trials," *Notice*, 62 Fed. Reg. 66113 (Dec. 17, 1997) (*FDA Guidance (ICH: E8): General Considerations*). The homepage, (www.ich.org), for the ICH describes the organization as follows: "The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health."

[44] *See, e.g.*, Henry I. Miller, "Failed FDA Reform," *Regulation* 21 (Summer 1998): 24-30.

[45] Kulynych, *infra* Appendix A, at 129 (citing 21 U.S.C. § 355(d)).

[46] Greenberg, *infra* Appendix A, at 307 (citing 21 C.F.R. § 314.126 (1999). FDA comprehensively revised NDA evaluation rules in what is commonly referred to as the "NDA Rewrite." *See Final Rule*, "New Drug and Antibiotic Regulations," 50 Fed. Reg. 7452 (Feb. 22, 1985). Section 314.126 was promulgated in that final rule. *Id.* at 7506-7.

[47] Kulynych, *infra* Appendix A, at 130.

experimental and control groups, under conditions in which neither the doctors nor the research subjects know who is getting the experimental drug and who the control.[48]

Each of the mandated features helps to eliminate bias in trial results. First, in "double-blinded" studies neither the patient nor the provider team (physician, nurse, etc.) knows the identity of the drug administered. If that is not possible, the person evaluating the trial results will not know which treatment has been administered to which subject. Second, a "randomized" study requires a random determination of which subject receives which treatment. This determination is often effected through computer-generated assignments done before clinical testing begins. Finally, comparison-control (also known as "comparator-control") requires that the experimental drug be compared *concurrently* to the current best treatment, or, alternatively, to a placebo. A placebo is used when the drug being tested represents the first treatment of its kind for the particular indication and no established treatment exists.

2. FDA Initiatives to Expedite the Approval of Drugs for the Very Sick

Largely in response to FDA's perceived slowness in approving drugs for human immunodeficiency virus ("HIV") patients, the agency undertook several initiatives to either expedite the ability of seriously or terminally-ill patients to have access to experimental drugs or to provide processes "intended to move drugs to market more quickly by compressing clinical development and FDA review times."[49] In 1988, FDA adopted an interim rule establishing Subpart E of 21 C.F.R. Part 312 ("Drugs Intended to Treat Life-Threatening and Severely-

[48] Greenberg, *infra* Appendix A, at 307-8 (footnotes omitted).

[49] Sheila R. Shulman and Jeffrey S. Brown, "The Food and Drug Administration's Early Access and Fast-Track Approval Initiatives: How Have They Worked?" *Food and Drug Law Journal* 50 (1995): 503-531, at 503-4.

Debilitating Diseases").[50] Subpart E embodied several of the new procedures that FDA had used to bring the HIV medication, AZT (zidovudine), to market quickly.[51] Subpart E also created a "collaborative framework in which early and repeated consultation between the FDA and pharmaceutical manufacturers served to facilitate clinical trials, and to insure ex ante that prospective research designs would meet with subsequent regulatory approval."[52] "Taken together," the innovations found in Subpart E, "served to radically alter the new drug approval process with regard to life-threatening illnesses, particularly for AIDS."[53]

On April 15, 1992, FDA took its procedural innovations further when it proposed an "Accelerated Approval" process (*i.e.*, Subpart H). Shulman and Brown believe that Subpart H "represent[ed] the most significant departure from the traditional FDA standards for drug approval."[54] Subpart H's "major point of departure" from previously existing approval regimes was its focus on granting drug approval "on the basis of the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit over time."[55] A "surrogate end point" or "surrogate marker" is "a laboratory parameter or physical sign that is used in a clinical trial as a substitute for a clinically meaningful end point, such as mortality."[56] The value of surrogate

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[50] *See Interim Rule*, "Investigational New Drug, Antibiotic, and Biological Drug Product Regulations; Procedures for Drugs Intended To Treat Life-Threatening and Severely Debilitating Illnesses," 53 Fed. Reg. 41,516 (Oct. 21, 1988). The Subpart E rules may be found at 21 C.F.R. §§ 312.80-88.

[51] *See* Greenberg, *infra* Appendix A, at 321.

[52] Greenberg, *infra* Appendix A, at 321 (citation omitted).

[53] Greenberg, *infra* Appendix A, at 323.

[54] Shulman and Brown, *infra* Appendix A, at 514.

[55] Shulman and Brown, *infra* Appendix A, at 514. Likewise, Greenberg observed that the "essential element of the accelerated approval regulations [*i.e.*, Subpart H] was the provision that 'surrogate endpoints' could be employed as the empirical basis for FDA approval of a new drug." Greenberg, *infra* Appendix A, at 323 (citation omitted).

[56] Dennis F. Thompson, "Surrogate End Points, Skepticism, and the CAST Study," editorial, *Annals of Pharmacotherapy*, 36 (Jan. 2002): 170-71, at 170 (citations omitted).

endpoints lies in their ability to predict clinical outcomes.[57] As "examples of surrogate end points that have been proven to be excellent predictors of clinical outcomes and, hence, have saved both money and precious time expediting drugs to the patient care arena," Dean Dennis Thompson cites "a diverse group of antihypertensive drugs approved on the basis of reduced blood pressure effects [that] has shown clear benefits in reducing cardiovascular events and mortality."[58] With the passage of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Congress effectively codified Section 314.510, the surrogate endpoint provision of Subpart H.[59]

Neither Shulman and Brown nor Greenberg focused on a second type of drug approval included in Subpart H – codified now at 21 C.F.R. § 314.520.[60] This second avenue for Subpart H approval is reserved for circumstances in which "FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted."[61] Pursuant to this provision "FDA may approve a treatment subject to special

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[57] *See* Thompson, *infra* Appendix A, at 170.

[58] Thompson, *infra* Appendix A, at 170.

[59] This codification was part of Congress's major reauthorization and modernization of the Federal Food, Drug & Cosmetic Act. Section 506(b) of FDAMA (21 U.S.C. § 356) "in effect, codifie[d] in statute FDA's Accelerated Approval Rule . . . , made final in 1992, which allows expedited marketing of certain new drugs or biological products intended to treat serious or life-threatening illnesses and that appear to provide meaningful therapeutic benefits to patients compared with existing treatments." FDA Centers for Drug Evaluation and Research and for Biologics Evaluation and Research, *Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review*, at 2 (Sept. 1998) (footnote omitted). While clearly codifying Subpart H's surrogate endpoint provision at 21 U.S.C. § 356(b)(1), Congress does not appear to have enacted a parallel provision to Section 314.520, which pertains to "restricted use" drugs, under which Mifeprex was approved.

[60] Section 314.520 (Approval with restrictions to ensure safe use.) states:

> (a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the drug product, such as:
> (1) Distribution restricted to certain facilities or physicians with special training or experience; or
> (2) Distribution conditioned on the performance of specified medical procedures.
> (b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

[61] *Subpart H Final Rule*, 57 Fed. Reg. at 58942.

distribution or use restrictions that address outstanding safety issues."[62] Section 314.520 balanced FDA's desire to bring clinically beneficial drugs to the market with the agency's concern that "[s]ome drugs, however, are so inherently toxic or otherwise potentially harmful that it is difficult to justify their unrestricted use."[63] The agency explained "that some clinically beneficial drugs can be used safely only if distribution and use are modified and restricted."[64]

Section 314.520 is intended for drugs that are vitally necessary, but which may impose greater than normal risks for the patient.[65] FDA was willing "to approve such high risk drugs for early marketing if the agency can be assured that postmarketing restrictions will be in place to counterbalance the known safety concerns."[66] Postmarketing restrictions would be designed "to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction."[67] FDA intended to employ restrictions on distribution "only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will *not* assure the product's safe use."[68] In the absence of restrictions, which "may vary with the circumstances of each drug[,] . . . the drug would be adulterated under Section 501 of the act, misbranded under Section 502 of the act, or not shown to be safe under Section 505 of the act."[69] In short, "[w]ithout such restrictions, the drugs would not meet the statutory criteria,

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[62] Geoffrey M. Levitt, James N. Czaban, and Andrea S. Paterson, "Chapter 6: Human Drug Regulation" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 200.

[63] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[64] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[65] Of course, "[v]irtually all drug[s] can be toxic to humans, and no drug is completely free of risk," but, as the seriousness of an illness and the effect of the drug on that illness increase, "the greater the acceptable risk from the drug." *Subpart H Proposed Rule*, 57 Fed. Reg. at 13236.

[66] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

[67] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[68] *Subpart H Final Rule*, 57 Fed. Reg. at 58952 (emphasis added).

[69] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13237.

could not be approved for distribution, and would not be available for prescribing or dispensing."[70] Mifeprex was the third of four drugs approved pursuant to Section 314.520.[71]

D. FDA'S APPROVAL OF MIFEPREX UNDER ITS ACCELERATED APPROVAL REGULATIONS (SUBPART H) WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

FDA's accelerated approval regulations (Subpart H) apply to certain new drug products "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)"[72] When it proposed Subpart H in 1992, FDA observed that the following types of illness would fall within the reach of Subpart H:

> The terms "serious" and "life-threatening" would be used as FDA has defined them in the past. The seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Thus, acquired immunodeficiency syndrome (AIDS), all other stages of human immunodeficiency virus (HIV) infection, Alzheimer's dementia, angina pectoris, heart failure, cancer, and many other diseases are clearly serious in their full manifestations. Further, many chronic illnesses that are generally well-managed by available therapy can have serious outcomes. For example, inflammatory bowel disease,

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[70] *Subpart H Final Rule*, 57 Fed. Reg. at 58951. The agency continued: "The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing." *Id.* at 58951-52.

[71] On June 7, 2002, the drug Lotronex (alosetron hydrochloride) was reintroduced to the market after a *Supplemental* NDA was approved pursuant to Subpart H's redistricted distribution provision. *See* Letter, FDA/CDER, Florence Houn, M.D., Director, Office of Drug Evaluation III to Olivia Pinkett, Product Director, Regulatory Affairs, GlaxoSmithKline (June 7, 2002): at 1 ("This supplemental application, considered for approval under 21 CFR 314, Subpart H at your request, narrows the original approved indication to use of the drug in a population for whom the benefits of the drug may outweigh the risks and provides for a risk management program. . . . You have indicated your agreement with approval under restricted conditions.").

[72] 21 C.F.R. § 314.500. The rule was amended in 1999 to remove the words "and antibiotic." *See* Conforming Regulations Regarding Removal of Section 507 of the Federal Food, Drug, and Cosmetic Act, *Final Rule*, 64 Fed. Reg. 396, 402 (Jan. 5, 1999).

> asthma, rheumatoid arthritis, diabetes mellitus, systemic lupus, erythematosus, depression, psychoses, and many other diseases can be serious for certain populations or in some or all of their phases.[73]

According to FDA, the agency has approved 38 NDAs, including the Mifeprex application, under Subpart H.[74] Of these approvals, 20 were for the treatment of HIV and HIV-related diseases, nine were for the treatment of various cancers and their symptoms, four were for severe bacterial infections, one was for erythema nodosum leprosum (leprosy), one was for hypotension, and, finally, one was for the termination of unwanted pregnancies.[75]

Pregnancy, without major complications, is not a "serious or life-threatening illness" for purposes of Subpart H. It is, rather, a normal physiological state experienced by most females one or more times during their childbearing years, and it is rarely accompanied by complications that threaten the life of the mother or the child. Following delivery, almost all women return to a normal routine without disability. Thus, pregnancy is not the kind of exceptional circumstance that falls within the scope of Subpart H. The fact that the Mifeprex Regimen is intended for healthy women provides further evidence of this point.

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[73] *Subpart H Proposed Rule*, 57 Fed. Reg. at 13235. In the *Subpart H Final Rule*, FDA asserted that "serious and life-threatening illnesses" would be readily identifiable: "FDA discussed the meaning of the terms 'serious' and 'life-threatening' in its final rules on 'treatment IND's' (52 FR 19466 at 19467, May 22, 1987) and 'subpart E' procedures (54 FR 41516 at 41518-41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every 'serious' and 'life-threatening' disease that would be within the scope of this rule. In FDA's experience with 'treatment IND's' and drugs covered by the 'subpart E' procedures there have not been problems in determining which diseases fall within the meaning of the terms 'serious' and 'life-threatening,' and FDA would expect no problems under this accelerated approval program." *Subpart H Final Rule*, 57 Fed. Reg. at 58945.

[74] These estimates are based on the version of FDA's webpage, dated February 5, 2002, listing Subpart H approvals, *infra* Appendix A.

[75] *See* FDA/CDER webpage, "NDAs Approved under Subpart H," *infra* Appendix A. A copy of the most recently available version is reproduced in Appendix C (available at: <http://www.fda.gov/cder/rdmt/accapp.htm>). *See also* "NDA Supplements Approved under Subpart H" (available at: <http://www.fda.gov/cder/rdmt/accappr1.htm>) (supplemental approvals are not included in the figures set forth in the text because they refer to FDA actions regarding drugs that have already been approved).

In fact, the Population Council argued strenuously that its application for mifepristone did not fall within the scope of Subpart H.[76] In a letter to FDA written approximately three weeks before the final approval of the mifepristone NDA, the Population Council's Sandra P. Arnold protested, ". . . it is clear that the imposition of Subpart H is unlawful, unnecessary, and undesirable. We ask FDA to reconsider."[77] Arnold argued correctly that "[n]either pregnancy nor unwanted pregnancy is an illness, and Subpart H is therefore inapplicable for that reason alone."[78] She continued, stating, "Neither is pregnancy nor unwanted pregnancy a 'serious' or 'life-threatening' situation as that term is defined in Subpart H."[79] In the next paragraph, after directly quoting the *Supbart H Final Rule*, Ms. Arnold asserted that "[t]he plain meaning of these terms does not comprehend normal, everyday occurrences such as pregnancy and unwanted pregnancy."[80] She added that, unlike HIV infection, pulmonary tuberculosis, cancer, and other illnesses, "pregnancy and unwanted pregnancy do not affect survival or day-to-day functioning as those terms are used in Subpart H."[81] She continued that, "although a pregnancy 'progresses,'" the development of a pregnancy "is hardly the same as the worsening of a disease that physicians call progression."[82]

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[76] The Population Council appears to have been concerned about getting the drug approved "without invoking the Subpart H regulatory provisions that signal 'big deal' to the pharmaceutical industry." Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 4 [FDA FOIA Release: MIF 001333-49]("Sandra Arnold Letter"). Sandra Arnold was "Vice President, Corporate Affairs" of the Population Council.

[77] Sandra Arnold Letter at 1.

[78] Sandra Arnold Letter at 1-2.

[79] Sandra Arnold Letter at 2.

[80] Sandra Arnold Letter at 2.

[81] Sandra Arnold Letter at 2.

[82] Sandra Arnold Letter at 2. Ms. Arnold also warned the agency that extending the scope of Subpart H to include pregnancy and unwanted pregnancy by exercising agency "judgment" was not defensible; the exercise of such judgment should go to whether or not "a particular disease actually is serious, not [act as] a means of stretching the meaning of serious to cover entirely new categories of non-serious situations." *Id.*

Additionally, Mifeprex fails to meet the second requirement set forth in Section 314.500 that drugs approved under Subpart H "provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy.)" As was noted above, the Mifeprex Approval Memo contends "that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H [and] [t]he meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure."[83] By defining the "therapeutic benefit" solely as the avoidance of the current standard of care's delivery mechanism, FDA effectively guarantees that a drug will satisfy this second prong of Subpart H as long as it represents a different method of therapy.[84] It does not appear that such considerations formed the basis of any other Subpart H approval.

When FDA adopted Subpart H, it cited as "readily understood illustrations of the intent of the [meaningful therapeutic benefit] requirement" an "improved response compared to available therapy" and the "ability to treat unresponsive or intolerant patients."[85] Based on these illustrations, Mifeprex does not fall within the intent of the requirement. First, there is a less dangerous, more effective alternative to Mifeprex available for the termination of pregnancies: namely, surgical abortions. Dr. Jeffrey Jensen conducted a study to compare the safety and

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[83] Mifeprex Approval Memo at 6.

[84] The view that merely making a different mode of therapy available *per se* produces a benefit is inconsistent with the position the agency has articulated elsewhere. MAPP 6020.3, which defines eligibility for FDA priority review, suggests that drug therapies are not inherently superior to non-drug therapies. Specifically, a drug may be afforded priority review if it would provide a significant improvement when compared with "marketed products . . . including non-"drug" products/therapies." *See* FDA/CDER, "Review Management: Priority Review Policy," MAPP 6020.3, at 1 (Apr. 22, 1996).

[85] *Subpart H Final Rule*, 57 Fed. Reg. at 58947.

efficacy of medical abortion with that of surgical abortion.[86] The study compared 178 patients who, as participants in the U.S. clinical trial in support of the Mifeprex NDA, underwent mifepristone/misoprostol abortions, with 199 patients who later received surgical abortions at the same clinical site. The primary procedure failed (*i.e.*, there was a subsequent surgical intervention) in 18.3 percent of the mifepristone/misoprostol patients and 4.7 percent of the surgical patients.[87] Of the mifepristone/misoprostol patients who failed their primary procedure, 12.5 percent required surgical intervention for acute bleeding, 43.8 percent for persistent bleeding, 15.6 percent for incomplete abortion, and 28.1 percent for ongoing pregnancy.[88] By contrast, the sole cause for surgical intervention among the surgical patients who failed their primary procedure was persistent bleeding.[89] In addition, mifepristone/misoprostol patients "reported significantly longer bleeding" and "significantly higher levels of pain . . . , nausea . . . , vomiting . . . , and diarrhea" than their surgical counterparts.[90]

Second, Mifeprex does not treat a subset of the female population that is unresponsive to, or intolerant of surgical abortion. To the contrary, because "medical abortion failures should be managed with surgical termination" the option for surgical abortion must be available for any Mifeprex patient.[91] As the U.S. trial conducted in support of the NDA indicated, the possibility

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[86] Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 ("Jensen Study")[FDA FOIA Release: MIF 000438-44].

[87] *See* Jensen Study, *infra* Appendix A, at 155, Table 2.

[88] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[89] *See* Jensen Study, *infra* Appendix A, at 156, Table 3.

[90] Jensen Study, *infra* Appendix A, at 156.

[91] Mifeprex Label ("Warnings").

for failure is substantial.[92] Thus, any patient who would be intolerant of surgical abortion, if such a class of patients exists, cannot use the Mifeprex Regimen.

As discussed below, FDA approved Mifeprex pursuant to Section 314.520 in order to impose safety restrictions to counteract the risks it had identified. FDA, confronted by the sponsor's refusal to establish voluntary restrictions on distribution,[93] viewed Subpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe.[94] The inappropriate application of Section 314.520 served the agency's immediate need of conditioning the drug's approval on certain safety measures. However, Mifeprex fails to satisfy the Subpart H requirements because, although it presents great risk to the user, it neither treats a serious or life-threatening illness nor provides a therapeutic benefit above existing treatments. A drug with such characteristics should not have been approved.

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[92] FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 11 (Table 1) (reporting a failure rate of 8% for pregnancies less than or equal to 49 days' duration) ("Medical Officer's Review").

[93] Early in the approval process, FDA anticipated that the Population Council would cooperate, thus obviating the need for Subpart H restrictions: "[B]ecause the applicant has voluntarily proposed a system of limited distribution, imposition of further distribution restrictions under the Agency's Subpart H regulations does not appear warranted." *See* Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62]. The voluntary restrictions placed on the drug Accutane, a drug for severe acne, illustrate that a cooperative drug sponsor may be able to obviate the need for Subpart H restrictions. Because Accutane can cause birth defects, the restrictions are designed to ensure that women taking the drug are not and do not become pregnant. The "System to Manage Accutane Related Teratogenicity™ (S.M.A.R.T.™)," controls the distribution of the drug through the issuance of yellow Accutane Qualification Stickers. These stickers are distributed to physicians who meet a number of qualifications and they, in turn, distribute them to patients, who must undergo two tests to confirm they are not pregnant and must commit to use two forms of contraception. Pharmacists may fill prescriptions for the drug only if they bear the qualification sticker, were issued within the past week, and prescribe no more than 30 days' worth of the drug. *See* Accutane Label.

[94] This interpretation of the agency's actions is supported by FDA spokeswoman Crystal Rice, who said "that outside of Subpart H, the FDA does not have another regulatory program to mandate safety restrictions on drug marketing for drugs used to treat 'serious or life-threatening illnesses'" and "that 'other agreements [or restrictions on the drug] not under Subpart H worked out between FDA and a sponsor would be essentially voluntary.'" "Danco Medical Director Explains Mifepristone's FDA Approval Not Fast-Tracked or Accelerated, Despite Media Reports," *Kaiser Daily Reproductive Health Report* (March 29, 2001) (available at: <http://report.kff.org/archive/repro/2001/3/kr010329.5.htm>).

E. THE CLINICAL TRIALS DID NOT PRESENT "SUBSTANTIAL EVIDENCE" THAT THE MIFEPREX REGIMEN IS SAFE AND EFFECTIVE

FDA's approval of the Mifeprex NDA ran counter to Congress's statutory requirements, the agency's regulations and guidance documents, and FDA's well-established standards for the quality and quantity of scientific evidence needed to support an agency finding that a new drug is safe and effective. The clinical trials submitted by the Population Council to support its NDA did not use the full set of design features FDA typically requires to produce unbiased investigations of drug safety and effectiveness. Because these trials were not blinded, randomized, or concurrently controlled, they did not establish the safety and effectiveness of the Mifeprex Regimen. Inexplicably, FDA failed to perform a statistical analysis of the data from the American trial. Furthermore, FDA's approval of Mifeprex pursuant to Subpart H compounds the deficiencies in the trials because sponsors of Subpart H drugs must demonstrate that the drug for which approval is being sought provides a "meaningful therapeutic benefit over existing therapy." Because Mifeprex was approved in reliance on French and American trials that did not compare the Mifeprex Regimen with the existing standard of care for ending pregnancies (*i.e.*, surgical abortion), the trials cannot support this Subpart H approval.

1. The Clinical Trials Underlying FDA's Approval of Mifeprex

FDA based its approval of Mifeprex on safety and effectiveness data derived from two French clinical trials ("French Clinical Trials") and one U.S. clinical trial ("U.S. Clinical Trial").[95] Neither the French Clinical Trials nor the U.S. Clinical Trial was blinded, randomized,

[95] *See* Mifeprex Approval Memo, *infra* Appendix A, at 1.

or concurrently controlled – the hallmarks of unbiased, scientific analysis generally relied upon by FDA.

a. The French Clinical Trials

The French Clinical Trials, which formed the basis for the Population Council's original NDA submission in 1996, were open-label, multi-center studies.[96] One of these trials consisted of 1,286 patients at 24 centers in France ("French Trial I").[97] The trial was limited to women who had pregnancies of no more than 49 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[98] On the first day of the procedure, the patient received 600 mg of mifepristone orally "in the presence of a study investigator."[99] Approximately 48 hours later, she returned and, unless the abortion had already taken place, ingested 400 micrograms of misoprostol "in the presence of a study investigator."[100] The patient remained under observation for four hours or more after the ingestion of misoprostol and returned for "a final assessment of the pregnancy termination procedure" eight to 15 days later.[101]

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[96] FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"), which met in July 1996 to consider the mifepristone NDA, based its conclusion primarily on the French trial along with preliminary data from the U.S. Clinical Trial. *See* FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 6, 132-33 (July 19, 1996) (*FDA Hearings Transcript*)[FDA FOIA Release: MIF 005200-90]. Committee member Dr. Mary Jo O'Sullivan asked why the Committee meeting was being held "at this time when the data is not finalized." *Id.* at 37. Dr. C. Wayne Bardin, who was responsible for overseeing the Population Council's NDA preparation, responded that "we have sufficient data . . . [f]rom the non-U.S. data to allow us to submit an application to the FDA." *Id.*

[97] *See* FDA, Statistical Review and Evaluation, at 2-4 (May 21, 1996) ("Statistical Review"). This French trial is referred to as FFR/91/486/14.

[98] *See* Statistical Review, *infra* Appendix A, at 2. "Since the ultrasound estimate of gestational age was more reliable than the patient's estimate . . . gestational age based on the ultrasound examination was used if available." *Id.* Investigators, in violation of study protocol, included some women with pregnancies of more than 49 days. *See* Statistical Review, *infra* Appendix A, at 3.

[99] *See* Statistical Review, *infra* Appendix A, at 2.

[100] *See* Statistical Review, *infra* Appendix A, at 2.

[101] *See* Statistical Review, *infra* Appendix A, at 2.

The efficacy analysis of French Trial I encompassed only 1,205 patients, while the safety analysis included all 1,286 participants.[102] The regimen resulted in "complete expulsion" in 95.4 percent of the 1,189 participants whose pregnancies were 49 days or less.[103] The rate of complete expulsion declined with increased gestational age.[104] Sixty-one women had complete expulsions before taking misoprostol.[105] Almost 86 percent of patients in French Trial I experienced at least one adverse event as a result of the procedure.[106]

The second French clinical trial ("French Trial II") enrolled 1,194 patients at 11 centers.[107] The trial was limited to women who had pregnancies of no more than 63 days' gestational age, as established by ultrasound, if available, or by the patient's estimate.[108] The regimen used in French Study II was essentially the same as that described above in connection with French Study I, except that an additional 200 micrograms of misoprostol was administered if complete expulsion did not occur within three hours after taking the initial 400 microgram dose of misoprostol.[109] Patients who received the second dose of misoprostol remained under observation for a total of five hours.[110]

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[102] *See* Statistical Review, *infra* Appendix A, at 3.

[103] *See* Statistical Review, *infra* Appendix A, at 3. Patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (2.8%), ongoing pregnancies (1.5%), and those who needed surgical procedures for bleeding (.3%) were classified as failures. *See id.* at 3 and 9 (Table 1).

[104] *See* Statistical Review, *infra* Appendix A, at 3 ("[T]here was a statistically significant . . . inverse relationship between gestational age and the success rate as the success rate generally declined with increasing gestational age.").

[105] *See* Statistical Review, *infra* Appendix A, at 3. Twenty-six of these women received misoprostol anyway, because the investigators did not realize that they had had complete abortions. *See id.*

[106] *See* Statistical Review, *infra* Appendix A, at 4.

[107] *See* Statistical Review, *infra* Appendix A, at 4-7. This French trial is designated as FF/92/486/24.

[108] *See* Statistical Review, *infra* Appendix A, at 4-5.

[109] *See* Statistical Review, *infra* Appendix A, at 5.

[110] *See* Statistical Review, *infra* Appendix A, at 5.

The efficacy analysis of French Trial II encompassed only 1,104 patients, while the safety analysis included all 1,194 participants.[111] The regimen resulted in "complete expulsion" in 92.8 percent of the participants.[112] The rate of complete expulsion declined with increased gestational age.[113] Twenty-six women had complete expulsions before taking misoprostol.[114] Almost 93 percent of patients in French Trial II experienced at least one adverse event as a result of the procedure.[115]

Among the deficiencies that characterized both French Clinical Trials was the absence of an appropriate control group. Consequently, as an FDA statistician concluded after reviewing the data from the French Clinical Trials: "In the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy."[116]

b. The U.S Clinical Trial

The U.S. Clinical Trial was carried out from September 13, 1994 to September 12, 1995 at various qualified university hospitals and clinics.[117] Patients had to satisfy a number of criteria

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[111] *See* Statistical Review, *infra* Appendix A, at 5.

[112] *See* Statistical Review, *infra* Appendix A, at 6. As in French Study I, patients for whom expulsion of the embryo was complete at the end of the process were categorized as successes, while patients with incomplete expulsions (4.0%), ongoing pregnancies (2.3%), and those who needed surgical procedures for bleeding (.9%) were classified as failures. *See id.* at 5 and 12 (Table 4).

[113] *See* Statistical Review, *infra* Appendix A, at 6.

[114] *See* Statistical Review, *infra* Appendix A, at 6.

[115] *See* Statistical Review, *infra* Appendix A, at 7.

[116] Statistical Review, *infra* Appendix A, at 7-8.

[117] *See* Medical Officer's Review, *infra* Appendix A, at 6. More specifically, the U.S. Clinical Trial consisted of "two prospective, open-label, multicenter clinical trials in the United States according to two identical protocols." Medical Officer's Review, *infra* Appendix A, at 6 and 9. In this Petition, the trials will be referred to as "the U.S. Clinical Trial," because the protocols employed were identical, the results of the two trials were analyzed jointly, and the results were published in the same article. *See* Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri

to be included in the study.[118] All patients were screened by pelvic examination and ultrasound to ensure that their pregnancies were not too advanced for the procedure.[119] On their first visit, patients took 200 mg of mifepristone orally "[i]n the presence of the investigator."[120] Patients returned 36 to 60 hours later to ingest 400 micrograms of misoprostol orally in the presence of the investigator, unless the investigator determined that the termination was already complete.[121] Following ingestion of misoprostol, patients were observed for a minimum of four hours.[122] Patients were instructed to return again 12 days later for a follow-up assessment.[123] A patient's pregnancy was terminated surgically "at any time if the investigator believed there was a threat to a woman's health (medically indicated), at a woman's request, or at the end of the study for an ongoing pregnancy or incomplete abortion."[124]

Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 ("Spitz Article") ")[FDA FOIA Release: MIF 006692-97]. The members of the FDA Advisory Committee who were still working for FDA at the time of publication received a copy of the Spitz Article. *See* Medical Officer's Review, *infra* Appendix A, at 29. Although FDA considered data from the entire U.S. Clinical Trial, it appears that the agency formally approved Mifeprex based only on the portion of the U.S. Clinical Trial data that was generated among women whose pregnancies were no more than 49 days' gestational age. *See* Mifeprex Approval Memo, *infra* Appendix A, at 1 ("The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period."). *See also* Mifeprex Label ("Clinical Studies").

[118] Among the inclusion criteria were requirements that a patient be at least 18 years old, be in good health, have an intrauterine pregnancy of no more than 63 days (confirmed by a pelvic examination *and* ultrasound), and have agreed to a surgical abortion if the mifepristone-misoprostol abortion failed. Medical Officer's Review, *infra* Appendix A, at 7-8. The study excluded women with certain health problems, such as liver, respiratory, or renal disease, cardiovascular disease, chronic hypertension, anemia, clotting problems, pelvic inflammatory disease, and ectopic pregnancies. *See id.* at 8. In addition, women who were over 35 and smoked, had IUDs, were breastfeeding, were unlikely to comply with study requirements, or who "[l]ived or worked more than one hour from the emergency care facility" were excluded. *See id.* at 8-9.

[119] *See* Medical Officer's Review, *infra* Appendix A, at 8.

[120] Medical Officer's Review, *infra* Appendix A, at 9.

[121] *See* Medical Officer's Review, *infra* Appendix A, at 9.

[122] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[123] *See* Medical Officer's Review, *infra* Appendix A, at 7.

[124] Medical Officer's Review, *infra* Appendix A, at 16.

The U.S. Clinical Trial consisted of 2,121 subjects.[125] Of these patients, 2,015 were evaluated for efficacy,[126] which "was defined as the termination of pregnancy with complete expulsion of the conceptus without the need for a surgical procedure."[127] The remaining 106 patients did not return for the third visit.[128] The mifepristone-misoprostol combination was effective in 92 percent of patients with pregnancies no greater than 49 days, 83 percent of patients with pregnancies between 50 and 56 days, and 77 percent of women with pregnancies between 57 and 63 days.[129] All 2,121 subjects were evaluated for safety.[130] Ninety-nine percent of patients experienced adverse events and most of these experienced multiple adverse events.[131] Twenty-three percent of the adverse effects experienced by each gestational age group were "severe."[132]

Finally, FDA did not conduct a statistical review of the results of the U.S. Clinical Trial. FDA's statistical reviewer explained this failure by noting that "[a] statistical evaluation of the European studies was completed previously "and "[t]he clinical results of the supporting U.S.

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[125] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[126] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[127] Medical Officer's Review, *infra* Appendix A, at 16. The failure to establish a pre-trial, statistical definition for drug efficacy was a defect in trial design.

[128] *See* Medical Officer's Review, *infra* Appendix A, at 16. It would have been appropriate to include these 106 patients in the efficacy analysis as "failures," if for no other reason than that they did not appear for all three required visits. Although "[f]or 92 of these patients, there was some information suggesting a successful outcome," *id.* at 10, there was neither definitive evidence of complete abortion nor, apparently, any information with respect to whether these women subsequently experienced any adverse effects. In fact, during their second visit, five of these 106 women were diagnosed as having continuing pregnancies. *Id.* at 10. *See also* Spitz Article, *infra* Appendix A, at 1246 ("The ultimate outcome of these pregnancies is unknown, despite our repeated attempts to contact the women.").

[129] *See* Medical Officer's Review, *infra* Appendix A, at 11 (Table 1).

[130] *See* Medical Officer's Review, *infra* Appendix A, at 10.

[131] *See* Medical Officer's Review, *infra* Appendix A, at 11.

[132] *See* Medical Officer's Review, *infra* Appendix A, at 11.

studies . . . are similar enough to the results of the European studies that, in the opinion of the medical reviewer, a statistical evaluation of the results of the U.S. studies is not required."[133]

2. Requirements for Proving Drug Safety and Effectiveness

FDA has developed a rigorous default standard for scientific demonstrations of safety and effectiveness of human drug products.[134] Section 505(d)(5) of the FD & C Act provides, in relevant part, that FDA shall refuse to approve a new drug application when "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling."[135] Section 505(d) defines "substantial evidence" to mean "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved . . . ."[136] FDA has stated that "substantial evidence" requires a showing of clinically significant evidence of effectiveness rather than mere statistical evidence of significance.[137] No such showing was made for Mifeprex, which has been demonstrated to be less effective than surgical abortion for all segments of the population.

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[133] FDA, "Statistical Comments on Amendment 024," Memorandum to File NDA 20-687 (Feb. 14, 2000). This document is available along with the agency's Statistical Review. *See* Statistical Review, *infra* Appendix A.

[134] *See* the discussion of the development and requirements of FDA's "gold standard," *supra* Section III.C.1.

[135] 21 U.S.C. § 355(d)(5).

[136] 21 U.S.C. § 355(d) ("the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.").

[137] *See Warner-Lambert Co. v. Heckler*, 787 F.2d 147, 155 (D.C. Cir. 1986) ("It is important to note that the Commissioner does not contend that the effectiveness shown must amount to a 'medical breakthrough', as ARW complains, but contends in his brief that he would be satisfied with even a modest clinical or therapeutic effect.").

Section 314.126 of FDA's rules states that "[r]eports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."[138] The rule states that a major purpose of an adequate and well-designed study is to "permit[ ] a valid comparison with a control to provide a quantitative assessment of drug effect."[139] According to Section 314.126(b), an adequate and well-controlled study serves to ensure that the subjects of the trial have the disease or condition being studied,[140] that the method of assigning patients to treatment and control groups minimizes bias (*e.g.*, using randomization),[141] and, that "[a]dequate measures are taken to minimize bias on the part of the subjects, observers, and analysts of the data" (*e.g.*, blinding).[142] The criteria that the rule establishes "have been developed over a period of years and are recognized by the scientific community as the essentials of an adequate and well-controlled clinical investigation."[143]

Agency guidance provides that FDA may approve an NDA based on only one, not two, effectiveness trials for drugs in one of the following three categories:

> 1) when effectiveness may be demonstrated adequately with existing studies of another claim or dose (e.g., approval for pediatric use on the basis of studies in adults); 2) when a controlled trial of a specific new use is supported by evidence from adequately controlled trials from related uses, dosages, or endpoints; and 3) when a single multicenter trial provides statistically convincing and clinically meaningful evidence of effectiveness, supported by confirmatory research.[144]

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[138] 21 C.F.R. § 314.126(a) ("Adequate and well-controlled studies.").

[139] 21 C.F.R. § 314.126(b)(2) (describing "placebo concurrent control," "dose-comparison concurrent control," "no treatment concurrent control," "active treatment concurrent control," and "historical control").

[140] 21 C.F.R. § 314.126(b)(3).

[141] 21 C.F.R. § 314.126(b)(4).

[142] 21 C.F.R. § 314.126(b)(5).

[143] 21 C.F.R. § 314.126(a).

[144] Kulynych, *infra* Appendix A, at 146 (citing FDA, *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) at 5-17 (*FDA Effectiveness Guidance*).

Mifepristone did not fall within any of these categories. The first and second categories were inapposite because mifepristone had not been approved for any use in any population in the United States; additionally, no evidence from adequate and well-controlled trials had ever been presented to FDA regarding any use for mifepristone. Because neither the French Clinical Trials nor the U.S. Clinical Trial was randomized, blinded,[145] or comparator-controlled, none of these trials could provide the type of data necessary for the third category either. Furthermore, these studies lacked "clear, prospectively determined clinical and statistical analytic criteria."[146]

Even though FDA takes the position elsewhere that the extent to which a trial's design controls for various types of bias "is a critical determinant of its quality and persuasiveness,"[147] neither the French Clinical Trials nor the U.S. Clinical Trial were randomized, concurrently controlled, or blinded. A control group "allow[s for] discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment."[148] Control groups also enable investigators to

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[145] Blinding is the normal method by which those who evaluate a medication's effectiveness and side effects, are kept unaware of whether they are evaluating the comparator drug (sometimes a placebo), or the new medication (or procedure) under study. If possible, the patient is also blinded and not allowed to know which treatment she is receiving ("double-blinding"). According to standard scientific and medical practice and the standards to which FDA holds pharmaceutical sponsors, all clinical research studies investigating the effects of new drugs should be subjected to an assessment by a blinded evaluator. Conducting a concurrently-controlled, randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable. There are study designs that would have also allowed for blinding. Had blinding proved too difficult to perform, the requirement could have been waived based upon a satisfactory showing by the sponsor.

[146] *FDA Effectiveness Guidance*, *infra* Appendix A, at 12.

[147] FDA, "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials," (Rockville, Md.: May 2001) at 3 (§ 1.2.1) (*FDA Guidance (ICH: E10): Choice of Control Group*). FDA's publication of "E10" is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf>.

[148] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2) (Introduction, "Purpose of Control Group").

determine "what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective."[149]

A trial that employs a concurrent control group drawn from the same population yields the most robust data. Concurrent control groups are chosen from the same population as the test group and are "treated in a defined way as part of the same trial that studies the test treatment, and over the same period of time."[150] When concurrent control groups are used, the treatment and non-treatment groups are similar in all baseline and non-treatment variables that could influence the outcome or introduce bias into the study.[151]

By contrast, in a trial using external or historical controls "the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent; i.e., there is no concurrently randomized control group."[152] FDA cautions:

> "The external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome). Use of the latter comparator is particularly treacherous (such trials are usually considered uncontrolled) because general impressions are so often inaccurate."[153]

In such a trial, "[t]he control group is thus not derived from exactly the same population as the treated population."[154] If, as is most common, the external control group is composed of "a well-documented population of patients observed at an earlier time," the trial is said to be

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[149] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[150] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2).

[151] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 3 (§ 1.2). "Bias here . . . means the systematic tendency of any aspects of the design, conduct, analysis, and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value." *Id.*

[152] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

[153] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 5 (§ 1.3.5).

[154] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1).

"historically" controlled.[155] Blinding and randomization are also not available to minimize bias when external or historical controls are used.[156]

According to FDA, the "[i]nability to control bias is the major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable."[157] A legal commentator recently cautioned courts about the scientific validity of experiments and trials that have no concurrent control.[158] She explained that "historically controlled subjects have not been subjected to exactly the same conditions as the test subjects."[159] Consequently, "one must be wary of" non-concurrently controlled studies (*i.e.*, historical, external, or uncontrolled studies) because their conclusions can be manipulated more easily than if concurrent controls are used.[160]

3. FDA's Acceptance of the French and U.S. Clinical Trial Data Violated Section 314.126(e) of the Agency's Rules

Section 314.126(e) of FDA's rules states unequivocally that "[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness."[161] The section authorizes the use of uncontrolled trials merely to present supporting evidence for controlled trials; uncontrolled trials, if they are "carefully conducted and

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[155] *See FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.1) ("but it could be a group at another institution observed contemporaneously, or even a group at the same institution but outside the study.").

[156] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.2).

[157] *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 26 (§ 2.5.2).

[158] Erica Beecher-Monas, "The Heuristics of Intellectual Due Process: A Primer for Triers of Science," *New York University Law Review* 75: 1563-1657, 1628.

[159] Beecher-Monas, *infra* Appendix A, at 1628, n.357.

[160] Beecher-Monas, *infra* Appendix A, at 1628, n.357 (" 'you can prove anything with selective controls,' so one must be wary of historical controls," Beecher-Monas quoting Jon Cohen, "Cancer Vaccines Get a Shot in the Arm," 262 Science 841, 843 (1993)).

[161] 21 C.F.R. § 314.126(e)(emphasis added).

documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug."[162]

FDA recognizes a limited role for external, historically controlled studies. The agency takes the position that "[h]istorical (external) controls can be justified in some cases, but particular care is important to minimize the likelihood of erroneous inference."[163] Similarly, Section 314.126 cautions that "[b]ecause historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent controlled populations, historical control designs are usually reserved for special circumstances."[164] FDA cites as an example, "studies of diseases with high and predictable mortality (for example, certain malignancies),"[165] in which a decision might be made to offer all trial participants a potentially effective drug. Externally controlled studies also may suffice because "the effect of the drug is self-evident (general anesthetics, drug metabolism)."[166]

The French and U.S. Clinical Trials, which did not employ either external or historical control groups, were uncontrolled. During the Advisory Committee Hearings, FDA's Dr. Ridgley C. Bennett, who summarized the data from the French Clinical Trials, stated:

> There are very few studies comparing medical methods and vacuum aspiration for termination of early pregnancy. To date, no large randomized controlled trials have compared mifepristone plus misoprostol with suction curettage abortion. However, large published series have demonstrated morbidity rates associated with mifepristone plus prostaglandin to be similar to those of suction-curettage.[167]

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[162] 21 C.F.R. § 314.126(e).

[163] *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.2.2.2). According to FDA guidance, the "main advantage" of an externally controlled trial "is that all patients can receive a promising drug, making the study more attractive to patients and physicians." *FDA Guidance (ICH: E10): Choice of Control Group, infra* Appendix A, at 27 (§ 2.5.6).

[164] 21 C.F.R. § 314.126(b)(2)(v) ("Historical control.").

[165] 21 C.F.R. § 314.126(b)(2)(v).

[166] 21 C.F.R. § 314.126(b)(2)(v).

[167] FDA Hearings Transcript, *infra* Appendix A, at 130. Jensen and his fellow researchers conducted "[a] prospective, noncurrent, single center cohort comparison." *See* Jensen Study, *infra* Appendix A, at 153. The study

"Published series" and uncontrolled studies cannot serve as a substitute for the well-controlled clinical trials that FDA requires. A concurrent control group would have been feasible because the trial participants were prepared to receive surgical abortion in the event of a failed mifepristone abortion.

The unusual circumstances that sometimes justify relying on externally controlled trials are not applicable with respect to pregnancy termination, generally, or the termination using mifepristone and misoprostol, specifically. Randomized, concurrently-controlled, blinded trials would have allowed investigators to compare not only the relative rates of complete termination and expulsion, but also the nature, intensity, and duration of the numerous side effects. In the absence of concurrent controls and blinding, the duration and intensity of cramping, nausea, bleeding, pain, and any emotional or psychological effects of the treatments would be subject to investigator and patient bias. The design of the U.S. Clinical Trial precluded unbiased comparison groups that could have helped analysts arrive "at a complete understanding of potential advantages, disadvantages and differences" between medical and surgical abortion.[168] FDA's *de facto* waiver of Section 314.126(e) constituted a gross departure from its past practice and announced standards for the conduct of adequate and well-controlled clinical trials.[169]

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compared the data from Mifeprex patients at one of the sites that participated in the U.S. Clinical Trial with data from patients who subsequently underwent surgical abortions at the same site. Although the methodological quality of this study is arguably superior to either the French or U.S. Clinical Trials, had it been offered as trial data it also would have been a weak substitute for a randomized controlled trial establishing equivalent or superior efficacy to surgical abortion.

[168] *See* Jensen Study, *infra* Appendix A, at 156. Dr. Cassandra Henderson, a member of the FDA Advisory Committee, wondered about this point as well: "Since this regimen is not without any side effects and we know that spontaneous abortion is not an infrequent occurrence, is it appropriate to use historical controls in trying to evaluate the efficacy of this regimen and not a randomized placebo trial?" FDA Hearings Transcript, *infra* Appendix A, at 131 (FDA's Dr. Ridgely C. Bennett gave the following puzzling response: "Well, I think it would be difficult to do a randomized trial of this nature. But I think it is fair to use a historical control for efficacy.").

[169] There is no evidence that FDA formally issued a waiver under Section 314.126(c) of the requirement for well-controlled studies or that the Population Council ever requested such a waiver.

4. Subpart H's Standard for Proving Drug Effectiveness

The approval of a drug under Subpart H does not lower the applicable standards for proving the drug's effectiveness. As FDA stated when it adopted Subpart H, "[a]ll drugs approved [under Subpart H] will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."[170] In fact, Subpart H is available only for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients *over existing treatments* (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."[171] Neither the French nor the U.S. Clinical Trials yielded scientifically valid comparisons with the existing therapy, surgical abortion, to support a finding of a "meaningful therapeutic benefit over existing treatments." FDA should have required the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone has a meaningful therapeutic benefit over the standard method for terminating pregnancies. FDA did not require the drug sponsor to perform such trials for Mifeprex, which departs from FDA's normal treatment of Subpart H drugs generally and for the other drugs approved under the restricted distribution provisions in Section 314.520.

Mifeprex appears to be the only drug that FDA has approved under Section 314.520 of Subpart H without requiring compliance with the statutory and regulatory requirements that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials capable of providing data for subjection to rigorous statistical analysis.

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[170] *Subpart H Final Rule*, 57 Fed. Reg. at 58953.

[171] 21 C.F.R. § 314.500 (emphasis added). The class of "existing treatments" to which there must be a comparison, as specified in this rule section, is not limited to pharmaceuticals. For example, a potential chemotherapeutic agent might be compared to radiation therapy.

Aside from Mifeprex, only four drugs have been approved pursuant to Section 314.520, the restricted distribution prong of Subpart H. Each of these drugs, Xeloda,[172] Thalomid,[173] Actiq,[174] and Tracleer,[175] was an appropriate candidate for approval under Section 314.520. Moreover, in each case, studies were performed that allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care. FDA's decision to require randomized, comparator-controlled, blinded trial design for each drug, even in the face of urgent need for the treatments at issue, supports the claim that FDA's treatment of the mifepristone NDA was aberrant.

Xeloda™ (capecitabine) was approved for use in treating patients with widely metastatic ("Stage IV") terminal breast cancer, for whom all other modalities of chemotherapy have failed or are contraindicated.[176] The average lifespan of a patient with multi-drug resistant tumors participating in the clinical trials for this drug was only 8.5 months. Because Xeloda was only modestly effective (25% of the recipients improved for an average of five months), exhibited significant toxicity, and was a last resort treatment for dying patients, FDA approved it under Section 314.520 with use restrictions and commitments to further study the drug. Subsequent randomized, concurrent controlled, blinded evaluator trials demonstrated Xeloda's statistical superiority to the standard of care for metastatic colon and breast cancers.[177]

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[172] NDA 20896.

[173] NDA 20785.

[174] NDA 20747.

[175] NDA 21290.

[176] *See* "NDAs Approved under Subpart H," *infra* Appendix A. The current version of the Subpart H approval chart (updated Aug. 8, 2002) indicates that Xeloda is a "surrogate endpoint" drug, rather than a restricted distribution drug. However, the two previous postings of the chart state the opposite. Furthermore, FDA's approval letter states that the NDA "[was] approved under 21 CFR 314.520." Letter, FDA/CDER to Cynthia Dinella, Group Director, Regulatory Affairs, Hoffman-La Roche Inc. (Apr. 30, 1998).

[177] *See* Xeloda package insert.

Thalidomide (Thalomid™) was approved under Section 314.520 for the treatment of leprosy, a disfiguring, chronically disabling, and often lethal skin infection.[178] Thalidomide is a drug the severe toxicity of which, particularly to fetuses, is well-documented. Children exposed to this drug *in utero* suffer dramatic birth defects, namely the partial absence of hands, feet, arms and legs. The public outcry following the discovery that thalidomide causes these alarming malformations helped to spur the scientific modernization of FDA drug approval policy and practices in the 1960s. Clinical trials involving leprosy are difficult and require long periods of time because the disease is very rare in the United States. Three randomized, double-blinded comparator-controlled clinical trials were performed to support the Thalomid NDA.[179]

Oral fentanyl citrate (Actiq™) was approved under Section 314.520 as a powerful sedating narcotic painkiller, primarily for use to relieve the suffering of dying cancer patients.[180] Actiq can be lethal, particularly to children, because it quickly abolishes a patient's drive to breathe, unless the patient is already accustomed to narcotic analgesics. Moreover, Actiq, a powerful narcotic, has a high potential for abuse and diversion into the illegal drug market. Actiq was evaluated in a "double blinded, placebo controlled" study for the treatment of breakthrough cancer pain and was shown to "produce statistically significantly more pain relief compared with placebo."[181] Actiq is restricted for use only by oncologists and pain specialists who are familiar with the management of the side effects and complications of the drug's use as approved.

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[178] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[179] *See* Thalomid package insert.

[180] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[181] Actiq package insert.

Tracleer™ (bosentan tablets) was approved pursuant to Section 314.520 for use in treating pulmonary hypertension, a life threatening and frequently progressive condition of excessively high blood pressure in the lung blood vessels resulting from chronic scarring and injury of the lung tissue.[182] Tracleer can cause liver damage and major birth defects. Two randomized, double-blinded, placebo-controlled clinical trials demonstrated the superiority of the drug over a placebo. Tracleer was compared to a placebo because there is no alternate standard of care for pulmonary hypertension. Despite its potential toxicity, Tracleer was approved subject to usage restrictions under Section 314.520 because it is the only treatment available for a life threatening and debilitating condition.[183]

5. FDA Failed to Require a Comprehensive Audit of French Clinical Trial Data after Discovering Violations of Good Clinical Practices

In June 1996, FDA inspected the trial records of a "French government-supported abortion clinic" that participated in the French Clinical Trials. FDA issued a Form 483 detailing problems uncovered during the inspection. The problems identified by the investigator suggested carelessness, fraud, evidence tampering, and the systematic under-reporting of serious adverse events. The inspection "revealed a failure to maintain complete and accurate records." The violations that were discovered included: "laboratory reports that were missing" for 11 patients, "missing ultrasound documents" for 20 patients, "pages missing from the case record files and unreported aspirations," inclusion of 4 ineligible patients, and "consent forms were dated after the start of study for some subjects, and the investigator had signed consent form

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[182] *See* "NDAs Approved under Subpart H," *infra* Appendix A.

[183] *See* Tracleer package insert.

sometimes in advance, up to 4 days before the subjects had signed."[184] There were also "under-reported side effects" such as "a patient bleeding with two subsequent aspirations; convulsions reported as fainting; and expulsion which was actually a surgical evacuation; bleeding, nausea and contractions, or bleeding and pelvic pain."[185] After elaborating on the deficiencies found, the FDA inspector concluded: "Notwithstanding these objectionable conditions, [redacted name of an FDA official] assured Dr. Aubeny that he would not recommend that the studies not be included in the evaluation of the NDA application."[186]

FDA should not have allowed tainted data to support the Mifeprex NDA. A complete audit of all French Clinical Trial data is warranted to determine whether another set of clinical trials must be performed to replace the tainted French trial data.

F. THE AGENCY'S DE FACTO APPROVAL OF MISOPROSTOL'S NEW USE WAS ARBITRARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

When FDA approved Mifeprex, it also took action with respect to a second drug – misoprostol. Taken alone, mifepristone is ineffective as an abortifacient.[187] In order to achieve an abortion rate greater than 90 percent, the administration of mifepristone is followed approximately two days later by a prostaglandin to complete the abortion. In the U.S. Clinical

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[184] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1 [FDA FOIA Release: MIF 004135-45].

[185] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 1.

[186] Summary of Findings, Memorandum Accompanying FDA Form 483 Issued to Dr. Elizabeth Aubeny (June 28, 1996): at 9.

[187] Although some studies using mifepristone alone have produced completion rates as high as 60 to 80 percent, it is widely recognized that, on its own, mifepristone is not a viable substitute for surgical abortion. *See, e.g.,* Mitchell D. Creinin, "Early Medical Abortion with Mifepristone or Methotrexate: Overview," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 3 (reporting that "[f]or gestations up to 49 days, complete abortion occurs in approximately 60% to 80%" of women using mifepristone alone); Helena von Hertzen, M.D., "Research on Regimens for Early Medical Abortion," *Journal of the American Medical Women's Association* 55 (Supplement 2000): 133-36.

Trial, the prostaglandin used was misoprostol, which was distributed by G.D Searle & Co. ("Searle") as the anti-ulcer drug Cytotec™.[188] Ultimately, FDA based its approval of Mifeprex on the combined action of a mifepristone and misoprostol regimen. On the day FDA approved mifepristone, it notified Searle that "[t]he drug mifepristone is now approved in a regimen with misoprostol for termination of pregnancy of 49 days or less."[189]

Searle, which opposed the use of its drug in conjunction with Mifeprex as an abortifacient,[190] did not file a Supplemental NDA for the use of misoprostol as part of an abortion regimen.[191] Absent such an application, FDA lacked the basis for sanctioning a new indication for misoprostol. As Peter Barton Hutt, former FDA general counsel, observed, the agency's treatment of misoprostol "set[ ] an extraordinary precedent" because FDA was "seemingly

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[188] After a series of corporate transactions, Searle is now part of Pharmacia Corporation, which is headquartered in Peapack, New Jersey. In 1985, G.D. Searle & Co. became the pharmaceutical unit of Monsanto. In April 2000, Monsanto merged with Pharmacia & Upjohn to create the Pharmacia Corporation. Pharmacia & Upjohn had been created in 1995 when Pharmacia AB and the Upjohn Company merged. On July 15, 2002, Pfizer Inc. announced that it would purchase Pharmacia.

[189] Letter, Dr. Lilia Talarico, M.D., Director, FDA/CDER, Division of Gastrointestinal and Coagulation Drug Products, Office of Drug Evaluation III to Dr. Mary Jo Pritza, G.D. Searle & Co. (Sept. 28, 2000): at 1 [FDA FOIA Release: MIF 008847-48]. The Talarico Letter came in response to the August 8, 2000 application by Searle to obtain approval for changes that would have bolstered the Cytotec label's discussion of adverse effects (presumably in anticipation of FDA's approval of the mifepristone NDA). FDA chided Searle for attempting to make the proposed changes and summarily rejected them. *Id.* at 1. When it announced the Mifeprex approval, FDA referred to the "approved treatment regimen." *See* FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000). *See also* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 4 (referring to the "mifepristone treatment regimen").

[190] In fact, on August 23, 2000, Searle wrote an open letter to all health care practitioners stating that "Cytotec is not approved for the induction of labor or abortion." The letter listed a number of potential "[s]erious adverse events reported following off-label use of Cytotec in pregnant women includ[ing] maternal or fetal death." Michael Cullen, M.D., Medical Director U.S., Searle, Open Letter to Health Care Providers (Aug. 23, 2000)[FDA FOIA Release: MIF 008022]. Officials of the American College of Obstetricians and Gynecologists, among others, decried Searle's lack of cooperation. *See* Ralph W. Hale, M.D., and Stanley Zinberg, M.D., "The Use of Misoprostol in Pregnancy," editorial, *New England Journal of Medicine* 344 (Jan. 4, 2001): 59-60. FDA's approval of the Mifeprex Regimen in the face of Searle's opposition appears to have usurped Searle's rights to control the distribution of its drug.

[191] Because Searle's patent on misoprostol did not expire until July 2000, no other party would have been able to file a timely supplemental NDA for the use of a generic form of misoprostol as an abortifacient.

encouraging a drug's unapproved use."[192] He added that the agency is in an "embarrassing and uncomfortable position."[193] FDA did more than encourage the unapproved use of misoprostol; it *mandated* the unapproved use.

1. Misoprostol's Use as an Abortifacient is a New Indication for which the Requisite Supplemental New Drug Application Was Not Filed

A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective.[194] Furthermore, a drug already being used to treat one disease or part of the body may be a new drug when used to treat another disease or part of the body.[195] Misoprostol's new use as an abortifacient, therefore, marks it as a "new drug."[196]

New drugs must be shown to be safe and effective. Specifically, FDA requires that "[a]ll indications shall be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) . . . unless the requirement is waived . . . ."[197]

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[192] Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1.

[193] Zimmerman at B1.

[194] *See Thompson v. Western Medical Center*, Brief for the Petitioners (filed by the Solicitor General of the United States), No. 01-344 (Dec. 2001): at 4 ("See *United States v. Generix Drug Corp.*, 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a 'new drug').

[195] A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

[196] The "newness" of misoprostol in this indication was heightened by the fact that, when Mifeprex was approved, misoprostol was explicitly contraindicated for pregnant women. The misoprostol label included the following black-box warning: "CYTOTEC (MISOPROSTOL) ADMINISTRATION BY ANY ROUTE IS CONTRAINDICATED, BECAUSE IT CAN CAUSE ABORTION, IN WOMEN WHO ARE PREGNANT . . . ." In April 2002, the Cytotec label was changed to "remove[ ] the contraindication and precaution that Cytotec should not be used in women who are pregnant." FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). The label now restricts the contraindication to pregnant women who are using Cytotec as a non-steroidal anti-inflammatory drug ("NSAID"). The revised Cytotec label and, more specifically, the "Indications and Usage" section, however, continue to lack any reference to the use of misoprostol in the Mifeprex Regimen.

[197] 21 C.F.R. § 201.57(c)(2). To the best of the Petitioners' knowledge, FDA did not formally waive the requirement for misoprostol as part of an abortion regimen.

A Supplemental NDA provides the necessary evidence in support of a new indication.[198] Absent a waiver, a Supplemental NDA permits FDA to consider the evidence in support of the proposed change and approve related labeling changes in advance.[199] Even though a new use for misoprostol is an integral part of the Mifeprex Regimen, FDA sanctioned this new misoprostol indication without having received and considered a Supplemental NDA.

Among the changes for which FDA approval is necessary are changes to statements in a drug's labeling indicating whether "[t]he drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy."[200] A well-known treatment regimen illustrates how FDA has typically dealt with the labeling of two drugs that have been approved for combined use. The regimen pairs methotrexate and Leucovorin Rescue. Methotrexate, a chemotherapeutic agent, kills cancer cells by depriving them of folic acid which is necessary for DNA synthesis, but, in the process, methotrexate deprives normal bone marrow cells of the folic acid they need. Leucovorin Rescue serves as an antidote to the toxic effects of methotrexate. The labeling for Leucovorin Rescue refers to its use "after high-dose methotrexate therapy in osteosarcoma," which is an approved

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[198] A recent article noted: "To obtain FDA approval for an additional use of a previously approved drug, the sponsor must submit a supplemental application (sNDA, sBLA, or sPMA) demonstrating the safety and efficacy of the drug when used in the new way or for the new indication. The supplemental application typically requires clinical data similar to those in the original application, but does not require the same extensive chemistry, manufacturing and controls, and preclinical pharmacology and toxicology data as in the original application." Shane M. Ward, "*Washington Legal Foundation* and the Two-Click Rule: The First Amendment Inequity of the Food and Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," *Food and Drug Law Journal* 56 (2001): 41-56, at 44 (citations omitted).

[199] *See* 21 C.F.R. § 314.70(b). *See also* Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1775 ("FDA takes the position, which no manufacturer has sought to challenge in court, that any potentially significant modification of an approved new drug [application] likewise requires advance agency approval. As a consequence, not only attempts to expand the indications for a drug but other changes in labeling, in inactive ingredients, in the method or location of manufacture, or in packaging must first be the subject of an approved Supplemental New Drug Application.").

[200] *See* 21 C.F.R. § 201.57(c)(1)(iv).

indication for methotrexate.[201] Similarly, methotrexate's labeling refers to an approved use of Leucovorin Rescue.[202]

By contrast, in the Mifeprex labeling, an *unapproved* indication for misoprostol is discussed. In approving such labeling, FDA has taken the aberrant position that the maker of one drug (Mifeprex) can secure approval of a new indication for another company's drug (misoprostol) merely by describing that new use as part of a combined therapy. FDA circumvented its own regulations by failing to require that both drugs in the Mifeprex Regimen be approved for the indication in question – pregnancy termination.[203]

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[201] *See* Leucovorin Calcium for Injection Package Insert ("Indications and Usage") ("Leucovorin calcium rescue is indicated after high-dose methotrexate therapy in osteosarcoma. Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists."). The package insert is available at: <http://www.xanodyne.com/leucovorin_calcium_pl_2002.pdf>.

[202] The methotrexate package insert states that "[m]ethotrexate in high doses followed by leucovorin rescue in combination with other chemotherapeutic agents is effective in prolonging relapse-free survival in patients with non-metastatic osteosarcoma who have undergone surgical resection or amputation for the primary tumor." The package insert is available at: <http://www.rxlist.com/cgi/generic/mtx_ids.htm>.

[203] A recent approval of a biologic product also illustrates the principle that FDA-approved labeling lists only approved indications. On February 19, 2002, FDA approved Zevalin for use in combination with Rituxan (rituximab) to treat low-grade B-cell non-Hodgkins Lymphoma (NHL). Rituxan had been approved previously and was already indicated "for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma." *See* Rituxan Package Insert ("Indications and Usage"). Rituxan and Zevalin are monoclonal antibodies that can significantly shrink tumors by targeting white blood cells (B-cells) including malignant B cells. The "Indications and Usage" section of Zevalin's label describes the drug as being "part of the ZEVALIN therapeutic regimen (see Dosage and Administration)." The "Dosage" section directs that Rituxan be administered and then followed by Zevalin on Day One and then again seven to nine days later. After the Zevalin NDA was approved, detailed information about the administration of the "Zevalin Therapeutic Regimen" was added to the Rituxan label. On February 19, 2002, FDA's Center for Biologics Evaluation and Research approved a supplement to the Rituximab biologics license application "to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen . . . ." Letter, Dr. Karen D. Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research, to Alice Wei, IDEC Pharmaceuticals (Feb. 19, 2002) (*see* <http://www.fda.gov/cber/approvltr/rituide021902L.htm>).

2. FDA Sanctioned the Promotion of Misoprostol for an Unapproved Use as Part of the Mifeprex Regimen

The use of misoprostol as an abortifacient is an unapproved or "off-label" use.[204] FDA objects to the *promotion* of off-label uses of drugs by manufacturers.[205] "Off-label" uses of drugs are common as physicians explore new ways of using approved drugs, but normally FDA strives to ensure that physicians and patients are not misled into believing that FDA has approved such uses. In an effort to curb the promotion of off-label uses by pharmaceutical manufacturers, FDA issued regulatory guidance in 1996 pertaining to the dissemination of off-label use information.[206] In this case, however, FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol. FDA oversaw the creation of the promotional materials for Mifeprex,[207] which discussed the off-label use of misoprostol.[208] FDA itself disseminated information about

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[204] *See generally* James M. Beck and Elizabeth D. Azari, "FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions," *Food & Drug Law Journal* 53 (1998): 71-104, at 71 n.2, which explains "off-label" use as follows:

> "Off-label" has more accurately been termed "extra label" use. It means only that a product is used for a condition or in a way not appearing on its FDA-regulated labeling, not that the agency has judged the use adversely. *See, e.g., Washington Legal Found. v. Kessler*, 880 F.Supp. 26, 28 n.1 (D.D.C. 1995). . . . Off-label can mean many things. "[U]sing an approved drug to treat a disease that is not indicated on its label, but is closely related to an indicated disease, treating unrelated, unindicated diseases, and treating the indicated disease but varying from the indicated dosage, regimen, or patient population may all be considered off-label use." William L. Christopher, *Off-Label Drug Prescription: Filling the Regulatory Vacuum*, 48 FOOD & DRUG L.J. 247, 248 (1993) (footnotes omitted).

[205] *See, e.g., Subpart H Final Rule*, 57 Fed. Reg. at 58,953 ("Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved.").

[206] *See* FDA, "Advertising and Promotion; Guidances," Notice, 61 Fed. Reg. 52,800 (Oct. 8, 1996) (publishing two guidance documents: "Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data" and "Guidance for Industry Funded Dissemination of Reference Texts").

[207] FDA reminded the Population Council in the Mifeprex Approval Letter that, pursuant to 21 C.F.R. § 314.550, the drug sponsor is obligated to submit Mifeprex promotional material for review by the agency prior to dissemination to physicians and the public. *See* Mifeprex Approval Letter at 3.

[208] A Danco Laboratories webpage, for example, contains the following question and answer:

> Q: How Does Mifeprex Work?
>
> A: Mifeprex blocks progesterone, a hormone necessary for a pregnancy to continue. You take Mifeprex followed by a prostaglandin, misoprostol, which causes uterine contractions that help to end pregnancy.
>
> In more detail, Mifeprex blocks progesterone, a naturally produced hormone that prepares the lining of the uterus for a fertilized egg and helps maintain pregnancy. Without progesterone, the lining of the uterus

the off-label use of misoprostol in documents such as the press release announcing the approval of Mifeprex for use in conjunction with misoprostol.[209] Recently it did so again when the agency emphasized the importance of adhering to the approved regimen, including the off-label use of misoprostol.[210]

3. Mifeprex Is Misbranded: Its Labeling Promotes an Unapproved Use of Another Drug

The labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved.[211] FDA's ability to regulate the marketing and distribution of drugs rests largely on its legal capacity to strictly control the content of a drug's labeling. A fundamental tenet of drug regulation is that FDA requires approval for every indication listed in the labeling of a drug.[212] FDA would undercut its own authority if it did not also apply this rule to uses for a drug referenced on another drug's labeling.

The Mifeprex labeling creates false expectations about misoprostol. Physicians and patients are justified in believing that any use or indication for a drug, included in the "Indication

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> softens, breaks down and bleeding begins. Mifeprex is followed by a prostaglandin that causes the uterus to contract, which helps to complete the process. . . . The prostaglandin used following Mifeprex is misoprostol, a drug already available in the United States.

"Using Mifeprex: Frequently Asked User Questions," Danco Laboratories website at <http://www.earlyoptionpill.com/may_faqs.php3>. The electronic version of the Mifeprex Label contains a hyperlink to the Danco Laboratories website, <www.earlyoptionpill.com>, which contains the above-referenced webpage. (When printed, the hyperlink appears to be ordinary text.)

[209] *See*, FDA, Press Release, "FDA Approves Mifepristone for the Termination of Early Pregnancy" (Sept. 28, 2000) ("Under the approved treatment regimen, a woman first takes 600 milligrams of mifepristone (three 200 milligram pills) by mouth. Two days later, she takes 400 micrograms (two 200-microgram pills) of misoprostol, a prostaglandin.").

[210] *See* FDA webpage, *infra* Appendix A, "Mifepristone Questions and Answers 4/17/2002," at Question 6. In this same document, however, FDA cautions health care providers against "using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses . . . ." *Id.* at Question 9.

[211] Misoprostol receives more than a passing mention on the Mifeprex Label; the word "misoprostol" appears 34 times (compared to 57 appearances of "mifepristone" and 34 appearances of "Mifeprex").

and Usage" section of an FDA-approved label, has been subjected to the rigorous approval process set forth in Section 505 of the FD&C Act. Section 201.6(a) of the Agency's rules states that misbranding may arise from "a false or misleading representation with respect to another drug."[213] "When a physician, manufacturer, or *other third party* steps in to promote an unapproved use of a drug by advertising or distribution to other physicians, the drug may become unlawful under Section 301(k) the FD&C Act, 21 U.S.C. § 331(k)(1994), which prohibits misbranding, and Section 502(f)(1), 21 U.S.C. § 352(f)(1)(1994), which requires a drug's labeling to bear 'adequate directions for use.'"[214] Mifeprex is, therefore, misbranded.

Mifeprex is also misbranded because it is unsafe when used as directed in the approved labeling. Section 502(j) of the FD& C Act states that "[a] drug or device shall be deemed to be misbranded . . . [i]f it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."[215] As discussed in the next section, FDA's approved regimen is unsafe because it lacks important safeguards.

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[212] *See* Elizabeth A. Weeks, "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 645-65, at 647 n.13 (citing Merrill, (*infra* Appendix A), at 1853).

[213] *See* 21 C.F.R. § 201.6(a).

[214] Merrill, *infra* Appendix A, at n.318 (emphasis added). *See also* 21 C.F.R. § 314.530(a)(5) (authorizing the Secretary to withdraw approval of a Subpart H drug if "[t]he promotional materials are false or misleading").

[215] 21 U.S.C. § 352(j). *See also* Jeffrey N. Gibbs and Judith E. Beach, "Chapter 7: Adulteration and Misbranding of Drugs" in *Fundamentals of Law and Regulation: An In-Depth Look at Therapeutic Products* (David G. Adams, Richard M. Cooper, and Jonathan S. Kahan, eds.), vol. II (Washington, D.C.: Food and Drug Law Institute, 1997): at 229 ("When the drug is dangerous to the health of the user even when used as recommended on the label, it is misbranded.").

G. WOMEN'S LIVES ARE BEING ENDANGERED BY THE LACK OF SAFEGUARDS IN FDA'S APPROVED REGIMEN

On February 18, 2000, FDA informed the Population Council that "adequate information ha[d] *not* been presented to demonstrate that [mifepristone], when marketed in accordance with the terms of distribution proposed [by the Population Council], is safe and effective for use as recommended."[216] Over the next several months, the Population Council and Danco refused to supplement its distribution plan with a meaningful patient safety component. This prompted FDA, on June 1, 2000, to privately convey to the sponsor a set of proposed restrictions intended to rectify the sponsor's omission. The agency's proposed restrictions were soon leaked to the public. Amidst a vigorous political and editorial backlash, the sponsor not only rejected FDA's proposal but, in what was described by FDA as a "very significant change," repudiated restrictions the sponsor itself had proposed in 1996.[217] FDA succumbed and soon approved a regimen that did not embody restrictions sufficient to address the agency's legitimate safety concerns.

Early in the approval process, FDA expressed its intention to place restrictions on the use of mifepristone.[218] FDA's position was informed, in part, by the international experience with

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[216] 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5 (emphasis added).

[217] *See* FDA Email (June 23, 2000): at 1 (explaining that the Population Council's attorney "affirmed that the 1996 proposals for distribution system as presented by the Pop Council then and agreed to by the [FDA Advisory Committee] and FDA are NOT what the Pop Council wants today. I explained that this change is very significant and that they need to provide their justification/rationale.")[FDA FOIA Release: MIF 002523].

[218] In order to allay concerns of the drug's European owner, FDA pledged, in the course of securing the U.S. patent rights for the Population Council, to "take appropriate measures . . . to assist through the NDA-approval process in the creation of a regime for the distribution and use that will protect against misuse of the drug." Letter, David A. Kessler, Commissioner of Food and Drugs, to the President & CEO of Roussel Uclaf [name redacted] and to Margaret Catley-Carlson, President of Population Council (May 16, 1994): at 1 [FDA FOIA Release: MIF 004992-93].

mifepristone.[219] The NDA submitted by the Population Council on March 14, 1996 included a plan that would have limited distribution of mifepristone to "licensed physicians (with prior training in assessing the length of pregnancy, in diagnosing ectopic pregnancy, and [redacted]), who will attend educational seminars on the safe use of this regimen."[220]

The FDA Advisory Committee, when it met in July 1996, was not satisfied with the restrictions proposed by the Population Council and expressed "serious reservations on how [the proposed drug distribution system] is currently described in terms of assuring safe and adequate credentialing of providers."[221] The Committee recommended additional restrictions designed to ensure "that this drug not be expanded to hands of physicians who are not already skilled in managing pregnancies, terminations, and complications of both."[222] Accordingly, FDA's 1996 Approvable Letter required the submission of "a comprehensive description of the proposed distribution system."[223]

In subsequent submissions, however, the Population Council insisted that the drug was safe and proffered restrictions designed primarily to control the manufacturing and retailing of the drug product. On August 18, 1999, the Population Council proposed to:[224] (i) limit the number and type of distributors; (ii) limit distribution to distributor-registered physicians who

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[219] In Europe, for example, mifepristone is used under more highly controlled conditions than were ultimately required in the United States. *See* Amendment to NDA 20-687, International Product Labeling with English Translations (submitted March 21, 2000) (presenting English translation of mifepristone product label, approved July 6, 1999, used in Austria, Belgium, Denmark, France, Germany, Greece, the Netherlands and Spain)[FDA FOIA Release: MIF 000493-506].

[220] Memorandum, FDA/CDER to NDA 20-687 File (Sept. 16, 1996): at 2 [FDA FOIA Release MIF 000560-62].

[221] FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45].

[222] FDA Memorandum, "Highlights of the July 19, 1996 Reproductive Health Products Advisory Committee (AC) Meeting on Mifepristone: Outstanding Issues for FDA to Address" (undated): at 3-4 [FDA FOIA Release: MIF 000534-38].

[223] 1996 Mifepristone Approvable Letter , *infra* Appendix A, at 1.

had provided certain assurances;[225] and, (iii) make available "training materials and information" and medical consultation to health care providers and product information to patients.[226] On January 21, 2000, Danco opined that "[r]egardless of the distribution system for mifepristone, the medical safety of this drug is well documented."[227] and proposed a distribution system that was designed only to ensure that Danco would "exert[ ] positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient."[228]

In reaction to the sponsor's recalcitrance, FDA took the position "that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product."[229] The agency nevertheless continued to encourage the sponsor to take an active role in devising appropriate restrictions on the use of mifepristone. Instead, in March 2000, the Population Council again protested that such restrictions were unwarranted.[230] It submitted a

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[224] *See* Medical Officer's Review, *infra* Appendix A, at 21-23 (setting forth the Population Council's complete response submitted to FDA on August 18, 1999).

[225] The physician would be required to provide a *self*-attestation covering the physician's ability to accurately date pregnancies and determine the patient's blood Rh factor and the physician's access to emergency medical facilities. Registering physicians would also agree to obtain from each patient an acknowledgement that she has received full information and is willing to comply with the treatment regimen, to maintain certain records (including ultrasound and blood test records) for each patient, to report adverse events and information about ongoing pregnancies, and to "[u]se every effort to ensure patients return for their follow up visit 14-20 days after taking the product." *See* Medical Officer's Review, *infra* Appendix A, at 22-23.

[226] *See* Medical Officer's Review, *infra* Appendix A, at 23.

[227] Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26]. Danco attempted to attribute any deleterious effects of mifepristone abortions to misoprostol: "More serious adverse events are quite rare and are related to the entire treatment (not mifepristone *per se*), almost always following the use of the prostaglandin." *Id.* at 2.

[228] *See* Amendment 039 to the NDA, Mifeprex Distribution Plan Executive Summary (Jan. 21, 2000): at 3 [FDA FOIA Release: MIF 000530-31].

[229] *See* 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5. *See supra* Section III.C.2 and III.D. for a discussion of Subpart H, Section 314.520, which is reserved for drugs that are so inherently dangerous that their distribution and use must be restricted.

[230] In the course of objecting to the approval of the drug under subpart H, which is "likely to falsely 'mark' mifepristone as a highly toxic and risky drug," the Population Council insisted that "the FDA knows, [Mifeprex] is

distribution plan that it characterized as "detailed and comprehensive" and "surely equal to its purpose."[231] Once again, the plan consisted of restrictions intended only to control the manufacturing and retailing of the drug product.[232] Again FDA objected that "[t]he proposed distribution system as submitted primarily addresses security for the manufacturer and distributor; it must also include safeguards for the patient."[233] The agency requested "that sponsor present a proposal regarding provider qualifications that addresses safety concerns of patients receiving the drug product."[234]

On June 1, 2000, FDA proposed the following set of "Qualifications for Physician Recipients:" (1) the physician must demonstrate that she is licensed to practice medicine; (2) the physician must be "trained and authorized by law" to perform surgical abortions; (3) the physician must have "been trained to and ha[ve] the ability to assess the age of a pregnancy accurately by ultrasound examination, to monitor abortion by ultrasound examination, and to diagnose an ectopic pregnancy by ultrasound examination;" (4) the physician must have "satisfactorily completed training certified by the distributor in the mifepristone treatment procedure, including mechanism of action, appropriate use, proper administration, follow-up, efficacy, adverse events, adverse event reporting, complications, and surgical indications;" and

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exceptionally safe and effective." Responses by Population Council to "FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)" (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24]("March 2000 Response").

[231] March 2000 Response, *infra* Appendix A, at 2.

[232] Specifically, the plan provided for "secure manufacturing and shipping procedures, controlled returns, tracking of distribution of individual packages to the patient level, use of a limited number of distributors [redacted], account registration and other detailed ordering requirements for practitioners, direct distribution only to practitioners (not through retail pharmacies), and the use of signed patient agreements." March 2000 Response, *infra* Appendix A, at 2.

[233] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1 [FDA FOIA Release: MIF 007811-13].

[234] Teleconference Meeting Minutes (between FDA staff and representatives of Population Council and Danco) (May 19, 2000): at 1. FDA wanted the sponsor to provide a set of auditable provider qualifications, a plan for auditing providers to ensure that they were meeting these criteria, and an arrangement for discontinuing distribution to unqualified providers. *See id.* at 2.

(5) the physician must have "continuing access (e.g., admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility."[235] FDA's proposals were intended to address concerns about the safety of the women undergoing mifepristone-misoprostol abortions that the Population Council and Danco had refused to take into account in crafting restrictions for the drug.[236]

The Population Council and Danco objected strenuously to the proposed restrictions and aired their complaints in public.[237] FDA reprimanded the Population Council for leaking the restrictions to the public and misrepresenting the nature of the restrictions.[238] The Executive Vice President of the American College of Obstetricians and Gynecologists submitted an analysis of the leaked restrictions to FDA.[239] The editorial and political reaction,[240] together with the

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[235] *See* FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000)[FDA FOIA Release: MIF 000522]. *See also* American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

[236] It should be noted, that even these restrictions would not have been sufficient to make mifepristone-misoprostol abortions safe. Among the key safeguards missing from FDA's proposal were requirements that every prospective patient undergo an ultrasound and that prescribing physicians be required to have admitting privileges at facilities able to provide emergency care.

[237] Paul Blumenthal, M.D., Jane Johnson, and Felicia Stewart, M.D., "The Approval of Mifepristone (RU486) in the United States: What's Wrong with this Picture?" *Medscape Women's Health* 5 (2000) (reproduced in an internal FDA email)[FDA FOIA Release: MIF 00002597-99] ("At a meeting of early abortion providers and abortion advocates, the Population Council and Danco revealed that the U.S. Food and Drug Administration (FDA) had made a series of proposals regarding the labeling and distribution of mifepristone that would severely limit women's access to the drug if and when it is approved.").

[238] *See* Teleconference Meeting Minutes (between FDA staff and representatives of the Population Council and Danco) (June 7, 2000): at 1 ("Meeting Objective: . . . to discuss the misrepresentations by the Press regarding the proposed distribution system, and to agree on the need for serious, candid, and confidential discussions to resolve deficiencies of the application.")[FDA FOIA Release: MIF 002136-37]; FDA internal email (June 23, 2000): at 1 (re: telephone conversation with Population Council attorney, Nancy Buc, on 6/23/00) ("I also said that we were looking to Pop Council to be a responsible entity in manufacturing, distributing, and shepherding this drug and that most responsible entities make proposals rather than expect FDA to write labels and distribution systems and obtain comments through the media.")[FDA FOIA Release: MIF 002523].

[239] *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) to Jane Henney, M.D. (July 24, 2000) and enclosure: ACOG, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000)[FDA FOIA Release: MIF 001366-69]. ACOG and the American Medical Association ("AMA") also attempted to secure a meeting with

impending approval deadline of September 30, 2000,[241] however, had the desired effect of undermining FDA's resolve.

At a meeting on July 19, 2000, FDA yielded to the Population Council and Danco on a number of important issues.[242] FDA abandoned its proposal for auditable physician qualifications and agreed instead to permit physicians to attest to their own qualifications.[243] Instead of requiring formal training, FDA merely "request[ed] that the physician also attest to having read and understood the training materials and labeling."[244] FDA also agreed not to

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Dr. Jane Henney, FDA Commissioner, and her staff, in order to further discuss their opinion of the restrictions. *See* Letter, Ralph Hale, M.D. (Executive Vice President, ACOG) and E. Ratcliffe Anderson, Jr., M.D. (Executive Vice President, AMA) to Jane Henney, M.D. (July 24, 2000): at 1 ("The undersigned organizations . . . are very concerned about restrictions . . . [FDA] has proposed for . . . mifepristone. . . . We would like the opportunity to meet with you and your staff to discuss this important issue. It's imperative that the FDA fully understands the effect that these proposals would have on the quality of health care. It's equally imperative that the FDA's work be based solely on evidence from the drug's clinical trials, and be entirely from political influence.")[FDA FOIA Release: MIF 001363]. They were permitted only to meet with officials in FDA's Office of Women's Health, an office within the agency that was not involved in reviewing the NDA. *See* Letter, Jane Henney to Hale and Anderson (Aug. 11, 2000): at 1-2 [FDA FOIA Release: MIF 001361]. The questionable scientific basis for this challenge to FDA's proposed restrictions was recently brought to the attention of ACOG by one of the Petitioners. Letter, Donna Harrison, M.D. (Chairperson, AAPLOG Committee on Mifeprex Use) to Ralph Hale, M.D. (Executive Vice President, ACOG) (May 23, 2002) (available at <http://www.aaplog.org/acogmifeprexletter.htm>).

[240] *See, e.g*, Letter, U.S. Senator Barbara Boxer to Dr. Jane Henney (June 9, 2000): at 1 ("According to news reports, the FDA is considering placing draconian restrictions on the accessibility of RU-486 as a condition of its approval . . . . In 1996, the FDA found RU-486 to be safe and effective. Therefore, it is a mystery to me why the FDA would even consider restricting access to it.")[FDA FOIA Release: MIF 006376]; Letter, Mark Green, Public Advocate for the City of New York, to Dr. Jane Henney (Sep. 22, 2000): at 1 ("Earlier this week Planned Parenthood of New York City, NARAL-New York, the Access Project and Physicians for Reproductive Health and Choice joined me in convening a public hearing in New York City on pending action by [FDA] on mifepristone . . . . [I am] also concerned about the restrictions on access to RU-486 that FDA is said to be considering.")[FDA FOIA Release: MIF 001288-1302]; Sheryl Gay Stolberg, "F.D.A. Adds Hurdles in Approval of Abortion Pill," *New York Times* (June 8, 2000): at A21 ("The long-running effort to bring the French abortion pill to women in this country has encountered yet another obstacle: a suggestion by [FDA] that it may place tight restrictions on how the drug, RU-486, is distributed and who can prescribe it."); Letter, U.S. Representative Lynn Woolsey to Dr. Jane Henney (June 22, 2000): at 1 ("However, I am deeply concerned about recent press reports about proposed restrictions.") [FDA FOIA Release: MIF 006372].

[241] As noted above, because FDA had accorded priority review to mifepristone, the approval process was slated for completion by September 30, 2000.

[242] *See* Meeting Minutes, re: Approvability Issues Related to Labeling and Distribution Plan for Mifepristone (July 19, 2000): at 2-4 [FDA FOIA Release: MIF 004661-65].

[243] *See id.* at 2.

[244] *Id.* at 2.

require pre-procedure ultrasounds.[245] Furthermore, FDA stated "that it is not necessary to require the patient to take the drugs in the presence of health care provider."[246]

Among the unresolved issues at the conclusion of the July 19, 2000 meeting was the question of whether prescribing physicians should be limited to those who were able to perform surgical abortions, a provider qualification FDA believed was necessary:

> FDA requests that the ability to perform vacuum aspirations and/or D&Cs be added to provider qualifications. Providers also need to have access to emergency services. The need for surgical intervention is predictable unlike with other drugs. All OB/GYNs and other practitioners of women's health have these skills. The countries with experience with mifepristone have tight provision of complete services and have a long record of good outcomes.[247]

The Population Council later rejected FDA's request,[248] and the agency acquiesced.[249]

Despite its persistent concerns, FDA approved a regimen that posed the very risks to women's health that the agency had previously identified. When it approved Mifeprex, FDA stated that "[u]nder 21 CFR 314.520, distribution of the drug is restricted as follows:"

> Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex™.

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[245] *See id.* at 3.

[246] *Id.* at 3.

[247] *Id.* at 3.

[248] *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 6 (arguing that bolstering the provider qualifications in this way would be "not only unnecessary, but also in fact potentially counterproductive for patients")[FDA FOIA Release: MIF 0001373-81].

[249] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 [FDA FOIA Release: MIF 004587-88].

- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement, and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's records.[250]

In addition, the restrictions include a requirement that distribution be carried out in accordance with the plan submitted to FDA by the Population Council in a March 30, 2000 submission.[251] Even as it assented to a regimen that lacked critical safeguards, FDA took a number of steps that indicated its lingering concerns about the safety of the drug. First, FDA ultimately decided to rely on an infrequently used provision in Subpart H in hopes of ensuring that mifepristone would be used safely and, if necessary, could be withdrawn from market rapidly.[252] Second, the staff insisted that the mifepristone label "include a black boxed warning describing the major requirements and conditions for use."[253] "FDA generally reserves boxed warnings for serious or

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[250] Mifeprex Approval Letter at 2.

[251] *See* Mifeprex Approval Letter at 2.

[252] *See* 21 C.F.R. 530 ("Withdrawal Procedures"). *See also* FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85]. As late as July 19, 2000, the question of whether to use Subpart H was deemed to be an "Outstanding Issue." *See* Meeting Minutes, re: Approvability Issues (July 19, 2000): at 4 [FDA FOIA Release: MIF 004661-65].

[253] FDA, Memorandum, re NDA 20-687 (Feb. 17, 2000): at 2. The Population Council, which opposed the inclusion of such a warning, ultimately persuaded FDA to agreed to a pared-down Black Box Warning, which would merely direct the prescribing physician (i) to plan in advance for emergency care, and (ii) to make available to the patient and provide her with the opportunity to discuss the patient information and patient agreement. *See* Amendment 054 to the NDA, re: Further Response Regarding Labeling and Distribution: Follow up to July 19, 2000 Meeting (July 27, 2000): at 1-2 [FDA FOIA Release MIF 0001373-81].

life-threatening risks that best can be minimized by conveying critical information to the prescribing doctor in a highlighted manner."[254]

FDA's willingness to tailor the restrictions on Mifeprex to suit the demands of the Population Council and Danco will continue to manifest itself in serious adverse events among the women who use the Mifeprex Regimen. Some of the most critical flaws in the approved regimen are discussed below along with serious adverse events that have already been reported.

1. The Approved Regimen Is Unsafe Because It Does Not Require Ultrasound

a. Ultrasound Is Necessary to Accurately Date Pregnancies

The gestational age of a woman's pregnancy is a critical factor in determining whether she is an appropriate candidate for a mifepristone abortion. In order to minimize the risks of hemorrhage, incomplete abortion and continuing pregnancy, the gestational age of the pregnancy must be less than or equal to 49 days.[255] The authors of the Spitz Article, for example, found that "[f]ailures, defined as cases requiring surgical intervention for medical reasons or because the patient requested it, the abortion was incomplete, or the pregnancy was ongoing, increased with increasing duration of the pregnancy."[256] Through the combination of mifepristone and

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[254] Judith E. Beach et al., "Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs," *Food and Drug Law Journal* 53 (1998): 403-412, at 403 (available at: <http://www.fdli.org/pubs/Journal%20Online/53_3/art2.pdf>). *See also* 21 C.F.R. § 201.57(e) ("Warnings").

[255] As noted above, the gestational age of a pregnancy is based on the first day of a woman's last menstrual period, which is designated as Day 1 of the pregnancy.

[256] Spitz Article, *infra* Appendix A, at 1241. "The largest increase was in failures representing ongoing pregnancy, which increased from 1 percent in the [less than or equal to] 49-days group to 9 percent in the 57-to-63 days group (P<0.001)." Children born from ongoing pregnancies, after a failed application of the Mifeprex Regimen, may suffer birth defects, fertility problems, or other health problems later in life. Researchers have found evidence linking misoprostol and birth defects such as missing or deformed limbs and misshapen skulls. Much of this research was conducted in Brazil, where numerous women have attempted to induce abortions using misoprostol alone. *See, e.g.*, Sylvia Pagán Westphal, "Birth Defects Caused by Ulcer Drug Abortions," *NewScientist.com* (29 Aug. 2001) ("Several studies in Brazil, where up to 75 percent of clandestine abortions involve misoprostol, suggest the drug causes birth defects such as fused joints, growth retardation and a condition known as Möbius syndrome, which is characterised by paralysis of the face."); Iêda M. Orioli and Eduardo E. Castilla, "Epidemiological

misoprostol, "pregnancy was terminated in 762 of the 827 women pregnant for [less than or equal to] 49 days (92 percent), 563 of the 678 women pregnant for 50 to 56 days (83 percent), and 395 of the 510 women pregnant for 57 to 63 days (77 percent) . . . ."[257] The study also found that "[a]bdominal pain, nausea, vomiting, diarrhea, and vaginal bleeding also increased with advancing gestational age."[258] Due to the significant increase in failures and complications with increasing gestational age, FDA approved Mifeprex only for pregnancies of less than or equal to 49 days' gestation.[259]

The only way to date a pregnancy with the degree of accuracy necessary to exclude women whose pregnancies are beyond 49 days' gestation is by use of transvaginal ultrasound. FDA severely undermined the limitation on gestational age, however, when it failed to require

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Assessment of Misoprostol Tetratogenicity," *British Journal of Obstetrics and Gynaecology* 107 (April 2000): 519-23, at 522 (". . . there is an association of prenatal use of misoprostol as an abortifacient and congenital defects of vascular disruption type."); F.R. Vargas *et al.*, "Prenatal Exposure to Misoprostol and Vascular Disruption Defects: A Case-Control Study," *American Journal of Medical Genetics* 95 (2000): 302-306, at 306 ("add[ing] epidemiological basis to the growing body of evidence that prenatal exposure to misoprostol is related to the occurrence of vascular disruption defects in some exposed fetuses."). FDA determined that data submitted by the Population Council from a survey of fetal abnormalities in 82 pregnancies that were exposed to mifepristone alone or in combination with misoprostol was inconclusive. *See* FDA Mifeprex Approval Memorandum, *infra* Appendix A, at 4. FDA acknowledged, however, the possible link between misoprostol and birth defects. *See* Medical Officer's Review, *infra* Appendix A, at 18 (". . . medical follow-up is required to ensure that surgical termination is performed in case the medical termination attempt fails since misoprostol has been reported to be teratogenic in humans (limb defects and skull defects)."). The need for a study of the possible joint effects of mifepristone and misoprostol on babies born after a failed application of the Mifeprex Regimen was highlighted by the abnormalities discovered in a fetus exposed to misoprostol and mifepristone. *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Number 3877547-X (March. 1, 2002) (French report of numerous deformities in fetus that was exposed to mifepristone and misoprostol but survived until a subsequent surgical abortion was performed; "The anatomopathology examination showed a meningo-encephalocele. The left hand was constituted of only two fingers (oligodactylia), left and right foot were constituted of only one finger (monodactylia). There was a facial dysmorphia.").

[257] Spitz Article, *infra* Appendix A, at 1241.

[258] Spitz Article, *infra* Appendix A, at 1241. In order to treat vaginal bleeding, "[t]wo percent of the women in the [less than or equal to] 49-days group, as compared with 4 percent in each of the other two groups, were hospitalized, underwent surgical intervention, and received intravenous fluids (P=0.008)." *Id.*

[259] FDA's Medical Officer's Review noted: "The success of medical termination of pregnancy decreased with advancing gestational age and the incidence of adverse events increased with advancing gestational age." Medical Officer's Review, *infra* Appendix A, at 18. The review stated further: "This method of pregnancy termination is of limited value because of the relatively short window of opportunity, in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period." *Id.*

the ultrasound dating of pregnancies. FDA's approved regimen relies instead on a patient's recollection of her menstrual history and a physical examination. Dating based on menstrual history is inherently inaccurate because women may not have a perfect 28-day menstrual cycle[260] and because 25 percent of women experience bleeding during the early stages of pregnancy.[261] Gestational dating through physical examination, even when carried out by experienced clinicians, can also be inaccurate.[262] Factors such as patient body size, uterine fibroids, previous parity, and uterine position may impair a clinician's ability to assess uterine size.[263] Transvaginal ultrasound, by contrast, is accurate within plus or minus 3 days at gestational ages of 5 to 7 weeks.[264] "Transvaginal ultrasonographic examination is necessary to ensure accurate gestational

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[260] *See, e.g.,* Leon Speroff, M.D., Robert H. Glass, M.D., and Nathan G. Kase, M.D., *Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 219 ("The perfect 28 day cycle is indeed the most common mode, but it totaled only 12.4% of Vollman's cycles. Overall, approximately 15% of reproductive age cycles are 28 days in length. Only 0.5% of women experience a cycle less than 21 days long, and only 0.9% a cycle greater than 35 days. Most women have cycles that last from 24-35 days, but at least 20% of women experience irregular cycles.").

[261] *See* Peter W. Callen, M.D., *Ultrasonography in Obstetrics and Gynecology* 2nd ed. (Phila, Pa: W.B.Saunders Company; Harcourt, Brace, Jovanovich, 1988) at 32 ("Threatened abortion is a common complication that occurs in approximately 25% of clinically apparent pregnancies."); Speroff, *et al, Clinical Gynecologic Endocrinology and Infertility*, 5th ed. (Baltimore: Lippincott Williams and Wilkins, 1994) at 536 (noting that "pregnancy and pregnancy-related problems such as ectopic pregnancy or spontaneous abortion" can cause uterine bleeding).

[262] Steven R. Goldstein, M.D., Francis R. M. Jacot, M.D., Claude Poulin, M.D., and D. Scott Poehlmann, M.D., "Documenting Pregnancy and Gestational Age," Chapter 4, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999) ("*A Clinician's Guide*"): at 41 ("Although clinical sizing of the uterus during the first trimester can provide a rough estimate of gestational age, it is imprecise; misestimation of gestational age by uterine sizing alone can occur even in the hands of experienced clinicians.").

[263] *See A Clinician's Guide, infra* Appendix A, at 41 ("a number of conditions such as leiomymas, multiple gestation, and obesity may severely limit the accuracy of gestational age assessment by physical examination, warranting preprocedure assessment by ultrasonography in known or suspected cases") (footnotes omitted).

[264] *See* Salim Daya, M.B., "Accuracy of Gestational Age Estimation Using Fetal Crown-rump Measurements," *American Journal of Obstetrics and Gynecology* 168 (March 1993): 903–908; Ivar K. Rossavik, M.D., George O. Torjusen, M.D., and William E. Gibbons, M.D., "Conceptual Age and Ultrasound Measurements of Gestation Age and Crow-Rump Length in *in Vitro* Fertilization Pregnancies," *Fertility and Sterility* 49 (1988): 1012-17. *See also* Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): 35-41. In this study comparisons of gestational age estimates based on the last reported menstrual period to those generated through ultrasound in patients presenting for medical abortion, revealed the former method to be significantly inaccurate in approximately half the cases. The authors observed: "It is interesting that in this population of women seeking abortion the gestational age according to the LMP [last menstrual period] was verified

dating for provision of medical abortion according to current standards in clinical guidelines established by the National Abortion Federation."[265]

b. Ultrasound Is Necessary to Identify Ectopic Pregnancies

Approximately two percent of all pregnancies in the United States are "ectopic pregnancies," in which the pregnancy is located outside the uterus – often in the fallopian tube.[266] Mifeprex does not terminate ectopic pregnancies.[267] Therefore, if a woman who has an ectopic pregnancy undergoes a mifepristone-misoprostol abortion, she is at risk for tubal rupture and subsequent hemorrhage due to delay in diagnosis and delay in treatment. The symptoms of an ectopic pregnancy – vaginal bleeding, pelvic pain, and cramping – are confusingly similar to certain side effects of the Mifeprex Regimen.[268] A woman with an ectopic pregnancy is at risk of suffering massive intra-abdominal hemorrhage, damage to her reproductive organs, permanent

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by the transvaginal ultrasonographic examination only 48% to 56% of the time when a gestational sac was present and only 55% to 64% of the time when an embryonic pole was present . . . . These results, though, do not even include those women who were excluded from the studies because the ultrasonographic examination findings were so different from the dates by LMP that the estimation of gestational age was changed too much for them to be included." *Id.*

[265] Mitchell D. Creinin, M.D. and Heather Jerald, "Success Rates and Estimation of Gestational Age for Medical Abortion Vary with Transvaginal Ultrasonographic Criteria," *American Journal of Obstetrics and Gynecology* 180 (1999): at 35-41 (text preceding n. 8) (citation omitted).

[266] Centers for Disease Control, "Ectopic pregnancy – United States, 1990-1992," *Morbidity and Mortality Weekly Report* (*MMWR*) 44 (No. 3) (Jan. 27, 1995): at 46. The number of ectopic pregnancies may be even higher now because sexually transmitted diseases and other causes of ectopic pregnancy are more widespread than they were in 1992 – the latest year for which the Centers for Disease Control have reported the number of ectopic pregnancies. *Id.* at 46-7.

[267] *See, e.g.*, Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-S75, at S72 ("Mifepristone has not proved effective in treating extrauterine pregnancy . . . .").

[268] *See* American College of Obstetricians and Gynecologists, "Medical Management of Abortion," *ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists* 26 (April 2001): at 6 (noting that in medical abortions, "women may even experience symptom resolution consistent with a complete medical abortion and still have a persistent gestational sac or even an ectopic pregnancy") ("ACOG Practice Bulletin"). Vaginal bleeding, for example, is a normal consequence of the Mifeprex Regimen and may continue for weeks after a woman ingests Mifeprex and misoprostol. *See, e.g.*, Spitz, *infra* Appendix A, at 1243 ("Vaginal bleeding is a natural consequence of the abortion process, and it occurred in all the women whose pregnancies were terminated

sterility, and even death if not promptly treated by emergency surgery. The authors of a French mifepristone study in which a participant with an ectopic pregnancy underwent emergency surgery to stop heavy bleeding, concluded that:

> The case of undiagnosed ectopic pregnancy, which ruptured suddenly 2 days after misoprostol intake, indicates that (1) mifepristone plus misoprostol is not an effective treatment of ectopic pregnancies and should not be used for this purpose, and (2) all medical means of detecting an ectopic pregnancy should be used before prescribing mifepristone plus misoprostol.[269]

Although the Mifeprex Label states that the Mifeprex Regimen is contraindicated for women with a "[c]onfirmed or suspected ectopic pregnancy,"[270] FDA did not require that ultrasound be used to exclude women with ectopic pregnancies. Instead, the approved regimen relies solely on a self-certification by the prescribing physician that she has the "[a]bility to diagnose ectopic pregnancies."[271] A physical examination alone cannot accurately identify ectopic pregnancies. Ultrasound, "[i]n addition to providing the best information for gestational age determination . . . can also provide useful diagnostic information regarding a wide variety of pathologies of early pregnancy," including ectopic pregnancies.[272]

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medically. The median duration of bleeding or spotting was 13 days in the [less than or equal to] 49-days group and 15 days in the other two groups (P<0.001).").

[269] Elizabeth Aubény, *et al.*, "Termination of Early Pregnancy (Up to 63 Days of Amenorrhea) with Mifepristone and Increasing Doses of Misoprostol," *International Journal of Fertility & Menopausal Studies* 40 (1995): 85-91, at 91.

[270] *See* Mifeprex Label ("Contraindications").

[271] *See* Mifeprex Prescriber's Agreement.

[272] *A Clinician's Guide*, *infra* Appendix A, at 47-8.

2. FDA's Approved Regimen Is Not Restricted to Properly Trained Physicians who Have Admitting Privileges to Emergency Facilities

FDA's approved regimen lacks any objective qualifications for prescribing physicians and administering health care providers.[273] The health care provider administering the Mifeprex Regime need not undergo training, may not necessarily be an obstetrician or gynecologist, may not have any surgical training or training in the management of abortion complications, and may not even be a physician.[274] For example, the Mifeprex Regimen could be administered by a nurse untrained in any type of abortion and under the remote supervision of a family practitioner who does not regularly practice obstetrics and is incapable of providing emergency care.

Physicians and the health care staff that they supervise require formal training in both pharmaceutical and surgical abortion to minimize the morbidity inherent in performing mifepristone abortions.[275] National Abortion Federation guidelines provide that "[a]ll personnel performing abortions must receive training in the performance of abortions and in the prevention,

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[273] Self-certifications do not provide an effective substitute for imposing objective, auditable requirements. The Mifeprex Prescriber's Agreement, for example, merely requires that the prescribing physician profess to have the "[a]bility to assess the duration of pregnancy accurately." The vacuity of this stipulation is illustrated in remarks made by Dr. Susan Allen (who later became an FDA official) before the FDA Advisory Committee. Dr. Allen stated, "If you also recall when you go through medical school you learn how to date a pregnancy." FDA Hearings Transcript, *infra* Appendix A, at 319.

[274] *See* Teleconference Meeting Minutes, re: status of pending review issues pertaining to this drug product (Aug. 11, 2000): at 1 ("the distribution system would allow for physicians to obtain the drug product after meeting all qualifications, but Mifeprex could be administered by someone who is under the supervision of that physician such as midwives or nurse practitioners")[FDA FOIA Release: MIF 004587-88]; *see also*, Mifeprex Approval Memo, *infra* Appendix A, at 4-5 ("Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician from dispensing the drug to patients, provided state laws permit this.").

[275] A survey of methotrexate abortion providers underscores the necessity of training in both medical and surgical abortion. *See* S. Marie Harvey, Linda J. Beckman, and Sarah J. Satre, "Experiences and Satisfaction with Providing Methotrexate-Induced Abortions among U.S. Providers," *Journal of the American Medical Women's Association* 55 (2000): 161-63, at 162 (In a study comparing methotrexate and surgical abortion, "[m]ost providers felt strongly that all clinic staff should be familiar with both procedures and, thus, the training needs would be equivalent. This thought was echoed not only by physicians, who must be prepared to perform an emergency surgical abortion if methotrexate fails, but also by other clinic personnel. Thirty-nine percent of providers thought that medical abortion

recognition, and management of complications."[276] Additionally, ACOG recommends that "[c]linicians other than obstetrician-gynecologists who wish to provide medical abortion services should work in conjunction with an obstetrician-gynecologist or be trained in surgical abortion in order to offer medical abortion treatment."[277] The necessity for training in surgical abortion as well as mifepristone abortion stems primarily from the high failure rate of the Mifeprex Regimen. In the U.S. Clinical Trial, the Mifeprex Regimen failed for 8 percent of women with pregnancies of less than or equal to 49 days' gestational age.[278]

Excessive bleeding, which is much more common following a Mifeprex abortion than a surgical abortion, is particularly likely to necessitate urgent surgical intervention. Based on an international study comparing surgical and medical abortion, FDA's Medical Officer noted that "[o]n the whole, medical abortion patients reported significantly more blood loss than did surgical abortion patients" and characterized this as a "serious potential disadvantage of the medical method."[279] In the U.S. Clinical Trial among patients whose pregnancies were of no more than 49 days' gestation, excessive bleeding resulted in one blood transfusion, two hospitalizations, two emergency room treatments, and thirteen surgical interventions.[280] In

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required more training; specifically, learning to do a vaginal ultrasound and to handle the unpredictable outcomes of methotrexate abortion required lengthy training.").

[276] National Abortion Federation, "National Abortion Federation Clinical Policy Guidelines, 1998," Appendix, in Maureen Paul et al., eds., *A Clinician's Guide to Medical and Surgical Abortion* (Philadelphia: Churchill Livingstone / Harcourt Brace, 1999): at 256 ("*A Clinician's Guide*").

[277] ACOG Practice Bulletin, *infra* Appendix A, at 6.

[278] *See* Medical Officer's Review, *infra* Appendix A, at Table 1. Seventeen percent of women with pregnancies of between 50 and 56 days' gestational age and 23 percent of women with pregnancies between 56 and 63 days were failures. *See id.* In an international study reviewed by the Medical Officer, failure rates for mifepristone abortion were 5.2 percent, 8.6 percent and 16 percent in India, China and Cuba respectively, while comparable failure rates for surgical abortion were 0, 0.4 percent, and 4.0 percent. *See* Medical Officer's Review, *infra* Appendix A, at 19.

[279] Medical Officer's Review, *infra* Appendix A, at 19 (no citation by FDA Medical Officer).

[280] Medical Officer's Review, *infra* Appendix A, at 17.

addition, 5 percent of the patients in this group received uterotonic agents to stem bleeding.[281] A delay in intervention may be life-threatening,[282] as was illustrated by the experience of one of the participants in the U.S. Clinical Trial. The treating physician described the incident to the FDA Advisory Committee:

> In November of 1994, I was called to the [emergency room] for a woman who was bleeding due to a miscarriage, and was in obvious shock. A blood test showed that she had lost between one-half to two thirds of her blood volume . . . .
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> I had thought she was having an incomplete miscarriage, but her husband . . . told me that she had taken RU486 approximately 2 weeks before. It was my clinical opinion that she would die soon if she did not have an immediate [dilation and curettage].
>
> Without even doing the routine preparation we normally do for surgery, I realized that I had to take her immediately to surgery to save her life. I took her to the operating room and removed the contents of her uterus surgically. I gave her two units of packed red blood cells intraoperatively.
>
> Even later that evening, . . . [s]he required two more units of blood because she was still orthostatic and symptomatic.[283]

The Mifeprex Regimen is contraindicated for "any patient who does not have adequate access to medical facilities equipped to provide emergency treatment."[284] FDA's approved regimen, however, does not require prescribing physicians to have *admitting* privileges to emergency facilities. The approved regimen requires only that a physician who is not able "to provide surgical intervention in cases of incomplete abortion or severe bleeding . . . ma[k]e plans to provide such care through others, and [be] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[285] Plans for back-up care

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[281] Medical Officer's Review, *infra* Appendix A, at 17.

[282] When surgery is indicated because of acute bleeding, significant, or even life threatening blood loss, has already taken place. The preoperative preparation of the patient is often compromised in the rush to complete the surgery, which results in higher infection rates and more anesthetic complications, such as aspiration during intubation.

[283] FDA Hearings Transcript, *infra* Appendix A, at 223-25 (testimony of Dr. Mark Louviere).

[284] *See* Mifeprex Label ("Contraindications").

[285] Mifeprex Prescriber's Agreement. FDA, however, took two steps that suggested that it has lingering concerns about the absence of a surgical intervention qualification for Mifeprex prescribers. First, the Mifeprex Label includes a "black box" warning governing surgical back-up. Second, FDA required the Population Council to perform a post-approval study "[t]o ensure that the quality of care is not different for patients who are treated by

may be nothing more than "having the ability and responsibility to direct patients to hospitals, if needed."[286] Moreover, the approved regimen does not include an objective geographical limitation to ensure that the patient has easy access to the designated emergency care facility.[287]

3. The Sponsor's Recent "Dear Doctor Letter" and FDA's Explanatory Webpage Announcing Serious Adverse Events Validate the Petitioners' Concerns

On April 17, 2002,[288] Danco, with FDA's assistance, issued a letter to health care providers to alert them to "New Safety Information," to remind them that Mifeprex was approved for use in a prescribed regimen, and to encourage them to provide patient counseling and report adverse events.[289] The "New Safety Information" consisted of a number of reports of serious adverse events that had been experienced by women who were undergoing or had

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physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention . . . ." Mifeprex Approval Memo, *infra* Appendix A, at 5.

[286] Mifeprex Approval Memo, *infra* Appendix A, at 5. FDA's decision not to include a requirement that the prescribing physician have admitting privileges at a hospital could delay the patient's admission for emergency care. Another likely consequence of not requiring the prescribing physician to have admitting privileges is underreporting of serious adverse events related to the Mifeprex Regimen. The treating physician, not privy to the Prescriber's Agreement, may not file a serious adverse event report or notify the abortion provider of the complications that arose from the Mifeprex Regimen.

[287] The Chinese experience with mifepristone suggests that mifepristone should not be administered in facilities unable to provide potentially necessary emergency services. Thus, recently, the Chinese State Drug Administration responded to concerns that women were suffering as a result of lax controls on mifepristone by reiterating its policy that the drug "can only be administered at a hospital under a doctor's supervision and cannot be sold at pharmacies even with a prescription." *See* Kaiser Family Foundation, "China Reaffirms Restrictions on Unsupervised Mifepristone Use," *Kaiser Daily Reproductive Health Report* (Oct. 15, 2001) (available at: <http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=2&DR_ID=7453>) (reporting also that, "[t]hree years ago, the Shanghai Health Bureau restricted the use of mifepristone to certain hospitals in the area because of fears of complications").

[288] The letter bears the date, April 19, 2002, but was disseminated to the public on April 17, 2002.

[289] Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>). Coincidentally, on the same day FDA and Danco publicized these serious adverse events, the agency also announced major changes to the Cytotec (misoprostol) label. *See* FDA, "Major Changes to Cytotec Labeling" (April 17, 2002). Pursuant to these labeling changes, pregnancy was removed from the list of contraindications on the Cytotec label and the black box warning cautioning pregnant women not to take the drug was also removed.

recently completed the Mifeprex Regimen.[290] A number of patients had suffered from ruptured ectopic pregnancies and one of these women died from hemorrhage.[291] The letter also reported "[t]wo cases of serious systemic bacterial infection (one fatal)."[292] The fatality apparently precipitated a halt in the Population Council's Canadian clinical trials of mifepristone.[293] Finally, a 21 year old woman suffered a heart attack three days after she completed the Mifeprex Regimen.[294] These and other adverse events had been reported to FDA through its Adverse Event Reporting System (AERS).[295] Two of the patients who were reported to have suffered life-threatening adverse events were 15 years old.[296] These incidents bear out the concerns about the safety of the regimen detailed above, and the relatively high rate of serious adverse events among adolescents is of particular concern.

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[290] The letter did not specify the number of adverse events about which Danco had been informed, but five individual cases were discussed.

[291] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[292] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[293] It appears that the woman reported to have died from a systemic bacterial infection was a Canadian trial subject. *See* Marnie Ko, "A Volunteer Dies While Testing a Controversial New Drug, Bringing the Trial to a Halt," The Report (Oct. 8, 2001) (available at: <http://report.ca/archive/report/20011008/p48ai011008f.html>). *See* also Henry P. Kaiser Family Foundation, "Population Council Announces Death of Woman Involved in Canadian Mifepristone/Misoprostol Trial," Daily Reproductive Health Report (Sept. 11, 2001) (available at: <http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=6877>). A *Clostridium sordellii* infection apparently caused the woman to suffer septic shock. *See generally* G.L. Mandell, J.E. Bennett, and R. Dolin, *Principles and Practice of Infectious Diseases* (5th ed. 2000): at 2551 (explaining that a disease process in which "clostridia clearly play a major pathogenic role i[s] uterine gas gangrene, now a rare complication that was previously seen in the setting of septic abortion." "*C. sordellii* has been reported as a cause of uterine gas gangrene . . . ."). *See also* FDA Q & A's, *infra* Appendix A, at Question 3 ("Serious systemic bacterial infection is a severe life-threatening infection that spreads throughout the body and can cause death.").

[294] *See* Dear Doctor Letter, *infra* Appendix A, at 1.

[295] *See, e.g.*, Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3819498-2 (Nov. 2, 2001) (intervention to prevent permanent impairment or damage); 3806144-7 (Oct. 9, 2001) (death of a patient with an ectopic pregnancy); 3769840-6 (July 30, 2001) (hospitalization of patient with an ectopic pregnancy); 3769842-X (July 30, 2001) (intervention to prevent permanent impairment or damage); 3719885-7 (May 8, 2001) (death in conjunction with the use of misoprostol and Mifegyne, which is the trade name of mifepristone distributed in France); 3713452-7 (Apr. 27, 2001) (intervention to prevent permanent impairment or damage); and, 3769838-8 (July 30, 2001) (intervention to prevent permanent impairment or damage). The AERS depends on voluntary reporting and the accuracy of these reported adverse events cannot be verified, nor can the cause of these events be identified with certainty. There may have been other adverse events that were not reported.

Simultaneously with Danco's distribution of the *Dear Doctor Letter*, FDA published a webpage with 14 questions and answers related to mifepristone in an attempt to answer some of the questions likely to be prompted by the letter and to urge health care providers to adhere to the approved regimen.[297] FDA's answers, however, leave much to be desired from a medical and scientific standpoint.

First, FDA has understated the possibility that the Mifeprex Regimen caused the serious adverse events reported in the letter.[298] FDA did not adequately explain why women who were apparently healthy prior to undergoing the Mifeprex Regimen experienced life-threatening or fatal complications such as ruptured ectopic pregnancies, heart attacks, and systemic bacterial infections.

Second, FDA inappropriately attempted to link these adverse events to the unapproved vaginal administration of misoprostol.[299] It was reckless for FDA to suggest that the vaginal administration of misoprostol caused these adverse events while overlooking critical flaws in the

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[296] *See* Office of Postmarketing Drug Risk Assessment, AERS Report, ISR Numbers 3803789-5 (Oct. 3, 2001) and 3815629-9 (Oct. 26, 2001).

[297] FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm).

[298] *See* Dear Doctor Letter, *infra* Appendix A, at 1 ("No causal relationship between any of these events and use of Mifeprex and misoprostol has been established."). An FDA official interviewed (without attribution) downplayed the connection between the Mifeprex Regimen and the adverse events. *See* Susan Okie, "Physicians Sent Abortion Pill Alert: Six Women Using RU-486 Taken Ill, and Two Died, Letter Says," *Washington Post* (Apr. 18, 2002): at A2 ("These are, in fact, a very small number of events. Some of them were clearly not caused by the drug regimen.").

[299] The repeated references to the unapproved vaginal use of misoprostol in the FDA Q & As give rise to the inference that the reported adverse events are attributable to this single departure from the Mifeprex Regimen. *See, e.g.*, FDA Q & As, *infra* Appendix A, at Question 1 ("In all of these cases, misoprostol was given vaginally, not orally, which is the approved regimen. FDA has not reviewed data on the safety and effectiveness of vaginal administration of misoprostol."); *id.* at Question 4 ("We do not know what role, if any, Mifeprex and 'off-label' use of vaginal misoprostol may have in developing serious infections."); *id* at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol vaginally at different doses? There are published studies of the use of mifepristone with vaginal administration of misoprostol for abortion. The misoprostol doses used in these studies are higher than those described in the Mifeprex labeling . . . ."); *id.* at Question 10 ("Are there risks with vaginal use of misoprostol?").

approved regimen for Mifeprex use in the United States. FDA should have first assessed essential aspects of this regimen.

It is clear, for example, that absent ultrasonographic screening for ectopic pregnancy, there is increased risk that an intact or rupturing ectopic pregnancy will be misdiagnosed as a normally progressing Mifeprex abortion. Additionally, Mifeprex abortions may be performed by practitioners who are not physicians, who cannot perform surgical abortions, or who are unable to diagnose ectopic pregnancies and their complications.

Nor is there reason to believe that systemic bacterial infection is more likely to occur following vaginal, rather than oral, administration of misoprostol. Misoprostol is commonly administered vaginally for the induction of labor without higher reported rates of either intrauterine or systemic infection when compared to orally administered misoprostol or other methods of labor induction. Rather, the occurrence of life-threatening infection in women undergoing a Mifeprex abortion should raise questions about whether prolonged genital tract bleeding in the artificial hormonal milieu created by the Mifeprex Regimen might foster or promote infectious complications. In addition, infection might occur in women who, believing that their abortion is complete and unaware that their uterus actually contains dead tissue, fail to return for follow-up visits.[300] This may be a particular problem when the Mifeprex Regimen is prescribed to adolescents.

The occurrence of a heart attack in a 21 year old woman is always cause for significant concern. A French woman undergoing a mifepristone abortion suffered a fatal heart attack in

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[300] A. Karen Kreutner, M.D., "Postabortion Infections," *Contemporary Ob/Gyn* 1 (2001): at 37-42 (". . . because medical termination may be incomplete in between 3% and 23% of patients, retained tissue and subsequent infection may go unrecognized in those lost to follow up. . . . Some experts fear there will be compliance problems with the third visit, especially when the patient terminates early. In these cases, retained tissue, thought by the patient to be normal bleeding, could lead to endometritis.").

1991. A different prostaglandin (Sulprostone) administered by injection was used in that case.[301] This new case highlights the need for further investigation into a possible causal link between mifepristone-prostaglandin abortions and myocardial infarction.[302]

The ratio of serious adverse events to total uses of the Mifeprex Regimen cannot be ascertained because serious adverse event reporting is likely incomplete and because it is not publicly known how many times the Mifeprex Regimen has been used. Regardless of the relative number of serious adverse events, the nature of these events demands immediate FDA action to prevent future patient injuries and deaths.[303] The Joint Commission on the Accreditation of Healthcare Organizations[304] ("JCAHO" or "Joint Commission") has developed an approach for investigating adverse events similar in gravity to those that prompted the issuance of the Dear Doctor Letter. The JCAHO looks for "sentinel events" which are "unexpected occurrence[s] involving death or serious physical or psychological injury, or the risk thereof."[305] "Sentinel events" *signal* the need for the commencement of a "root cause

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[301] *See* "Noticeboard: A Death Associated with Mifepristone/Sulprostone," *Lancet* 337 (April 20, 1991): at 969-70 ("A spokeswoman for Roussel-Uclaf SA, the company that manufactures mifepristone, said 'the death was clearly from cardiovascular shock following 'Nalador' (Schering) injection.'").

[302] The Mifeprex Regimen should be contraindicated for women with cardiovascular risk factors until further clinical experience indicates that such contraindication is unnecessary.

[303] Even FDA acknowledged the rarity of the events referenced in the Dear Doctor Letter. With respect to bacterial infection, for example, FDA observed that "the rate of serious infection as a complication of pregnancy is 3.5 per 1000 pregnancies. Uterine infection occurs in 0.1-4.7% of first trimester surgical abortions and in 0.0-6.1% of medical abortions. In the past, it was most often associated with illegal abortions. It rarely occurs with pelvic surgery or even with otherwise normal childbirth." FDA Q & A's, *infra* Appendix A, at Question 3. FDA similarly noted the unusual nature of a heart attack in a young woman: "The single heart attack occurred in a 21 year old. A heart attack in very young women is extremely rare. . . . In 1997, the rate among US women aged 20-24 years was 0.19 per 100,000 women." *See id.* at Question 4.

[304] The Joint Commission "evaluates and accredits nearly 18,000 health care organizations and programs in the United States. An independent, not-for-profit organization, JCAHO is the nation's predominant standards-setting and accrediting body in health care. Since 1951, JCAHO has developed state-of-the-art, professionally based standards and evaluated the compliance of health care organizations against these benchmarks." Joint Commission webpage at: <http://www.jcaho.org/whatwedo_frm.html>.

[305] Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#I. Sentinel Events>.

analysis" of the event(s),[306] with the goal of developing an appropriate administrative response from the health care organization that will prevent the occurrence of future serious adverse events. A root cause analysis of sentinel events is performed before a statistically significant number of injuries or deaths occurs. It seeks to discern the facts surrounding each occurrence, distinguish factors peculiar to individuals from those pointing to procedural or administrative deficiencies, and recommend corrective measures to such systemic failures in the delivery of a particular therapy.

It is particularly important that FDA react to these sentinel events because the clinical trials underlying the approval of the Mifeprex Regimen did not adhere to FDA's endorsed scientific methodology for such trials. The substandard trial design of the U.S. and French Clinical Trials precluded an accurate estimation of the safety of the Mifeprex Regimen compared to the existing available alternatives. Moreover, FDA did not require the sponsor to conduct rigorous Phase IV studies, which could have compensated for some of these deficiencies by generating additional safety data. The agency has not performed a root cause analysis, but has instead hastily postulated that the vaginal administration of misoprostol is the underlying cause of the adverse events.[307] The Petitioners believe that there are probably more scientifically sound explanations for these adverse events and that the supposed safety of the Mifeprex Regimen has been called into question. The occurrence of the adverse events related to ectopic pregnancies and life-threatening systemic bacterial infections adds significant weight to the concerns of those

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[306] The Joint Commission defines "root cause analysis" as "a process for identifying the basic or causal factors that underlie variation in performance, including the occurrence or possible occurrence of a sentinel event. A root cause analysis focuses primarily on systems and processes, not individual performance. It progresses from special causes in clinical processes to common causes in organizational processes and identifies potential improvements in processes or systems that would tend to decrease the likelihood of such events in the future, or determines, after analysis, that no such improvement opportunities exist." Joint Commission webpage at: <http://www.jcaho.org/sentinel/se_pp.html#Root cause analysis>.

who have long warned that mifepristone-misoprostol abortions are dangerous. FDA has previously dismissed such concerns but now must respond to the accumulating evidence and act accordingly. Withdrawal of the approval is warranted.[308]

H. FDA'S APPROVAL OF MIFEPREX SHOULD BE WITHDRAWN BECAUSE THE SPONSOR IS NOT ENFORCING THE LIMITED RESTRICTIONS ON THE USE OF MIFEPREX

Mifeprex abortion providers openly flout the restrictions included in the approved regimen without any reaction from FDA, Danco, or the Population Council.[309] Shortly after approval, FDA asserted that "[i]f restrictions are not adhered to, FDA may withdraw approval."[310] Subpart H authorizes FDA to withdraw approval of a drug approved under Section 314.520 if "[t]he applicant fails to adhere to the postmarketing restrictions agreed upon."[311] When it adopted Subpart H, FDA explained that "[t]he burden is on the applicant to ensure that

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[307] *See* FDA Q & As, *infra* Appendix A, at Nos. 1, 4, 9, 10, and 11.

[308] The Secretary of HHS is authorized by 21 C.F.R. § 314.530(a) to withdraw approval of a Subpart H drug, subject to the applicant's right to a hearing, if, among other things, "(3) [u]se after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug; (4) [t]he applicant fails to adhere to the postmarketing restrictions agreed upon; (5) [t]he promotional materials are false or misleading; or (6) [o]ther evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use."

[309] The absence of a reaction from Danco may not be surprising in light of the cavalier attitude towards the FDA approval process exhibited by Dr. Richard Hausknecht, who is Danco's medical director. As early as July 1994, Dr. Hausknecht, had used methotrexate and misoprostol in clinical tests in the U.S. that Dr. Mitchell Creinin, a prominent abortion researcher, described as "downright unethical" and which Sandra Waldman of the Population Council described as being "very risky." Dr. Hausknecht stopped these experiments in September 1994 when the FDA told him to "stop performing the abortions unless he gets the backing of a medical institution and submits his data and procedures to the FDA for review." Carol Jouzaitis, "Doctor's Abortion-Drug Technique Draws Fire," *Chicago Tribune* (Sept. 12, 1994): at 1 & 14. Dr. Hausknecht admitted, " 'This is a little bit uncharted.' . . . . But he declared: 'Damn it. I'm not going to wait. This is a step forward. This is important. I want to see this available to women where it's not available now.' " *Id.* In addition, Dr. Hausknecht's website explains step two of the Mifeprex procedure that he employs: "At the conclusion of the [first] visit, the patient receives a packet containing tablets of misoprostol which are to be taken orally or placed in the vagina depending on the regimen you and Dr. Hausknecht choose." Available at: <http://www.safeabortion.com/procedure.htm> (visited July 7, 2002). Both the home use and the vaginal administration of misoprostol contravene FDA's approved regimen.

[310] *See* Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

[311] 21 C.F.R. § 314.530(a)(4).

the conditions of use under which the applicant's product was approved are being followed."[312] FDA should exercise its authority to withdraw its approval for Mifeprex.

Among the common departures from the approved regimen is the practice of offering the Regimen to women with pregnancies beyond seven weeks.[313] The "Mifepristone Medication Guide" directs women not to take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began." Moreover, women who use the Mifeprex Regimen sign a Patient Agreement, which includes a representation by the patient that "I believe I am no more than 49 days (7 weeks) pregnant.").[314] Thus, the practice of offering Mifeprex to women beyond seven weeks not only contravenes the approved regimen, but it also effectively requires patients to make an untruthful representation in the Patient Agreement. The *Los Angeles Times* explained that, "[B]y offering mifepristone up to the ninth week of pregnancy," Family Planning Associates, "the nation's largest for-profit abortion chain," "obtains a competitive edge over Planned Parenthood, which stays within the seven-week guideline."[315]

In another common deviation from the approved regimen, some abortion providers have eliminated the second of the three prescribed visits. During the initial visit, these providers give

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[312] *Subpart H Final Rule*, 57 Fed. Reg. at 58952.

[313] Liberty Women's Health Care of Queens, NY, openly acknowledges its use of Mifeprex beyond seven weeks: "While the FDA has approved mifepristone for non-surgical abortions only up to 7 weeks, we use a modified method to extend this period of eligibility in selected patients an additional 14 days up to 9 weeks." Available at: <http://www.abortbypill.com/2.html> (visited Dec. 31, 2001). Likewise, Preterm, an abortion clinic in Cleveland, Ohio, states that abortion using Mifeprex "is effective in terminating pregnancies up to 63 days (9 weeks) from the last normal menstrual period." Available at: <http://www.preterm.org/nonsurg.htm> (visited July 7, 2002).

[314] *See* Item 4 of the Patient Agreement for Mifeprex (mifepristone) Tablets ("Patient Agreement").

[315] Denise Gellene, "RU-486 Abortion Pill Hasn't Caught on in U.S.," *Los Angeles Times* (May 31, 2000): at A1 (quoting Family Planning Associates' official as saying, "You can catch a lot of women in those two [extra] weeks"). Family Planning Associates' website confirmed that the abortion provider offers Mifeprex to women with pregnancies up to nine weeks' gestational age. Available at: <http://www.webworldinc.com/fpamg/abortion_pill.htm> (visited July 7, 2002) ("Medical abortion is limited to patients less than nine weeks pregnant as verified by ultrasound.").

the patient misoprostol, typically with instructions to administer it to herself vaginally[316] at home two days later.[317] Yet home administration of misoprostol runs counter to what patients agree to in the Patient Agreement, which states that "I will . . . return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant."[318] The Population Council argued in favor of and FDA considered the benefits of self-administration at home, chief among which is the reduced burden on abortion providers and their facilities, but the agency concluded that these benefits are outweighed by the significant risks to women.[319] The second visit affords the physician the opportunity to monitor the status of

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[316] The likely reason that FDA's approved regimen calls for oral administration is that it is the only mode of administering misoprostol that is currently approved by the FDA. As discussed above, however, the use of misoprostol in conjunction with mifepristone to effect abortions is itself an unapproved indication.

[317] Presidential Women's Center in West Palm Beach, Florida, for example, gives women "four Misoprostol 200 mcg tablets to take home. Forty eight hours after the Mifepristone tablets have been administered the woman moistens four Misoprostol tablets with tap water and inserts them high into her vagina with her fingers." Available at: <http://www.presidentialcenter.com/medical.html> (visited July 7, 2002). *See also*: <http://www.heritageclinic.com/abortion/medical_abortion_pill.htm> (visited July 4, 2002) (Two days after the patient takes mifepristone, she "inserts Cytotec vaginally, which causes the uterus to contract and expel the embryo. This is very similar to the procedure that was FDA approved in 2000 and is approximately 98% effective. **Note:** The FDA approved protocol calls for 3 Mifeprex pills taken orally the first day and 2 Cytotec pills taken orally two days later. However, subsequent studies have show[n] 1 oral Mifeprex and 4 vaginal Cytotec to be as effective with less gastro-intestinal upset."); *see also*: <http://www.fwhc.org/concord/pages/mifepristone.html> (visited July 7, 2002) (Concord Feminist Health Center's web site describes the second phase of the procedure: "In a few days she inserts misoprostol tablets into her vagina. The pregnancy usually ends at home within four hours."); *see also*: <http://www.gynemed.org/ru.html> (visited July 7, 2002) (Gynemed Surgi-Center's web site states: "You will be given two doses of Misoprostol tablets and instructions on how to insert them into your vagina, which you wil[l] do 48 hours after taking RU486."); *see also*: <http://www.hopeclinic.com/medab.htm> (visited July 7, 2002) (Hope Clinic for Women, Ltd. Explains: "You will receive pills, misoprostol ("miss o pross tul") to take home with you. You will be instructed when to use them; they are placed vaginally."). Even the National Abortion Federation, which initiated a nationwide advertising campaign for Mifeprex, sanctions home administration of misoprostol in its "Medical Abortion Start-Up Packet." *See* National Abortion Federation, "Protocol Recommendations for Use of Mifepristone and Misoprostol in Early Abortion," *Early Medical Abortion with Mifepristone or Methotrexate: Overview and Protocol Recommendations* (Washington, D.C.: National Abortion Federation, 2001) at 36 ("Home administration of vaginal misoprostol has been found to be safe and effective up to 63 days' gestation and is highly acceptable to patients.").

[318] *See* Patient Agreement, Item 14. *See also* Mifeprex Medication Guide, which explains that on "Day 3 at your provider's office," "your provider will check to see if you are still pregnant," and "[i]f you are still pregnant, take 2 misoprostol tablets."

[319] FDA, which in its 2000 Mifepristone Approvable Letter, agreed to the Population Council's proposal to allow home administration of misoprostol, rejected that option after reconsideration of the issue. *See* Mifeprex Approval Memo, *infra* Appendix A, at 2-3 ("The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the

the termination[320] and assess the need for misoprostol – tasks which cannot be delegated to the patient.[321] In addition, the second visit enables patients whose abortions are complete to avoid having to take misoprostol.[322]

Danco and the Population Council have not effectively constrained providers of Mifeprex to adhere to the approved regimen. It appears instead that Danco and the Population Council have ignored well-publicized departures from that regimen. Deviations from the approved regimen are particularly troubling because the patient is told to disregard the regimen that she reads about in the Medication Guide and pledges to follow in the Patient Agreement. When a drug is approved under Subpart H, the drug's sponsor is responsible for ensuring compliance

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prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. . . . Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.").

[320] Because of the complications that can arise, periodic monitoring during the termination process is important. For the significant percentage of patients that fail to return for the third visit, the second visit may be the last opportunity for a health care provider to monitor the termination. In the U.S. Clinical Trial, five percent of patients failed to return for the third visit. *See* Medical Officer's Review, *infra* Appendix A, at 10. In other studies, the "loss to follow-up has ranged from three to eleven percent." *See* Spitz Article, *infra* Appendix A, at 1246 (citations omitted). The rate of patients who do not complete the entire regimen in routine clinical practice is likely to be even higher as they will not necessarily be subject to the U.S. Clinical Trial's exclusion criteria, which, among other things, excluded women who were "unlikely to understand and comply with the requirements of the study." Medical Officer's Review, *infra* Appendix A, at 9.

[321] *See* ACOG Practice Bulletin, *infra* Appendix A, at 6 (*citing* Mitchell Creinin, *et al.*, "Methotrexate and Misoprostol for Early Abortion: A Multicenter Trial," *Contraception* 53 (1996): at 321-27) ("Women as well as their practitioners are often unable to judge correctly if the women have aborted by evaluating symptomatology. In clinical trials with methotrexate and misoprostol, only about half of women who thought they had aborted actually had done so."); Beth Kruse *et al.*, "Management of Side Effects and Complications in Medical Abortion," *American Journal of Obstetrics and Gynecology* 183 (2000): S65-375, S73 ("Studies demonstrate that women may be unable to judge correctly on the basis of symptoms whether abortion has occurred.").

[322] For those patients whose abortions are not complete, the benefits of in-clinic misoprostol use would be enhanced if patients were required to spend several hours afterward in the abortion facility, where they would have ready access to pain medication and other medical help even if the abortion does not occur during the observation period. The Population Council persuaded FDA not to include this requirement, which was included in the protocol for the U.S. Clinical Trial. Forty-nine percent of the participants expelled their pregnancies during the four-hour observation period after the administration of misoprostol. *See* Spitz Article, *infra* Appendix A, at 1243. Nevertheless, a post-misoprostol waiting period was likely disfavored because the protracted presence of large numbers of bleeding and cramping women could place a strain on abortion facilities.

with the restrictions included in the approved regimen for use of the drug.[323] The Population Council and Danco have shirked this responsibility. FDA, therefore, should withdraw its approval of Mifeprex.

I. THE U.S. CLINICAL TRIAL FOR MIFEPRISTONE DID NOT MIRROR THE ANTICIPATED CONDITIONS FOR THE ULTIMATE USE OF THE DRUG

As a general rule, "Phase 3 trials are usually [conducted] in settings similar to those anticipated for the ultimate use of the drug."[324] FDA, however, approved a regimen that does not contain important safeguards that were employed in the U.S. Clinical Trial.[325] In the U.S. Clinical Trial, for example, the investigators relied on transvaginal ultrasonography (along with menstrual history and pelvic examination) to confirm the gestational age of each pregnancy.[326] The use of ultrasonography also excluded women with ectopic pregnancies. Moreover, physicians participating in the U.S. Clinical Trial had experience in performing surgical abortions, were trained in the administration of the mifepristone-misoprostol procedure, and had admitting privileges at medical facilities that could provide emergency care and hospitalization.[327] In addition, "[a]ll patients were within one hour of emergency facilities or the

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[323] *See Subpart H Final Rule*, 57 Fed. Reg. at 58953 ("The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed.").

[324] Bertram G. Katzung, M.D., Ph.D., and Barry A. Berkowitz, Ph.D., "Basic & Clinical Evaluation of New Drugs" in Bertram G. Katzung, ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk: Appleton & Lange, 1989): at 56.

[325] The French Clinical Trials, which were not performed by the Population Council, are not discussed here because they were not conducted for the purpose of supporting the mifepristone NDA and, therefore, were not designed to reflect American conditions of use.

[326] *See* Spitz Article, *infra* Appendix A, at 1242.

[327] "The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and /or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists." Mifeprex Approval Memo, *infra* Appendix A, at 5. Medical Officer's Review,

facilities of the principle [*sic*] investigator."[328] In the U.S. Clinical Trial, after taking misoprostol, "women were monitored for four hours for adverse events."[329] FDA has not retained these requirements governing physician training, ultrasound, the post-misoprostol waiting period, or physician privileges at facilities that provide emergency care.[330] FDA should not have extrapolated conclusions about the safety and efficacy of FDA's approved regimen from data generated under trial conditions not mirroring the approved regimen. Effectively, therefore, the agency approved a drug regimen that it had not tested.

J. BY WAIVING THE PEDIATRIC STUDY REQUIREMENT, FDA MAY HAVE ENDANGERED THE HEALTH OF ADOLESCENT GIRLS

FDA's approval of Mifeprex violated FDA's regulations, effective April 1, 1999, requiring that new drugs be tested for safety and effectiveness in the pediatric population (collectively, the "*Pediatric Rule*").[331] Requiring data on girls age 18 and under also would have been consistent with the guidelines for trials in the pediatric population that FDA accepted at the

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infra Appendix A, at 6 (The U.S. Clinical Trial was "conducted at centers that could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.").

[328] Mifeprex Approval Memo, *infra* Appendix A, at 5. The "one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services." *Id.* FDA contends that concerns arising from the elimination of the geographical proximity rule have "been dealt with through labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated." Mifeprex Approval Memo at 5.

[329] *See* Spitz Study, *infra* Appendix A, at 1242.

[330] The Prescriber's Agreement requires only that the supervising physician be "able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary." By contrast, the protocol for the U.S. Clinical Trial required that the physician have "privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc." Mifeprex Approval Memo, *infra* Appendix A, at 5. The shift in focus from access by the provider of the abortion to access by the woman who has the abortion, attenuated the link between the abortion provider and the emergency care provider, a link that is critical to ensuring that women receive timely emergency care.

[331] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (*Pediatric Adopting Release*). The notice of proposed rulemaking was released as: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Proposed Rule*, 62 Fed. Reg. 43900 (Aug. 15, 1997).

International Conference on Harmonization.[332] Nevertheless, in the Mifeprex Approval Letter, FDA stated, "We are waiving the pediatric study requirement for this action on this application."[333] Thus, FDA approved Mifeprex for use without requiring safety and effectiveness testing for the pediatric population.[334]

As FDA noted when it adopted the *Pediatric Rule*, "many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established."[335] FDA observed that "the absence of pediatric labeling information poses significant risks for children."[336] The ICH has noted that adolescence "is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development."[337] Such hormonal changes may "influence the results of clinical studies."[338] These concerns for the health of infants, children, and adolescents

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[332] *FDA Guidance: E11 Clinical Testing for Pediatric Uses* at 9 and 11 (Heading for Section 2.5.5). FDA, cognizant of the need for such studies, obtained a commitment from the sponsor in 1996 to conduct Phase IV studies to examine the safety and efficacy of the regimen in girls under 18 years of age. FDA subsequently curtailed this Phase IV study requirement when it approved the Mifeprex NDA.

[333] Mifeprex Approval Letter at 3.

[334] The Mifeprex Label accordingly included the standard disclaimer employed in drug labeling when the drug sponsor has not provided sufficient information to support a pediatric use for the drug: "Safety and effectiveness in pediatric patients have not been established."

[335] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[336] *Pediatric Adopting Release*, 63 Fed. Reg. at 66632.

[337] FDA, "Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population" (Rockville, Md.: Dec. 2000): at 11 (§ 2.5.5) ("*FDA Guidance: E11 Clinical Testing for Pediatric Uses*"). Section 2.5.5 states that the adolescent subgroup should extend from "12 to 16-18 years (dependent on region)." *Id.* at 11-12 (§ 2.5.5).

[338] *See FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 12 (§ 2.5.5). These ICH concerns, quoted below, pertaining to the difficulty of testing drugs in the adolescent population amplify the need for FDA to have required clinical study of the difficulties that might arise when teenage girls undergo the Mifeprex Regimen:

> Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.
>
> Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect

prompted FDA to begin the rulemaking that culminated with the issuance of the *Pediatric Rule*, establishing "a presumption that all new drugs and biologics will be studied in pediatric patients" unless the requirement is waived.[339] More specifically, the *Pediatric Rule* requires that applicants seeking approval for new chemical entities, new biological products, new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration contain safety and effectiveness information on relevant pediatric age groups.[340]

FDA made clear that the Mifeprex NDA was covered by the *Pediatric Rule*.[341] Nevertheless, FDA fully waived the rule for Mifeprex without explanation. Full or partial

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appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol, and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.").

Id. at 12 (§ 2.5.5).

[339] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 (introduction to "II. Highlights of the Final Rule"). The importance of testing drugs in children was highlighted during the recent controversy surrounding FDA's attempt to suspend the *Pediatric Rule*. FDA's planned two-year suspension came in response to the passage of the Best Pharmaceuticals for Children Act, which offers incentives for manufacturers to test drugs in children. Public Law No. 107-109, 115 Stat. 1408 ("BPCA"). *See also* Association of American Physicians and Surgeons, Inc. v. FDA, Defendants' Motion for Stay of Proceedings, Civil Action No. 00-2898 (HHK) (Mar. 18, 2002). FDA later reversed its position in response to criticism from physicians and members of Congress. FDA's attempt to suspend the *Pediatric Rule* prompted the introduction of identical legislation in the House of Representatives and the Senate to codify the *Pediatric Rule*. *See* S. 2394, 107th Congress, 2nd Session (2002) (co-sponsors: Senators Hillary Rodham Clinton (D-NY), Mike DeWine (R-OH), and Chris Dodd (D-CT)); and H.R. 4730, 107th Congress, 2nd Session (2002) (co-sponsors: Representatives John D. Dingell (D-MI), Henry A. Waxman (D-CA), Rosa DeLauro (D-CT), Anna Eshoo (D-CA) and Sherrod Brown (D-OH)). As Senator Hillary Rodham Clinton, a co-sponsor of the Senate bill explained, "if we want to protect our children over the long term, then we in Congress need to step in and make the Pediatric Rule the law of the land. Short of taking that action, we risk denying children the protection that we require for adults." Press Release, "Senators Will Introduce Legislation to Codify Pediatric Rule" (Apr. 17, 2002) (available at: <http://clinton.senate.gov/~clinton/news/2002/04/2002417811.html>). *See also* Marc Kaufman and Ceci Connolly, "U.S. Backs Pediatric Tests In Reversal on Drug Safety," *Washington Post* (April 20, 2002): at A3.

[340] *Pediatric Adopting Release*, 63 Fed. Reg. at 66634 ("A. Scope of the Rule"), and as required pursuant to 21 C.F.R. § 314.55(a).

[341] The Mifeprex Approval Letter stated: "Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application." Mifeprex Approval Letter at 3. Because the Mifeprex NDA was filed before the Pediatric Rule went

waivers of the pediatric study requirement may be granted either upon request of the applicant or by FDA on its own motion.[342] Both FDA-initiated and sponsor-requested waivers must satisfy certain criteria. FDA is required to grant a full or partial waiver "if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver … have been met."[343]

Section 314.55 provides three procedural tracks by which an applicant may obtain a waiver of the study requirement. The first requires that two conditions being met: [344] (1)"[t]he drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients," *and* (2) the drug product "is not likely to be used in a substantial number of pediatric patients." With respect to this basis for waiver, FDA has "emphasize[d] that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa."[345] As noted above, FDA, in connection with its determination to approve Mifeprex under Subpart H, concluded that the Mifeprex Regimen provides a therapeutic benefit over the existing treatment – surgical

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into effect, if a waiver had not been granted, the Population Council would have had until December 2, 2000 to submit "an assessment of pediatric safety and effectiveness." *See Pediatric Adopting Release*, 63 Fed. Reg. at 66658-59 ("V. Implementation Plan").

[342] Although it appears that FDA waived the rule *sua sponte*, FDA should have required the manufacturer to provide certain information to support the waiver. The agency has not released such documents to the public in response to FOIA requests. When it adopted the *Pediatric Rule*, the agency noted: "FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request." *Pediatric Adopting Release*, 63 Fed. Reg. at 66648 (§ 29).

[343] 21 C.F.R. § 314.55(c)(4)("FDA action on waiver.").

[344] 21 C.F.R. § 314.55(c)(2)(i).

[345] *Pediatric Adopting Release*, 63 Fed. Reg at 66635 ("II.D.2. Waiver of the Study Requirement," *see* first paragraph).

abortion.[346] This conclusion by itself precludes FDA from using the first method for granting waiver of the *Pediatric Rule*.[347]

Even if FDA had not judged the Mifeprex Regimen to offer a "meaningful therapeutic benefit," the second requirement for waiver in this first track is not met because Mifeprex can be expected to be used in a "substantial number of pediatric patients," which FDA defines as "50,000 pediatric patients with the disease for which the drug or biological product is indicated."[348] In the *Pediatric Adopting Release*, FDA stated that the "relevant age groups will . . . be defined flexibly."[349] With respect to Mifeprex, it would have been appropriate to classify girls under the age of 18 as pediatric patients because safety and effectiveness in this population had not been studied.[350] If the pediatric population comprises all girls age 17 and under, then we estimate that there were 357,200 pediatric pregnancies per year from 1995 to 1997 in the United States.[351] If the pediatric population comprises all girls age 16 and under, then we estimate that there were a total of 196,520 pregnancies per year from 1995 to 1997.[352] Even if the pediatric population encompasses only girls age 15 and under, we estimate that there were

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[346] *See* Mifeprex Approval Memo at 6.

[347] FDA noted that, for purposes of the *Pediatric Rule*, it would rely "in part, on CDER's current administrative definition of a 'Priority' drug, applied to pediatric populations" to define "meaningful therapeutic benefit." The phrase, "meaningful therapeutic benefit," appears identical in the Subpart H and Priority review contexts. As noted above, Mifeprex was accorded priority review. The modifications to "meaningful therapeutic benefit" for purposes of the *Pediatric Rule* appear to have broadened the scope of the phrase. *See Pediatric Rule*, 63 Fed. Reg. at 66646.

[348] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647.

[349] *Pediatric Rule*, 63 Fed. Reg. at 66634 ("C. Age Groups"). After noting comments to the proposed rule that argued for flexibility in setting age definitions (including a comment arguing for "pediatric patient" to include those "from 0 to 21 years"), FDA stated that "the age ranges identified in the proposal may be inappropriate in some instances" and that it had "deleted the references in the rule to specific age ranges." *Id.* at 66651.

[350] Although FDA acknowledged that the safety and effectiveness of Mifeprex were not studied in girls under age 18 and required a statement to that effect in the labeling, the agency anticipated and even encouraged use in this population when it stated that: "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients." Mifeprex Approval Memo at 7.

[351] *See infra* Appendix B at B-3.

[352] *See infra* Appendix B at B-4.

85,960 pregnancies per year from 1995 to 1997 in this age range.[353] Thus, under any definition of the pediatric population, the 50,000 patient cut-off set forth in the *Pediatric Adopting Release* is exceeded. In sum, *neither* of the requisite conditions for a waiver of the *Pediatric Rule* under the first waiver track provided in Section 314.55 is satisfied.[354]

Second, FDA may also waive the pediatric study requirements if the "necessary studies are impossible or highly impractical because, *e.g.*, the number of such patients is so small or geographically dispersed."[355] FDA explained that "that this ground for waiver [must] be interpreted narrowly":[356]

> Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. . . . Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.[357]

Pediatric Mifeprex studies would not have been either "impossible or highly impractical." As described above and in Appendix B, the population of pediatric females that becomes pregnant each year is large and the female population is evenly distributed throughout the United States. Thus, this second waiver track available under Section 314.55 could not have been satisfied (and FDA apparently has not taken a position to the contrary).

FDA may waive the pediatric study requirement under Section 314.55's third waiver track when "[t]here is evidence strongly suggesting that the drug product would be ineffective or

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[353] *See infra* Appendix B at B-4.

[354] *See* 21 C.F.R. § 314.55(c)(2)(i).

[355] *See* 21 C.F.R. § 314.55(c)(2)(ii).

[356] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

unsafe in all pediatric age groups."[358] As noted above, FDA endorsed the proposition that "there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen."[359] Thus, by suggesting that Mifeprex could be used appropriately in the pediatric population, FDA eliminated this third track as a possible basis for waiver.

Absent a waiver or deferral, the *Pediatric Rule* requires any drug application to "contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric subpopulations . . . ."[360] FDA is authorized instead to extrapolate such data from adult studies "[w]here the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients."[361] The underlying adult studies, however, must be "adequate and well-controlled."[362] As noted above, the Population Council did not provide evidence from adequate and well-controlled studies as to the safety and effectiveness of Mifeprex in the *adult* population. Reliance on these flawed adult studies for a determination of the safety and effectiveness of Mifeprex in the pediatric population was inappropriate. Furthermore, to assume that the effects of a potent antiprogesterone, mifepristone, and a

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[357] *Pediatric Adopting Release*, 63 Fed. Reg. at 66647 (§ 26, final paragraph).

[358] 21 C.F.R. § 314.55(c)(2)(iii).

[359] Mifeprex Approval Memo at 7.

[360] 21 C.F.R. § 314.55(a). FDA stated that it was waiving the *Pediatric Rule*. Mifeprex Approval Letter at 3. The agency did not assert that it had made a determination that pediatric studies were not required because the adult trials were sufficient to support extrapolation of conclusions as to safety and effectiveness in the pediatric population. However, because FDA failed to provide any justification for its waiver, it is difficult to determine whether the agency was, in fact, relying on this provision to eliminate the pediatric study requirement for Mifeprex.

[361] *See* 21 C.F.R. § 314.55(a).

[362] *See* 21 C.F.R. § 314.55(a).

powerful prostaglandin analogue, misoprostol, in pregnant adults can be extrapolated to pregnant adolescents, who are still developing physiologically and anatomically, is medically unsound.[363]

FDA violated its own rules when it waived the Pediatric Rule in the face of explicit criteria that necessitated compliance with the rule.[364] Furthermore, FDA offered no explanation for its determination to waive the rule. As FDA's treatment of other drugs illustrates, a waiver would have been appropriate only if Mifeprex had already been tested in children and labeled accordingly, or if the *Pediatric Rule's* criteria for waiver were satisfied.[365] Because FDA waived the study requirement in the face of explicit criteria that appear to prohibit such action in this instance, the agency violated its rule. In addition to violating Section 314.55, FDA's unexplained waiver of the *Pediatric Rule* for the Mifeprex NDA constitutes agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.[366]

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[363] The Mifeprex Regimen acts upon the reproductive system, which changes dramatically during adolescence. Adolescents, for example, could face disruptions in ovulatory function as a result of concentrations of mifepristone in developing ovarian follicles, or other health problems. Moreover, teenagers may face heightened risks arising from decreased compliance with the full regimen, poor recall of their last menstrual period, and their reluctance to tell others about their pregnancies.

[364] Of course, a partial waiver of the study requirement is appropriate for the non-adolescent pediatric sub-groups. *See* 21 C.F.R. § 314.55(c)(3). According to *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses*, the pediatric sub-populations other than "adolescents" are: 1) preterm newborn infants; 2) term newborn infants (0 to 27 days); 3) infants and toddlers (28 days to 23 months); 4) children (2 to 11 years). *FDA Guidance (ICH: E11): Clinical Testing for Pediatric Uses* at 9 (§ 2.5).

[365] In April 2000, FDA approved a suitability petition for Pamidronate Disodium Injection, 3 mg/mL, 10 mL vials, and 9 mg/mL, 10 mL vials, the listed drug products for which are Aredia (Pamidronate Disodium for Injection), 30 mg/vial and 90 mg/vial, and determined that the "proposed change in dosage form is subject to the Pediatric Rule but that a full waiver of the pediatric study requirement . . . is appropriate." *See* Letter, FDA to Mitchall G. Clark (April 18, 2000): at 1 (Docket No. 00P-0091/CPI) (concluding "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population since the necessary studies are impossible or highly impractical because the number of patients is small and geographically dispersed"). *See also* Letter, FDA to The Weinberg Group, Inc. (June 13, 2000): at 1-2 (Docket No. 99P-5447/CPI) (approving a generic manufacturer's petition to file an Abbreviated New Drug Application for Cefaclor Chewable Tablets, 125 mg, 187 mg, 250 mg, and 375 mg, the listed drug products for which are Ceclor (Cefaclor) for Oral Suspension, 125 mg/5mL, 187 mg/5mL, 250 mg/5mL, and 375 mg/5mL because FDA determined that the "proposed change in dosage form is subject to the Pediatric Rule" but "that investigations are not necessary to demonstrate the safety and effectiveness of your proposed products in the pediatric population, because the specific drug products that you reference are adequately labeled for pediatric use").

[366] FDA has required numerous drug sponsors to comply with the *Pediatric Rule*, but it approved Mifeprex without stating its basis for waiving the requirement. *See, e.g.*, Letter, FDA to King & Spalding (June 13, 2000): at 1

K. FDA'S UNEXPLAINED REDUCTION OF THE SPONSOR'S PHASE IV REQUIREMENTS WAS ARBITARY, CAPRICIOUS, AN ABUSE OF DISCRETION, OR OTHERWISE NOT IN ACCORDANCE WITH LAW

Not only did FDA improperly and without explanation waive its own pediatric testing requirements, but it also inexplicably narrowed the scope of the Population Council's commitments to conduct post-approval Phase IV studies. As a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects.[367] Phase IV, which occurs after a drug is approved, provides the opportunity to "monitor[ ] the safety of the new drug under actual conditions of use in large numbers of patients."[368] Not only

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(Docket No. 99P-2776/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Oxycodone Hydrochloride and Acetaminophen Oral Solution, 7.5 mg/500 mg per 15 mL, the listed drug product for which is Oxycodone and Acetaminophen Tablets 7.5 mg/500 mg, based on the fact that FDA "has determined that your proposed change in dosage form is subject to the Pediatric Rule and has concluded that investigations are necessary to demonstrate the safety and effectiveness in the pediatric population . . . . Therefore, the Agency concludes that the proposed product should be evaluated for safety and efficacy in the pediatric population."); Letter, FDA to Abbott Laboratories (Sept. 29, 1999): at 1-2 (Docket No. 98P-0821/CPI) (denying a generic manufacturer's petition to file an Abbreviated New Drug Application for Hydromorphone Hydrochloride Injection, 0.2 mg/mL, 30 mL vials, the listed drug product for which is Dilaudid-HP Injection, 10 mg/mL, 5 mL ampoules and 50 mL vials, because the "proposed change in route of administration is subject to the Pediatric Rule," "clinical trials are required for this specific drug product," and "investigations are necessary to demonstrate the safety and effectiveness in the pediatric population").

[367] A.G. Gilman, T.W. Rall, A.S. Nies, P. Taylor, eds., *The Pharmacological Basis of Therapeutics*, 8th ed. (New York: Pergamon Press, 1990): at 77 ("Although assessment of risk is a major objective of [clinical trials], this is far more difficult than is the determination of whether a drug is efficacious for a selected condition. Usually about 500 to 300 carefully selected patients receive a new drug during phase-3 clinical trials . . . . Thus, the most profound and overt risks that occur almost immediately after the drug is given can be detected in a phase-3 study, if these occur more often than once per 100 administrations. Risks that are medically important but delayed or less frequent than 1 in 1000 administrations may not be revealed prior to marketing. It is thus obvious that a number of unanticipated adverse and beneficial effects of drugs are only detectable after the drug is used broadly.").

[368] Bertram G. Katzung, M.D., ed., *Basic and Clinical Pharmacology*, 4th ed. (Norwalk, CT: Appleton & Lange, 1989): at 56. "Final release of a drug for general prescription use should be accompanied by a vigilant postmarketing surveillance program. The importance of careful and complete reporting of toxicity after marketing approval by the FDA can be appreciated by noting that many drug-induced effects have an incidence of 1:10,000 or less. . . . Because of the small numbers of subjects in phases 1-3, such low-incidence drug effects will not generally be detected before Phase 4, no matter how carefully the studies are executed. Phase 4 has no fixed duration." *Id.* at 56-7.

did FDA approve the NDA on the basis of clinical trials so defective with respect to their design and execution as to render them insufficient to establish short-term safety and effectiveness, but FDA also permitted the Population Council to substantially pare down the Phase IV trials that it would perform.

In response to an FDA request, on September 16, 1996, the Population Council agreed to conduct a set of Phase IV studies.[369] FDA "reminded" the Population Council of these commitments in both the 1996 and 2000 Approvable Letters.[370] The Population Council agreed to perform studies with the following objectives:

1. To monitor the adequacy of the distribution and credentialing system.
2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of method failure.
3. To assess the long-term effects of multiple use of the regimen.
4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.
5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke.
6. To ascertain the effect on children born after treatment failure.[371]

These studies would have addressed some of the health issues that were not evaluated during pre-approval testing.

The Mifeprex Approval Letter released on September 28, 2000, however, contains only two Phase 4 study obligations, a radical curtailment of the earlier commitments.[372] The letter

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[369] FDA made its request on August 22, 1996, after it had received Phase IV study recommendations from the FDA Advisory Committee. *See* Medical Officer's Review, *infra* Appendix A, at 20-24.

[370] *See* 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[371] 1996 Mifepristone Approvable Letter, *infra* Appendix A, at 7-8 and 2000 Mifepristone Approvable Letter, *infra* Appendix A, at 5.

[372] *See* Mifeprex Approval Letter, *infra* Appendix A, at 2-3.

stated that "the following Phase 4 commitments, specified in [the Population Council's] submission dated September 15, 2000 . . . *replace all previous commitments* . . . ."[373]

(1) "A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[374]
(2) "A surveillance study on outcomes of ongoing pregnancies."[375]

FDA stated that "[p]revious study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms."[376] The agency, thus, compounded its failure to require the Population Council and Danco to comply with the strictures of the Pediatric Rule when it permitted them to consider the effect of the Mifeprex Regimen on patients under 18 as part of another study rather than as a separate Phase IV study.[377] The Approval Letter explained that

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[373] Mifeprex Approval Letter, *infra* Appendix A, at 2.

[374] Mifeprex Approval Letter, *infra* Appendix A, at 3. The Population Council acknowledged three weaknesses of this study. First, the sample size would be limited so that the sponsor "will only be able to determine whether the combined safety rates of hospitalizations, medically necessary surgical interventions, and IV fluids in each of the two cohorts are within plus or minus 5 percentage points of the expected 2% rate. We will not be able to detect differences of individual safety outcomes such as blood transfusions and deaths." *See* Amendment 062 to the NDA, Revised Materials (Sept. 19, 2000): at 3. [FDA FOIA Release: MIF 007896-7903]. Second, the Population Council predicted that it might have difficulty finding women who were referred to another provider for care. *Id.* at 3-4. Third, it might be difficult to find women who did not return for their follow-up visit. *Id.* at 4. These three study weaknesses appear, at least in part, to stem from faulty selection criteria for study subjects. Patients should not be enrolled in a study unless they are willing to comply with follow-up visits and telephone inquiries. Additionally, informed consent forms authorize investigators to request medical records from other health care providers.

[375] Mifeprex Approval Letter, *infra* Appendix A, at 3.

[376] Mifeprex Approval Letter, *infra* Appendix A, at 3. These issues were characterized by the sponsor as "Secondary Study Objectives." *See* Amendment 062 to the NDA (Sept. 19, 2000): at 1. The failure to consider each issue in a separate study is likely to compromise the quality of the data generated. Because the study is primarily focused on a provider-level variable (ability to provide surgical intervention), the study will not necessarily yield a meaningful sample size for each of the relevant patient-level variables (age and smoking status). Patients will be enrolled "consecutively from each provider until the provider's quota is met." *See id.* at 2.

[377] The Population Council submitted data from the Spitz Study on 106 women age 35 and older and 51 patients under age 20. *See* Mifeprex Approval Letter, *infra* Appendix A, at 7. However, the effects and potential age-specific risks of the Mifeprex Regimen on women outside the tested age range deserve separate consideration in studies with far more subjects. Approximately 279,000 girls nineteen and younger and more than 84,000 women over the age of 35 obtain abortions in the United States annually. *See* Appendix B, *infra*, at B-4 (§§ 5 and 6). The Mifeprex Regimen, which directly interacts with the reproductive system, could conceivably interfere with pubertal development, as discussed above, and might pose unique risks to women who are nearing the end of their reproductive years.

"the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996."[378]

It appears, however, that the modifications came largely in response to the Population Council's unwillingness to explore the ramifications of the Mifeprex Regimen. On August 18, 1999, the Population Council acknowledged its Phase IV commitments, but stated that "[w]e plan to discuss in more detail and develop a consensus with the FDA post-NDA approval."[379] The Population Council complained, for example, that "[a] prospective study of the long-term effects of multiple use of the regimen in all American women would be unduly burdensome, might result in an invasion of women's privacy and would not likely produce a meaningful scientific result for decades."[380] Similarly, the Population Council informed FDA that it was "not able to commit to tracking down those women who are lost to follow-up because this would be very difficult and extraordinarily expensive. We are also concerned about the ethics of doing

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[378] Mifeprex Approval Memo, *infra* Appendix A, at 7. FDA's conclusion that the reduction to only two Phase IV studies "reflect[s] current postmarketing questions" ignores a number of issues about Mifeprex that remain unexplored. Because mifepristone interferes with pregnancy by binding to the progesterone receptor in the placenta, there is concern that the drug may affect not only the uterus, but the brain, breasts, adrenal glands, ovaries, and immune cells, all of which also have progesterone receptors. Concerns that mifepristone may have a carcinogenic effect on breast tissue have also been expressed. *See, e.g.,* Testimony of Dr. Joel Brind, FDA Hearings Transcript, *infra* Appendix A, at 172-175. Mifepristone also could affect the pituitary gland, the adrenal glands, and immune cells, all of which have glucocorticoid receptors. In addition, it is unclear whether a woman who undergoes multiple mifepristone-misoprostol abortions could suffer adverse effects. *See* ACOG Practice Bulletin, *infra* Appendix A, at 9 ("No well-designed prospective studies address the issue of repeat medical abortion."). Questions also remain about possible effects on the children born to women who have terminated a previous pregnancy with the Mifeprex Regimen. *See, e.g.,* P. Van der Schoot and R. Baumgarten, "Effects of Treatment of Male and Female Rats in Infancy with Mifepristone on Reproductive Function in Adulthood," *Journal of Reproduction and Fertility* 90 (1990): 255-66 (finding that rats exposed to mifepristone in their infancy suffered infertility in adulthood)[FDA FOIA Release: MIF 007165- 007176].

[379] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999).

[380] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999); s*ee also* Mifeprex Approval Memo at 7 (agreeing with the Population Council's reasoning).

this, as it could violate women's privacy."[381] The Population Council's concerns about privacy lack merit. Patients who participate in clinical trials give their consent to participate and to be monitored, thus eliminating concerns about privacy. Similarly, FDA should not have accorded undue weight to the Population Council's protestations about the potential expense of the trials; drug sponsors, who stand to profit from a drug's sales, are responsible for bearing the expenses incurred in establishing the safety and efficacy of a drug.[382]

FDA's acquiescence in the Population Council's reduction in its Phase IV commitments compounded the Agency's earlier failure to require the sponsor to conduct clinical trials in accordance with the requirements of Section 314.126 of FDA's rules. FDA's inadequately justified curtailment of the sponsor's Phase IV study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law.

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[381] Medical Officer's Review, *infra* Appendix A, at 24 (quoting from the Population Council's submission to FDA on Aug. 18, 1999). The necessity of long-term monitoring is particularly critical to compensate for the unusually short tracking periods employed in the U.S. Clinical Trial, in which investigators generally did not track patients after their third visit. *See* Spitz Article, *infra* Appendix A, at 1242. "Follow-up was extended beyond visit 3 if there was uncertainty about the completeness of the abortion or if bleeding persisted." *Id.* Five percent of the participants in the U.S. Clinical Trial were not tracked through the third visit (which would have occurred on Day 15) because they failed to return for it, suggesting that each of these women was last seen on Day 3, only 2 days after the initial administration of mifepristone. *See* Medical Officer's Review, *infra* Appendix A, at 10. Abbreviated follow-up periods run counter to ICH standards, which state that in clinical trials of drugs intended for use during pregnancy, "followup of the pregnancy, fetus, and child is very important." *FDA Guidance (ICH: E8): General Considerations*, *infra* Appendix A, 62 Fed. Reg. at 66117 (§ 3.1.4.3) ("Special populations").

[382] In fact, the sponsors of Mifeprex received substantial outside funding to support their efforts. *See* "Mifepristone: FDA Approval Imminent, Advocates Predict," *Kaiser Daily Reproductive Health Report* (Sept. 28, 2000) (available at: <http://www.kaisernetwork.org/reports/2000/09/kr000928.3.htm>) ("Danco Laboratories, LLC, a small New York-based company, will market the drug with funding from billionaire financier Warren Buffet and hedge-fund czar George Soros and a $10 million loan from the David and Lucile Packard Foundation."); Sharon Bernstein, "Persistence Brought Abortion Pill to U.S.," *Los Angeles Times* (Nov. 5, 2000): at A1 ("The Population Council raised $16 million from like-minded foundations, including the Open Society Institute of New York, which is the philanthropic arm of billionaire George Soros, and the California-based Kaiser Family Foundation.").

IV. PETITIONERS SEEK LEAVE TO AMEND

The Petitioners respectfully inform FDA that they may file amendments to this Petition as information becomes available from Freedom of Information Act requests made before the filing date of this document.[383]

V. CONCLUSION

For the foregoing reasons, the Petitioners respectfully request that the Commissioner immediately enter an administrative stay to halt any further distribution and marketing of Mifeprex until final agency action is taken on this Petition. The Petitioners also respectfully request that the Commissioner revoke approval of Mifeprex for the medical termination of pregnancies less than 49 days' gestation. On the basis of the evidence presented above, the Petitioners respectfully request a full FDA audit of the French and U.S. Clinical Trials.[384]

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[383] The Petitioners have filed numerous Freedom of Information Act ("FOIA") requests with FDA that remain unanswered, including: 1) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of FDA's letter to the Population Council dated, or mailed, on or about June 1, 2000, along with any attachments, appendices, and other accompanying materials"); 2) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Aug. 31, 2001) (seeking "an entire copy of the new drug application . . . filed . . . on or about March 18, 1996 (NDA 20-687)"); 3) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001) (seeking a copy of data submitted by the sponsor "related to the use of mifepristone by women over the age of thirty-five, females under the age of eighteen, and women who smoke" and of the Phase IV study protocols submitted by the Sponsor and any Phase IV trial data); and, 4) FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Feb. 6, 2002) (seeking a correct listing of all drug applications approved pursuant to 21 C.F.R. § 314.520 and documents detailing FDA's reasoning for approving drugs under this section of its rules).

[384] An audit of the U.S. Clinical Trial is additionally warranted because of an unusual data management decision made by the Population Council with the apparent approval of the FDA:

> Thank you for speaking with me the other day about our data dilemma. In response to our conversation, we have decided to create two versions of our electronic database from the mifepristone study. The first will reflect exactly the physical copies of the patient record forms, and will be used as the basis for our regulatory submissions to you. The second version will closely match the first, particularly on safety and efficacy indicators, but certain variables will be modified to create an internally consistent database that we can use easily for our planned scholarly publications on the topic. We will keep careful track of the changes we make and we will be able to explain them to an FDA auditor should the need arise. One result

VI. ENVIRONMENTAL IMPACT

This Petition for withdrawal of approval of an NDA is categorically excluded under 21 C.F.R. § 25.31(d). An environmental impact statement is, thus, not required.

VII. ECONOMIC IMPACT

The Economic Impact information shall be submitted only when and if requested by the Commissioner following review of the Petition, in accordance with 21 C.F.R. § 10.30.

CERTIFICATIONS AND SIGNATURES

On behalf of the petitioner organizations listed below, we the undersigned hereby certify that, to the best of petitioners' knowledge, this Citizen Petition is true and accurate. It includes all available information relevant to this Petition, including information both favorable and unfavorable to Petitioners' position in this matter.

So executed this 15 day of August 2002.

Donna Harrison MD

Donna Harrison, M.D.
Chairperson, Subcommittee on Mifeprex
American Association of Pro-Life
Obstetricians and Gynecologists
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of this approach to handling the data is that certain aspects of our future publications may differ from tabulations that appear in our regulatory submissions.

Letter, Charlotte Ellertson, Population Council, to [Redacted], FDA/CDER (July 28, 1997): at 1 [FDA FOIA Release: MIF 006489].

So executed this 13 day of August 2002.

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So executed this 20th day of August 2002.

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Exhibit 14

FDA-Approved Label for Misoprostol (Cytotec) (Jan. 2017)

Cytotec®
misoprostol tablets

WARNINGS

CYTOTEC (MISOPROSTOL) ADMINISTRATION TO WOMEN WHO ARE PREGNANT CAN CAUSE BIRTH DEFECTS, ABORTION, PREMATURE BIRTH OR UTERINE RUPTURE.

UTERINE RUPTURE HAS BEEN REPORTED WHEN CYTOTEC WAS ADMINISTERED IN PREGNANT WOMEN TO INDUCE LABOR OR TO INDUCE ABORTION. THE RISK OF UTERINE RUPTURE INCREASES WITH ADVANCING GESTATIONAL AGES AND WITH PRIOR UTERINE SURGERY, INCLUDING CESAREAN DELIVERY (see also **PRECAUTIONS** and **LABOR AND DELIVERY**).

CYTOTEC SHOULD NOT BE TAKEN BY PREGNANT WOMEN TO REDUCE THE RISK OF ULCERS INDUCED BY NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) (see **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS**).

PATIENTS MUST BE ADVISED OF THE ABORTIFACIENT PROPERTY AND WARNED NOT TO GIVE THE DRUG TO OTHERS.

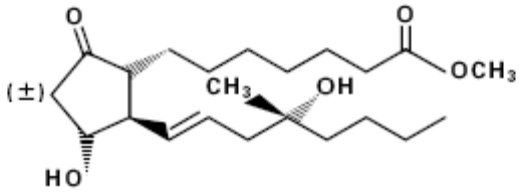
Cytotec should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, Cytotec may be prescribed if the patient

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy.
- is capable of complying with effective contraceptive measures.
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake.
- will begin Cytotec only on the second or third day of the next normal menstrual period.

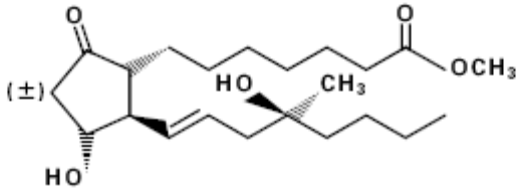
DESCRIPTION

Cytotec oral tablets contain either 100 mcg or 200 mcg of misoprostol, a synthetic prostaglandin E_1 analog.

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):



and



$C_{22}H_{38}O_5$ M.W. = 382.5

(±) methyl 11α,16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate

Misoprostol is a water-soluble, viscous liquid.

Inactive ingredients of tablets are hydrogenated castor oil, hypromellose, microcrystalline cellulose, and sodium starch glycolate.

CLINICAL PHARMACOLOGY

Pharmacokinetics: Misoprostol is extensively absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omega oxidation followed by reduction of the ketone to give prostaglandin F analogs.

In normal volunteers, Cytotec (misoprostol) is rapidly absorbed after oral administration with a T_{max} of misoprostol acid of 12 ± 3 minutes and a terminal half-life of 20–40 minutes.

There is high variability of plasma levels of misoprostol acid between and within studies but mean values after single doses show a linear relationship with dose over the range of 200–400 mcg. No accumulation of misoprostol acid was noted in multiple dose studies; plasma steady state was achieved within two days.

Maximum plasma concentrations of misoprostol acid are diminished when the dose is taken with food and total availability of misoprostol acid is reduced by use of concomitant antacid. Clinical trials were conducted with concomitant antacid, however, so this effect does not appear to be clinically important.

Mean ± SD	C_{max}(pg/ml)	AUC(0–4) (pg·hr/ml)	T_{max}(min)
Fasting	811 ± 317	417 ± 135	14 ± 8
With Antacid	689 ± 315	349 ± 108*	20 ± 14
With High Fat Breakfast	303 ± 176*	373 ± 111	64 ± 79*

* Comparisons with fasting results statistically significant, $p<0.05$.

After oral administration of radiolabeled misoprostol, about 80% of detected radioactivity appears in urine. Pharmacokinetic studies in patients with varying degrees of renal impairment showed an approximate doubling of $T_{1/2}$, C_{max}, and AUC compared to normals, but no clear correlation between the degree of impairment and AUC. In subjects over 64 years of age, the AUC for misoprostol acid is increased. No routine dosage adjustment is recommended in older patients or patients with renal impairment, but dosage may need to be reduced if the usual dose is not tolerated.

Drug interaction studies between misoprostol and several nonsteroidal anti-inflammatory drugs showed no effect on the kinetics of ibuprofen or diclofenac, and a 20% decrease in aspirin AUC, not thought to be clinically significant.

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs were administered 2 hours apart.

The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range.

After a single oral dose of misoprostol to nursing mothers, misoprostol acid was excreted in breast milk. The maximum concentration of misoprostol acid in expressed breast milk was achieved within 1 hour after dosing and was 7.6 pg/ml (CV 37%) and 20.9 pg/ml (CV 62%) after single 200 μg and 600 μg misoprostol administration, respectively. The misoprostol acid concentrations in breast milk declined to < 1 pg/ml at 5 hours post-dose.

Pharmacodynamics: Misoprostol has both antisecretory (inhibiting gastric acid secretion) and (in animals) mucosal protective properties. NSAIDs inhibit prostaglandin synthesis, and a deficiency of prostaglandins within the gastric mucosa may lead to diminishing bicarbonate and mucus secretion and may contribute to the mucosal damage caused by these agents. Misoprostol can increase bicarbonate and mucus production, but in man this has been shown at doses 200 mcg and above that are also antisecretory. It is therefore not possible to tell whether the ability of misoprostol to reduce the risk of gastric ulcer is the result of its antisecretory effect, its mucosal protective effect, or both.

In vitro studies on canine parietal cells using tritiated misoprostol acid as the ligand have led to the identification and characterization of specific prostaglandin receptors. Receptor binding is saturable, reversible, and stereospecific. The sites have a high affinity for misoprostol, for its acid metabolite, and for other E type prostaglandins, but not for F or I prostaglandins and other unrelated compounds, such as histamine or cimetidine. Receptor-site affinity for misoprostol correlates well with an indirect index of antisecretory activity. It is likely that these specific receptors allow misoprostol taken with food to be effective topically, despite the lower serum concentrations attained.

Misoprostol produces a moderate decrease in pepsin concentration during basal conditions, but not during histamine stimulation. It has no significant effect on fasting or postprandial gastrin nor on intrinsic factor output.

Effects on gastric acid secretion: Misoprostol, over the range of 50–200 mcg, inhibits basal and nocturnal gastric acid secretion, and acid secretion in response to a variety of stimuli, including meals, histamine, pentagastrin, and coffee. Activity is apparent 30 minutes after oral administration and persists for at least 3 hours. In general, the effects of 50 mcg were modest and shorter lived, and only the 200-mcg dose had substantial effects on nocturnal secretion or on histamine and meal-stimulated secretion.

Uterine effects: Cytotec has been shown to produce uterine contractions that may endanger pregnancy. (See boxed **WARNINGS.**)

Other pharmacologic effects: Cytotec does not produce clinically significant effects on serum levels of prolactin, gonadotropins, thyroid-stimulating hormone, growth hormone, thyroxine, cortisol, gastrointestinal hormones (somatostatin, gastrin, vasoactive intestinal polypeptide, and motilin), creatinine, or uric acid. Gastric emptying, immunologic competence, platelet aggregation, pulmonary function, or the cardiovascular system are not modified by recommended doses of Cytotec.

Clinical studies: In a series of small short-term (about 1 week) placebo-controlled studies in healthy human volunteers, doses of misoprostol were evaluated for their ability to reduce the risk of NSAID-induced mucosal injury. Studies of 200 mcg q.i.d. of misoprostol with tolmetin and naproxen, and of 100 and 200 mcg q.i.d. with ibuprofen, all showed reduction of the rate of significant endoscopic injury from about 70–75% on placebo to 10–30% on misoprostol. Doses of 25–200 mcg q.i.d. reduced aspirin-induced mucosal injury and bleeding.

Reducing the risk of gastric ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs): Two 12-week, randomized, double-blind trials in osteoarthritic patients who had gastrointestinal symptoms but no ulcer on endoscopy while taking an NSAID compared the ability of 200 mcg of Cytotec, 100 mcg of Cytotec, and placebo to reduce the risk of gastric ulcer (GU) formation. Patients were approximately equally divided between ibuprofen, piroxicam, and naproxen, and continued this treatment throughout the 12 weeks. The 200-mcg dose caused a marked,

statistically significant reduction in gastric ulcers in both studies. The lower dose was somewhat less effective, with a significant result in only one of the studies.

Reduction of Risk of Gastric Ulcers Induced by Ibuprofen, Piroxicam, or Naproxen
[No. of patients with ulcer(s) (%)]

	Therapy Duration			
Therapy	**4 weeks**	**8 weeks**	**12 weeks**	
Study No. 1				
Cytotec 200 mcg q.i.d. (n=74)	1 (1.4)	0	0	1 (1.4)*
Cytotec 100 mcg q.i.d. (n=77)	3 (3.9)	1 (1.3)	1 (1.3)	5 (6.5)*
Placebo (n=76)	11 (14.5)	4 (5.3)	4 (5.3)	19 (25.0)
Study No. 2				
Cytotec 200 mcg q.i.d. (n=65)	1 (1.5)	1 (1.5)	0	2 (3.1)*
Cytotec 100 mcg q.i.d. (n=66)	2 (3.0)	2 (3.0)	1 (1.5)	5 (7.6)
Placebo (n=62)	6 (9.7)	2 (3.2)	3 (4.8)	11 (17.7)
*Studies No. 1 & No. 2***				
Cytotec 200 mcg q.i.d. (n=139)	2 (1.4)	1 (0.7)	0	3 (2.2)*
Cytotec 100 mcg q.i.d. (n=143)	5 (3.5)	3 (2.1)	2 (1.4)	10 (7.0)*
Placebo (n=138)	17 (12.3)	6 (4.3)	7 (5.1)	30 (21.7)

* Statistically significantly different from placebo at the 5% level.
** Combined data from Study No. 1 and Study No. 2.

In these trials there were no significant differences between Cytotec and placebo in relief of day or night abdominal pain. No effect of Cytotec in reducing the risk of duodenal ulcers was demonstrated, but relatively few duodenal lesions were seen.

In another clinical trial, 239 patients receiving aspirin 650–1300 mg q.i.d. for rheumatoid arthritis who had endoscopic evidence of duodenal and/or gastric inflammation were randomized to misoprostol 200 mcg q.i.d. or placebo for 8 weeks while continuing to receive aspirin. The study evaluated the possible interference of Cytotec on the efficacy of aspirin in these patients with rheumatoid arthritis by analyzing joint tenderness, joint swelling, physician's clinical assessment, patient's assessment, change in ARA classification, change in handgrip strength, change in duration of morning stiffness, patient's assessment of pain at rest, movement, interference with daily activity, and ESR. Cytotec did not interfere with the efficacy of aspirin in these patients with rheumatoid arthritis.

INDICATIONS AND USAGE

Cytotec (misoprostol) is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin)–induced gastric ulcers in patients at high risk of

complications from gastric ulcer, e.g., the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Cytotec has not been shown to reduce the risk of duodenal ulcers in patients taking NSAIDs. Cytotec should be taken for the duration of NSAID therapy. Cytotec has been shown to reduce the risk of gastric ulcers in controlled studies of 3 months' duration. It had no effect, compared to placebo, on gastrointestinal pain or discomfort associated with NSAID use.

CONTRAINDICATIONS

See boxed **WARNINGS.**

Cytotec should not be taken by pregnant women to reduce the risk of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs).

Cytotec should not be taken by anyone with a history of allergy to prostaglandins.

WARNINGS

See boxed **WARNINGS.**

For hospital use only if misoprostol were to be used for cervical ripening, induction of labor, or for the treatment of serious post-partum hemorrhage, which are outside of the approved indication.

PRECAUTIONS

Caution should be employed when administering Cytotec (misoprostol) to patients with pre-existing cardiovascular disease.

Information for patients: Women of childbearing potential using Cytotec to decrease the risk of NSAID-induced ulcers should be told that they must not be pregnant when Cytotec therapy is initiated, and that they must use an effective contraception method while taking Cytotec.

See boxed **WARNINGS.**

Cytotec is intended for administration along with nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, to decrease the chance of developing an NSAID-induced gastric ulcer.

Cytotec should be taken only according to the directions given by a physician.

If the patient has questions about or problems with Cytotec, the physician should be contacted promptly.

THE PATIENT SHOULD NOT GIVE CYTOTEC TO ANYONE ELSE. Cytotec has been prescribed for the patient's specific condition, may not be the correct treatment for

another person, and may be dangerous to the other person if she were to become pregnant.

The Cytotec package the patient receives from the pharmacist will include a leaflet containing patient information. The patient should read the leaflet before taking Cytotec and each time the prescription is renewed because the leaflet may have been revised.

Keep Cytotec out of the reach of children.

SPECIAL NOTE FOR WOMEN: Cytotec may cause birth defects, abortion (sometimes incomplete), premature labor or rupture of the uterus if given to pregnant women.

Cytotec is available only as a unit-of-use package that includes a leaflet containing patient information. See *Patient Information* at the end of this labeling.

Drug interactions: See *Clinical Pharmacology*. Cytotec has not been shown to interfere with the beneficial effects of aspirin on signs and symptoms of rheumatoid arthritis. Cytotec does not exert clinically significant effects on the absorption, blood levels, and antiplatelet effects of therapeutic doses of aspirin. Cytotec has no clinically significant effect on the kinetics of diclofenac or ibuprofen.

Prostaglandins such as Cytotec may augment the activity of oxytocic agents, especially when given less than 4 hours prior to initiating oxytocin treatment. Concomitant use is not recommended.

Animal toxicology: A reversible increase in the number of normal surface gastric epithelial cells occurred in the dog, rat, and mouse. No such increase has been observed in humans administered Cytotec for up to 1 year.

An apparent response of the female mouse to Cytotec in long-term studies at 100 to 1000 times the human dose was hyperostosis, mainly of the medulla of sternebrae. Hyperostosis did not occur in long-term studies in the dog and rat and has not been seen in humans treated with Cytotec.

Carcinogenesis, mutagenesis, impairment of fertility: There was no evidence of an effect of Cytotec on tumor occurrence or incidence in rats receiving daily doses up to 150 times the human dose for 24 months. Similarly, there was no effect of Cytotec on tumor occurrence or incidence in mice receiving daily doses up to 1000 times the human dose for 21 months. The mutagenic potential of Cytotec was tested in several *in vitro* assays, all of which were negative.

Misoprostol, when administered to breeding male and female rats at doses 6.25 times to 625 times the maximum recommended human therapeutic dose, produced dose-related pre- and post-implantation losses and a significant decrease in the number of live pups

born at the highest dose. These findings suggest the possibility of a general adverse effect on fertility in males and females.

Pregnancy:
Teratogenic effects: See boxed **WARNINGS.** Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects.

Cytotec is not fetotoxic or teratogenic in rats and rabbits at doses 625 and 63 times the human dose, respectively.

Nonteratogenic effects: See boxed **WARNINGS**. Cytotec may endanger pregnancy (may cause abortion) and thereby cause harm to the fetus when administered to a pregnant woman. Cytotec may produce uterine contractions, uterine bleeding, and expulsion of the products of conception. Abortions caused by Cytotec may be incomplete. If a woman is or becomes pregnant while taking this drug to reduce the risk of NSAID-induced ulcers, the drug should be discontinued and the patient apprised of the potential hazard to the fetus.

Labor and delivery: Cytotec can induce or augment uterine contractions. Vaginal administration of Cytotec, outside of its approved indication, has been used as a cervical ripening agent, for the induction of labor and for treatment of serious postpartum hemorrhage in the presence of uterine atony. A major adverse effect of the obstetrical use of Cytotec is uterine tachysystole which may progress to uterine tetany with marked impairment of uteroplacental blood flow, uterine rupture (requiring surgical repair, hysterectomy, and/or salpingo-oophorectomy), or amniotic fluid embolism and lead to adverse fetal heart changes. Uterine activity and fetal status should be monitored by trained obstetrical personnel in a hospital setting.

The risk of uterine rupture associated with misoprostol use in pregnancy increases with advancing gestational ages and prior uterine surgery, including Cesarean delivery. Grand multiparity also appears to be a risk factor for uterine rupture.

The use of Cytotec outside of its approved indication may also be associated with meconium passage, meconium staining of amniotic fluid, and Cesarean delivery. Maternal shock, maternal death, fetal bradycardia, and fetal death have also been reported with the use of misoprostol.

Cytotec should not be used in the third trimester in women with a history of Cesarean section or major uterine surgery because of an increased risk of uterine rupture. Cytotec should not be used in cases where uterotonic drugs are generally contraindicated or where hyperstimulation of the uterus is considered inappropriate, such as cephalopelvic disproportion, grand multiparity, hypertonic or hyperactive uterine patterns, or fetal

distress where delivery is not imminent, or when surgical intervention is more appropriate.

The effect of Cytotec on later growth, development, and functional maturation of the child when Cytotec is used for cervical ripening or induction of labor has not been established. Information on Cytotec's effect on the need for forceps delivery or other intervention is unknown.

The use of Cytotec (misoprostol) for the management of postpartum hemorrhage has been associated with reports of high fevers (greater than 40 degrees Celsius or 104 degrees Fahrenheit), accompanied by autonomic and central nervous system effects, such as tachycardia, disorientation, agitation, and convulsions. These fevers were transient in nature. Supportive therapy should be dictated by the patient's clinical presentation.

Nursing mothers: Misoprostol is rapidly metabolized in the mother to misoprostol acid, which is biologically active and is excreted in breast milk. There are no published reports of adverse effects of misoprostol in breast-feeding infants of mothers taking misoprostol. Caution should be exercised when misoprostol is administered to a nursing woman.

Pediatric use: Safety and effectiveness of Cytotec in pediatric patients have not been established.

ADVERSE REACTIONS

The following have been reported as adverse events in subjects receiving Cytotec:

Gastrointestinal: In subjects receiving Cytotec 400 or 800 mcg daily in clinical trials, the most frequent gastrointestinal adverse events were diarrhea and abdominal pain. The incidence of diarrhea at 800 mcg in controlled trials in patients on NSAIDs ranged from 14–40% and in all studies (over 5,000 patients) averaged 13%. Abdominal pain occurred in 13–20% of patients in NSAID trials and about 7% in all studies, but there was no consistent difference from placebo.

Diarrhea was dose related and usually developed early in the course of therapy (after 13 days), usually was self-limiting (often resolving after 8 days), but sometimes required discontinuation of Cytotec (2% of the patients). Rare instances of profound diarrhea leading to severe dehydration have been reported. Patients with an underlying condition such as inflammatory bowel disease, or those in whom dehydration, were it to occur, would be dangerous, should be monitored carefully if Cytotec is prescribed. The incidence of diarrhea can be minimized by administering after meals and at bedtime, and by avoiding coadministration of Cytotec with magnesium-containing antacids.

Gynecological: Women who received Cytotec during clinical trials reported the following gynecological disorders: spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%). Postmenopausal vaginal

bleeding may be related to Cytotec administration. If it occurs, diagnostic workup should be undertaken to rule out gynecological pathology. (See boxed **WARNINGS.**)

Elderly: There were no significant differences in the safety profile of Cytotec in approximately 500 ulcer patients who were 65 years of age or older compared with younger patients.

Additional adverse events which were reported are categorized as follows:

Incidence greater than 1%: In clinical trials, the following adverse reactions were reported by more than 1% of the subjects receiving Cytotec and may be causally related to the drug: nausea (3.2%), flatulence (2.9%), headache (2.4%), dyspepsia (2.0%), vomiting (1.3%), and constipation (1.1%). However, there were no significant differences between the incidences of these events for Cytotec and placebo.

Causal relationship unknown: The following adverse events were infrequently reported. Causal relationships between Cytotec and these events have not been established but cannot be excluded:

Body as a whole: aches/pains, asthenia, fatigue, fever, chills, rigors, weight changes.

Skin: rash, dermatitis, alopecia, pallor, breast pain.

Special senses: abnormal taste, abnormal vision, conjunctivitis, deafness, tinnitus, earache.

Respiratory: upper respiratory tract infection, bronchitis, bronchospasm, dyspnea, pneumonia, epistaxis.

Cardiovascular: chest pain, edema, diaphoresis, hypotension, hypertension, arrhythmia, phlebitis, increased cardiac enzymes, syncope, myocardial infarction (some fatal), thromboembolic events (e.g., pulmonary embolism, arterial thrombosis, and CVA).

Gastrointestinal: GI bleeding, GI inflammation/infection, rectal disorder, abnormal hepatobiliary function, gingivitis, reflux, dysphagia, amylase increase.

Hypersensitivity: anaphylactic reaction

Metabolic: glycosuria, gout, increased nitrogen, increased alkaline phosphatase.

Genitourinary: polyuria, dysuria, hematuria, urinary tract infection.

Nervous system/Psychiatric: anxiety, change in appetite, depression, drowsiness, dizziness, thirst, impotence, loss of libido, sweating increase, neuropathy, neurosis, confusion.

Musculoskeletal: arthralgia, myalgia, muscle cramps, stiffness, back pain.

Blood/Coagulation: anemia, abnormal differential, thrombocytopenia, purpura, ESR increased.

OVERDOSAGE

The toxic dose of Cytotec in humans has not been determined. Cumulative total daily doses of 1600 mcg have been tolerated, with only symptoms of gastrointestinal discomfort being reported. In animals, the acute toxic effects are diarrhea, gastrointestinal lesions, focal cardiac necrosis, hepatic necrosis, renal tubular necrosis, testicular atrophy, respiratory difficulties, and depression of the central nervous system. Clinical signs that may indicate an overdose are sedation, tremor, convulsions, dyspnea, abdominal pain, diarrhea, fever, palpitations, hypotension, or bradycardia. Symptoms should be treated with supportive therapy.

It is not known if misoprostol acid is dialyzable. However, because misoprostol is metabolized like a fatty acid, it is unlikely that dialysis would be appropriate treatment for overdosage.

DOSAGE AND ADMINISTRATION

The recommended adult oral dose of Cytotec for reducing the risk of NSAID-induced gastric ulcers is 200 mcg four times daily with food. If this dose cannot be tolerated, a dose of 100 mcg can be used. (See *Clinical Pharmacology: Clinical studies.*) Cytotec should be taken for the duration of NSAID therapy as prescribed by the physician. Cytotec should be taken with a meal, and the last dose of the day should be at bedtime.

Renal impairment: Adjustment of the dosing schedule in renally impaired patients is not routinely needed, but dosage can be reduced if the 200-mcg dose is not tolerated. (See *Clinical Pharmacology.*)

HOW SUPPLIED

Cytotec 100-mcg tablets are white, round, with SEARLE debossed on one side and 1451 on the other side; supplied as:

NDC Number	Size
0025-1451-60	unit-of-use bottle of 60
0025-1451-20	unit-of-use bottle of 120
0025-1451-34	carton of 100 unit dose

Cytotec 200-mcg tablets are white, hexagonal, with SEARLE debossed above and 1461 debossed below the line on one side and a double stomach debossed on the other side; supplied as:

NDC Number	Size
0025-1461-60	unit-of-use bottle of 60
0025-1461-31	unit-of-use bottle of 100

0025-1461-34 carton of 100 unit dose

Store at or below 25°C (77°F), in a dry area.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

LAB-0170-7.0
Revised February 2018

PATIENT INFORMATION

Read this leaflet before taking Cytotec® (misoprostol) and each time your prescription is renewed, because the leaflet may be changed.

Cytotec (misoprostol) is being prescribed by your doctor to decrease the chance of getting stomach ulcers related to the arthritis/pain medication that you take.

Do not take Cytotec to reduce the risk of NSAID-induced ulcers if you are pregnant. (See boxed **WARNINGS**.) Cytotec can cause abortion (sometimes incomplete which could lead to dangerous bleeding and require hospitalization and surgery), premature birth, or birth defects. It is also important to avoid pregnancy while taking this medication and for at least one month or through one menstrual cycle after you stop taking it. Cytotec may cause the uterus to tear (uterine rupture) during pregnancy. The risk of uterine rupture increases as your pregnancy advances and if you have had surgery on the uterus, such as a Cesarean delivery. Rupture (tearing) of the uterus can result in severe bleeding, hysterectomy, and/or maternal or fetal death.

If you become pregnant during Cytotec therapy, stop taking Cytotec and contact your physician immediately. Remember that even if you are on a means of birth control it is still possible to become pregnant. Should this occur, stop taking Cytotec and contact your physician immediately.

Cytotec may cause diarrhea, abdominal cramping, and/or nausea in some people. In most cases these problems develop during the first few weeks of therapy and stop after about a week. You can minimize possible diarrhea by making sure you take Cytotec with food.

Because these side effects are usually mild to moderate and usually go away in a matter of days, most patients can continue to take Cytotec. If you have prolonged difficulty (more than 8 days), or if you have severe diarrhea, cramping and/or nausea, call your doctor.

Take Cytotec only according to the directions given by your physician.

Do not give Cytotec to anyone else. It has been prescribed for your specific condition, may not be the correct treatment for another person, and would be dangerous if the other person were pregnant.

This information sheet does not cover all possible side effects of Cytotec. This patient information leaflet does not address the side effects of your arthritis/pain medication. See your doctor if you have questions.

Keep out of reach of children.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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Exhibit 15

Maarit J. Mentula et al., *Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study*, 26 Hum. Reprod. 927 (2011)

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human reproduction

ORIGINAL ARTICLE *Reproductive epidemiology*

Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study

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BACKGROUND: Increasing gestational age is associated with an increased risk of complications in studies assessing surgical termination of pregnancy (TOP). Medical TOP is widely used during the second trimester and little is known about the frequency of complications. This epidemiological study was undertaken to assess the frequency of adverse events following the second trimester medical TOP and to compare it with that after first trimester medical TOP.

METHODS: This register-based cohort study covered 18 248 women who underwent medical TOP in Finland between 1 January 2003 and 31 December 2006. The women were identified from the Abortion Registry. Adverse events related to medical TOP within 6 weeks were obtained from the Hospital Discharge Registry.

RESULTS: When compared with first trimester medical TOP, second trimester medical TOP increased the risk of surgical evacuation [Adj. odds ratio (OR) 7.8; 95% confidence interval (CI) 6.8–8.9], especially immediately after fetal expulsion (Adj. OR 15.2; 95% CI 12.8–18.0). The risk of infection was also elevated (Adj. OR 2.1; 95% CI 1.5–2.9). Within the second trimester, increased length of gestation did not influence the risk of surgical evacuation or infection after medical TOP.

CONCLUSIONS: Medical TOP during the second trimester is generally safe. Surgical evacuation of the uterus is avoided in about two-thirds of cases, though it is much more common than after first trimester medical TOP. The risks of surgical evacuation and infection do not increase with gestational weeks in the second trimester TOP.

Key words: complication / adverse event / second trimester / termination of pregnancy / medical

Introduction

With an estimated 29 induced abortions per 1000 women aged 15–44 years globally per annum (Sedgh *et al.*, 2007), termination of an unwanted pregnancy is one of the most common gynaecological procedures. In developed countries, legal termination of pregnancy (TOP) is safe (Sedgh *et al.*, 2007), the overall death rate being 10 per 100 000 procedures (Guttmacher Institute, 2009).

While the overall risks are low, increasing gestational age is, nevertheless, associated with an increased risk of complications. For example, from 1988 to 1997 in USA the risk of death increased by 38% for each additional week of gestation (Bartlett *et al.*, 2004). However, these data are mostly derived from surgical abortion (Guttmacher Institute, 2009). In large studies medical TOP using the combination of mifepristone and misoprostol seems to be more effective in earlier gestation (Ashok *et al.*, 2002, 2004). Up to 9 weeks of gestation the overall rate of complete abortion can be up to 98% with only 2% needing a surgical intervention (Ashok *et al.*, 2002). At 13–21 weeks of gestation the rate of successful abortion has been reported to be as high as 97%, with only 8% needing a surgical intervention (Ashok *et al.*, 2004).

The method of second trimester TOP is still controversial, especially regarding adverse events and complications. Yet studies comparing surgical and medical second trimester TOP are rare and

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randomized comparison has proven difficult to carry out (Grimes, 2008; Lohr et al., 2008). In Northern Europe second trimester TOP is largely performed medically, i.e. using a combination of mifepristone and misoprostol (Lohr et al., 2008). Therefore there is a need for an epidemiological study evaluating the effects following the second trimester medical TOP.

The purpose of the present study was to assess the rate of adverse events and complications following the second trimester medical TOP and to compare it with those following the first trimester medical TOP. We focused in particular on haemorrhage, infection and surgical evacuation in cases of incomplete abortion.

Materials and Methods

We performed a register-based cohort study which included women who underwent medical TOP in Finland between 1 January 2003 and 31 December 2006. We linked three national registries: the study cohort was identified from the Abortion Registry (THL, 2010a) and data on adverse events were obtained from the Hospital Discharge Registry (THL, 2010b) (official name: Care Registry for Health Care Institutions) and the Cause-of-Death Registry of Statistics Finland (Statistic Finland, 2010).

The flow chart (Fig. 1) shows the formation of the cohorts. When a woman had more than one induced abortion during the study period, only the first TOP was included. Altogether, 695 (3.5%) women who underwent medical TOP were excluded from the study. The exclusion criteria were:

(i) Any other concomitant surgical procedure (laparoscopic sterilization, $n = 20$) performed at the same time.
(ii) Data could not be linked to hospital registry ($n = 668$), i.e. TOP performed at a private clinic as outpatient care.
(iii) Other reasons ($n = 7$): one woman with a kidney transplant and immunosuppressive medication, five women with twin pregnancies and one woman with previously diagnosed uterus bicornis.

Data concerning the method of induced abortion was derived from linkage of the Abortion Registry (THL, 2010a) and the Hospital Discharge Registry (THL, 2010b). During 2003–2006 medical TOP was defined in the Abortion Registry as: use of mifepristone alone or in combination with misoprostol or other prostaglandins, or prostaglandins alone. Details of the medical methods used were not available. However, mifepristone became available in Finland in 2000. Finnish national guidelines on TOP were published 25 September 2001 (Finnish Medical Society Duodecim, 2007). This guideline recommends a medical abortion regimen of 200 mg mifepristone orally followed by vaginal administration of 0.4–0.8 mg misoprostol. For second trimester TOP, the procedure is performed in a hospital setting and misoprostol doses (0.4 mg) are repeated every 3–4 h up to five times per day until abortion. Routine sonographic evaluation is not recommended following abortion. The decision to perform surgical evacuation is made on clinical grounds, i.e. in cases of heavy bleeding or retained placenta. Taking this into consideration, the years 2003–2006 were selected for analysis as to the best of our knowledge during this time period the medical TOP at all durations of gestation were performed using the combination of mifepristone and misoprostol throughout Finland.

Participants were divided into two groups according to the weeks of gestation at the time of TOP. First trimester was defined as gestational weeks up to 12 (84 days of amenorrhea) and second trimester as gestational weeks 13–24 (85–168 days of amenorrhea). This division was derived from Finnish legislation on induced abortion (FINLEX, 1970) as well as from national guidelines on TOP (Finnish Medical Society Duodecim, 2007). Data on background characteristics (age, previous pregnancies, socioeconomic and marital status, duration of gestation, year, indication for TOP, place of residence) were identified from the Abortion Registry (THL, 2010a). Women undergoing TOP for fetal indications, i.e. suspected or confirmed fetal anomalies or abnormalities (12 women, i.e. 0.07% during the first trimester and 844 women, i.e. 42% during the second trimester) were excluded. The final diagnosis of the fetal indication was not available and as the effect of fetal abnormalities on the adverse events or complications could not be assessed these pregnancies were excluded from the study analysis.

TOP is allowed in Finland up to 20 weeks of gestation (140 days of amenorrhea) or up to 24 weeks of gestation (168 days of amenorrhea) in cases of a confirmed medical condition of the fetus (FINLEX, 1970). Approval with a legal indication for TOP is needed, though the legislation is interpreted liberally. The indications can be grouped as medical (women's or fetal health), ethical (e.g. rape) and social reasons. Social reasons include pregnancy and childbirth being an unbearable burden to a woman, age under 17 or over 40 years, and 4 or more deliveries. The approval for TOP has to be applied for from The National Supervisory Authority for Welfare and Health (Valvira, 2010) for all terminations because of congenital anomalies or if gestational weeks are over 12.

The follow-up time after TOP was 6 weeks (42 days). From the registries described above, we retrieved information on the diagnoses, based on ICD-10, the International Statistical Classification of Disease (2010) and operation codes based on the Nordic Classification of Surgical Procedures (2010) concerning all hospital-inpatient episodes (all hospitals) and outpatient visits (all public hospitals) within the follow-up period. Diagnoses and codes were evaluated to select those considered to be of clinical importance and related to TOP.

Complications were divided into following outcomes:

(i) Haemorrhage (any reported haemorrhages).
(ii) Infection (pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections and septicemia).
(iii) Incomplete abortion (surgical evacuations or any reported incomplete abortion). Surgical evacuation was divided into three outcomes: total (all patients undergoing evacuation), evacuation at the time of TOP (i.e. following fetal expulsion and during the first stay at the hospital) and evacuation during follow-up (i.e. after the first hospital stay).

Some rare complications were considered as severe complications. They were:

(i) Injuries or other reasons for surgical procedures (all injuries, cervical laceration, uterine perforation, all surgical interventions during the time of follow-up).
(ii) Thromboembolic disease (pulmonary embolism, deep vein thrombosis).
(iii) Death (death from any cause, pregnancy-related death according to the World Health Organization definition).

This classification was based on that reported in the Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists (Davies et al., 2004) and further modified for our study.

This study was approved by the Ministry of Social Affairs and Health as required for registry-based studies in Finland. Statistics Finland also gave their permission to use confidential personal-level data from the death registry. The Data Protection Ombudsman was notified regarding data linkage before the analyses, as required by the national data-protection legislation.

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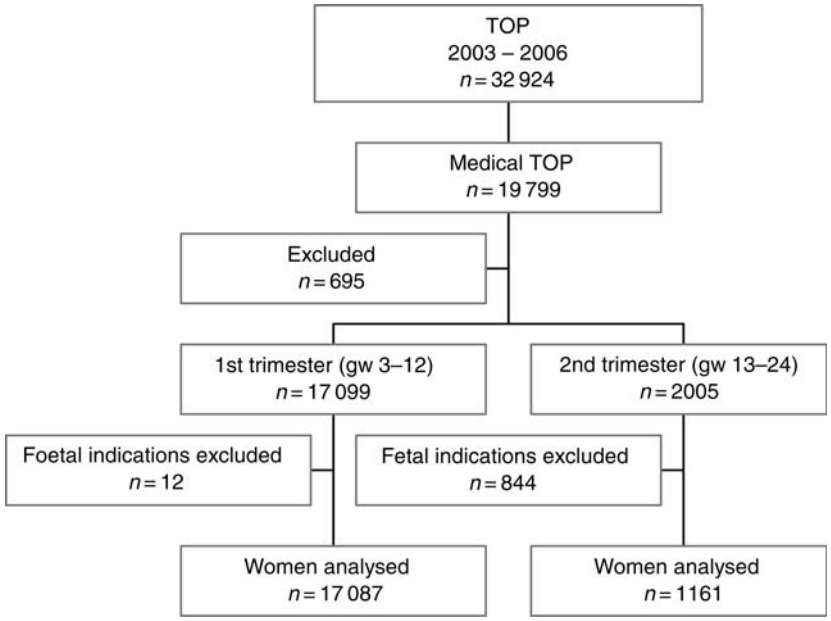

Figure 1 Flow chart detailing the study cohorts. Gw, gestational weeks.

All personal-level data that could be used to identify individuals was removed before the actual analysis was started.

Statistical analysis

Statistical analyses were performed using Predictive Analysis Software (PASW) 18.0 for Mac (SPSS Inc., Chicago, IL, USA). Differences in continuous variables were analysed with Mann–Whitney *U*-test for skewed data and data were presented as median and interquartile range (IQR). The χ^2 test or Fisher's exact test were used as appropriate for independent nominal data. The level of statistical significance was $P < 0.05$. In the analysis of surgical evacuation percentages during the observed time, 95% confidence interval (CI) for percentage was presented. Binary logistic regression models were used to adjust for differences in the background characteristics in comparison of the first and second trimester TOP. The background characteristics that differed statistically significantly between the groups were entered in the analysis. Estimated risks are presented as odds ratios (OR) with 95% CIs.

Results

The observed cohort consisted of 18 248 women who underwent medical TOP between 2003 and 2006, 94% during the first trimester and 6% during the second trimester. During that period 57 and 95% of all terminations of pregnancy were performed medically in the first and second trimester, respectively.

The duration of gestation [median (IQR)] was 7 weeks (7–8) during the first trimester and 15 weeks (14–17) during the second trimester. Table I shows the demographics of the study groups. Compared with the first trimester cohort, women undergoing medical TOP during the second trimester were younger, more often single or cohabiting and less often married. They were also more often of lower socioeconomic status and had had fewer previous deliveries. In the second trimester, the indication for medical TOP was more often age under 17 years, unknown or due to woman's health issues and less often social (i.e. continuation of pregnancy, and subsequent childbirth forming an unbearable burden to the woman) than for the first trimester medical TOP.

The main adverse events and complications (haemorrhage, infection, incomplete abortion, i.e. of the requirement for surgical evacuation) are shown in Table II. Medical second trimester TOP increased the risk of surgical evacuation, especially immediately after expulsion of the fetus when compared with the first trimester medical TOP. Second trimester medical TOP was also associated with a higher risk of infection. The risk of haemorrhage was lower during and after second trimester TOP, except in cases when surgical evacuation of residual tissue was needed.

Medical TOP was followed by 23 (0.13%) surgical procedures other than evacuation, i.e. severe complications. Of these, 20 (0.12%) occurred after first trimester medical TOP and 3 (0.26%) after second trimester medical TOP ($P < 0.2$). First trimester medical TOP was followed by a laparoscopic saturation of the uterus in three cases and 17 other repairing operations and second trimester medical TOP was followed by one abdominal hysterectomy, one saturation of the cervix and one other repair operation. There were no thromboembolic diseases during follow-up. There were no deaths as a result of TOP during the study period.

The effect of increasing gestation on the surgical evacuation, infection and haemorrhage was evaluated. The overall incidence of surgical evacuation following medical TOP was 9.9% (95% CI 9.5–10.3). The percentages of surgical evacuation compared with increasing gestation are shown in Fig. 2. The need for surgical evacuation increased as gestational weeks increased beyond 11. The overall incidence of infection following medical TOP was 2.1% (95% CI 0.8–3.9). The percentages of infection compared with increasing gestation are shown in Fig. 3. The risk of infection increased with increasing gestation. The

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Table I Demographics of the women undergoing medical TOP in 2003–2006.

	First trimester (n = 17087)	Second trimester (n = 1161)	P-value
Age (years)	25 (20–32)	22 (18–30)	<0.001
Marital status			
Married	3235 (18.9)	119 (10.2)	<0.001
Cohabiting	2843 (16.6)	222 (19.1)	0.03
Single	11009 (64.4)	820 (70.6)	<0.001
Residence			
Urban	12379 (72.4)	853 (73.5)	0.5
Densely populated	2494 (14.6)	155 (13.4)	0.2
Rural	2214 (13.0)	153 (13.2)	0.8
Socioeconomic status			
Upper white-collar workers	1010 (5.9)	27 (2.3)	<0.001
Lower white-collar workers	3299 (19.3)	159 (13.7)	<0.001
Blue-collar workers	2214 (13.0)	148 (12.7)	0.8
Students	5895 (34.5)	400 (34.5)	0.97
Others	1086 (6.4)	80 (6.9)	0.5
Unknown	3583 (21.0)	347 (29.9)	<0.001
Previous deliveries	7478 (43.8)	416 (35.8)	<0.001
Previous miscarriage	2164 (12.7)	152 (13.1)	0.7
Previous TOP	2664 (15.6)	184 (15.8)	0.8
Current TOP			
Year of TOP			
2003	3691 (21.6)	265 (22.8)	0.3
2004	4270 (25.0)	314 (27.0)	0.1
2005	4553 (26.6.)	295 (25.4)	0.4
2006	4573 (26.8)	287 (24.7)	0.1
Indication for TOP			
Woman's health	46 (0.3)	13 (1.1)	<0.001
Social	15317 (89.6)	914 (78.7)	<0.001
Ethical	6 (<0.1)	0	0.7
Age < 17	1035 (6.1)	160 (13.8)	<0.001
Age ≥ 40	417 (2.4)	27 (2.3)	0.8
≥4 deliveries	219 (1.3)	18 (1.6)	0.4
Unknown	47 (0.3)	29 (2.5)	<0.001

Data shown as numbers (percentages) or median (IQR, interquartile range).

overall incidence of haemorrhage following medical TOP was 16.9% (95% CI 15.6–18.2). The risk of haemorrhage varied according to gestation.

Discussion

We found that in comparison with the first trimester medical TOP, second trimester medical TOP was associated with an increased risk of surgical evacuation and infection. However, serious complications that need surgical repair after medical TOP and medical second trimester TOP were rare 0.1 and 0.3%, i.e. 1 and 3 per 1000 procedures, respectively. The present results also confirm that in Finland second trimester TOP (i.e. during gestational Weeks 13–24) is mostly (95%) performed medically.

This nationwide retrospective cohort study gives information about the contemporary use of medical abortion in non-selected material. It was derived from a registry, the coverage of which is almost 100% (Gissler *et al.*, 1996). In addition, the hospital registry data for in-patient care, the provision of which is mandatory, was available from all hospitals and out-patient care data were available from all public hospitals, adding to the information value of the study. There were, however, differences in coding treatments (Nordic Centre for Classifications in Health Care, 2010) and diagnoses (International Statistical Classification of Diseases, 2010) among Finnish hospitals. Thus, the severity of reported adverse events may vary considerably. Moreover, while the registry differentiates between medical and surgical TOP, the database does not provide precise information on the medication used to perform TOP. We therefore restricted our analysis to years 2003–2006, during

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Table II Adverse events and complications among women undergoing TOP between 2003 and 2006.

	First trimester (n = 17 087)	Second trimester (n = 1161)	OR (95% CI)	P-value	Adj. OR[a]	P-value
Adverse event						
1. Surgical evacuation (total)	1357 (7.9)	447 (38.5)	7.3 (6.4–8.3)	<0.001	7.8 (6.8–8.9)	<0.001
At the time of TOP	396 (2.3)	306 (26.4)	15.1 (12.8–17.8)	<0.001	15.2 (12.8–18.0)	<0.001
During follow-up	961 (5.6)	141 (12.1)	2.3 (1.9–2.8)	<0.001	2.5 (2.1–3.1)	<0.001
2. Haemorrhage (total)	2937 (17.2)	167 (14.4)	0.8 (0.7–0.96)	0.01	0.8 (0.7–0.98	0.03
Haemorrhage with surgical evacuation	541 (3.2)	96 (8.3)	2.8 (2.2–3.5)	<0.001	3.1 (2.4–3.9)	<0.001
3. Infection (total)	330 (1.9)	46 (4.0)	2.1 (1.5–2.9)	<0.001	2.1 (1.5–2.9)	<0.001
Infection with surgical evacuation	138 (0.8)	28 (2.4)	3.0 (2.0–4.6)	<0.001	3.3 (2.2–5.0)	<0.001

Data are shown as n (%).
[a]First trimester cohort was used as a reference adjusted for age, marital status, socio-economic status, previous deliveries and indication for TOP.

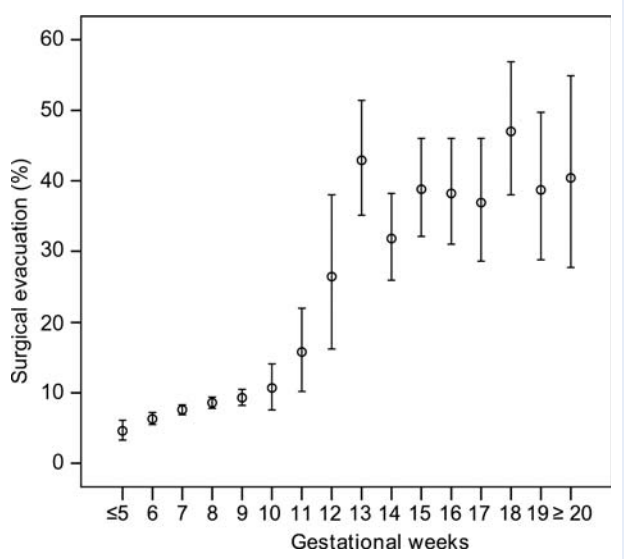

Figure 2 Percentage of surgical evacuation in relation to duration of gestation following medical TOP in 2003–2006. Bars represent 95% CI for percentage.

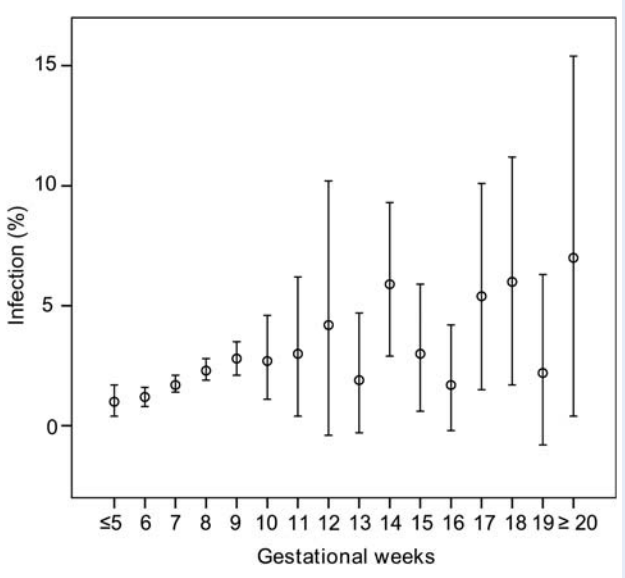

Figure 3 Percentage of infection in relation to duration of gestation following medical TOP in 2003–2006. Bars represent 95% CI for percentage.

which medical TOP using mifepristone and misoprostol was widespread throughout the country (THL, 2010a).

The rate of surgical evacuation associated with second trimester medical TOP was high (39%) in the present study. A potential explanation is that these data are derived from hospitals treating <200 second trimester terminations of pregnancy per year with all doctors performing the treatments. This may lead to unnecessary surgical treatments. Further, surgical evacuation of the uterus quickly after expulsion of the fetus was more or less routine until year 2000. For example, we published surgical evacuation percentages of 45–64% associated with second trimester medical TOP performed with mifepristone and misoprostol in 2001 (Heikinheimo *et al.*, 2004). Nevertheless, it will be interesting to see if the low rates in surgical evacuation (8%: Ashok *et al.*, 2004) following medical second trimester TOP, reported from centres with extensive experience with medical methods, can also be reached at a national level.

Reassuringly, the incidence of infection leading to a hospital visit (4%) following medical second trimester TOP in this nationwide study was similar to that 3% reported earlier (Ashok *et al.*, 2004; Lohr *et al.*, 2008). Moreover, the risk of infection was largely associated with evacuation of residual tissue.

It is interesting to note that the incidence of reported haemorrhage was lower during the second trimester TOP when compared with that of the first trimester. However, if haemorrhage occurred, it resulted in surgical intervention in more than half of the cases during the second trimester and in less than one-fifth of the cases during the first trimester.

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Also the need of surgical evacuation of residual tissue seemed to occur earlier following second than first trimester TOP. It may be speculated that the lower rate of haemorrhage seen after the second trimester TOP is due to the fact that these women are managed at the hospital and also undergo surgical evacuation more often. Thus, the lower incidence of reported haemorrhage following the second trimester TOP may be more due to different management than to a biological difference(s) between the first and second trimester TOP.

The optimal method for second trimester TOP continues to be debated, as medical second trimester TOP with mifepristone and misoprostol is associated with higher overall rate of adverse events and complications when compared with dilatation and evacuation (Grimes, 2008; Lohr *et al*., 2008). However, TOP performed with mifepristone and misoprostol during gestational Weeks 13–24 has been shown to be effective and acceptable (Ashok *et al*., 2004; Lohr *et al*., 2008). The safety of surgical TOP at more than 15 weeks of gestation depends on the skills of the practitioners (Grimes, 2008; Lohr *et al*., 2008). As the medical method for TOP is less dependent on the skills of doctors, it might be the preferred method in some health care settings.

We conclude that in comparison with medical TOP performed during the first trimester, medical second trimester TOP was associated with increased frequency of adverse events, most of which are minor. However, the risks of surgical evacuation or infection did not increase with increasing gestation duration in the second trimester. These data encourage further development and use of medical methods for second trimester TOP.

Authors' roles

All authors have equally participated in the planning of the study, analysis of the data and preparing of the manuscript.

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Exhibit 16

Maarit Niinimäki et al., *Immediate Complications After Medical Compared With Surgical Termination of Pregnancy*, 114 Obstetrics & Gynecology 795 (2009)

Immediate Complications After Medical Compared With Surgical Termination of Pregnancy

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OBJECTIVE: To estimate the immediate adverse events and safety of medical compared with surgical abortion using high-quality registry data.

METHODS: All women in Finland undergoing induced abortion from 2000–2006 with a gestational duration of 63 days or less (n=42,619) were followed up until 42 days postabortion using national health registries. The incidence and risk factors of adverse events after medical (n=22,368) and surgical (n=20,251) abortion were compared. Univariable and multivariable association models were used to analyze the risk of the three main complications (hemorrhage, infection, and incomplete abortion) and surgical (re)evacuation.

RESULTS: The overall incidence of adverse events was fourfold higher in the medical compared with surgical abortion cohort (20.0% compared with 5.6%, *P*<.001). Hemorrhage (15.6% compared with 2.1%, *P*<.001) and incomplete abortion (6.7% compared with 1.6%, *P*<.001) were more common after medical abortion. The rate of surgical (re)evacuation was 5.9% after medical abortion and 1.8% after surgical abortion (*P*<.001). Although rare, injuries requiring operative treatment or operative complications occurred more often with surgical termination of pregnancy (0.6% compared with 0.03%, *P*<.001). No differences were noted in the incidence of infections (1.7% compared with 1.7%, *P*=.85), thromboembolic disease, psychiatric morbidity, or death.

CONCLUSION: Both methods of abortion are generally safe, but medical termination is associated with a higher incidence of adverse events. These observations are relevant when counseling women seeking early abortion. *(Obstet Gynecol 2009;114:795–804)*

LEVEL OF EVIDENCE: II

Termination of pregnancy is one of the most common gynecologic procedures. For instance, in the United States, nearly half of pregnancies are unintended,[1] and 22% of all pregnancies (excluding miscarriages) end in termination.[2] Abortion practices have changed dramatically in recent years since the medical method with antiprogestin mifepristone and prostaglandins was introduced. For example, in 2007 in Finland 64%,[3] in Sweden 61%,[4] and in the United Kingdom 35%[5] of all abortions were performed using the medical method. Thus, the safety of induced abortion in general, especially that of the medical method, is of great public health interest.

Most previous studies focused on the short-term complications of induced abortion have been small or have not involved comparison of the two dominant methods of abortion (medical and surgical). In a large, register-based study, 5% of the patients had a complication (bleeding, infection, or (re)evacuation) after surgical abortion during a short-term follow-up period of 2 weeks.[6] In a previous meta-analysis in which medical and surgical termination of pregnancy in the

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first trimester were compared, no differences in pelvic infection or ongoing pregnancies were noted between the methods. Evidence of different rates of other potential side effects or complications between the two abortion techniques could not be confirmed because the trials included were small.[7]

Only a few randomized controlled trials have been performed to compare success rates and complications between medical and surgical abortion.[8–10] In a previous, partly randomized study, no difference in the number of complications was noted. Although the rate of complete abortion was significantly higher in the surgical group (98% compared with 94%), the surgically treated women had a higher incidence of antibiotic treatment than did those undergoing medical abortion.[8] In another randomized controlled trial, complete abortion without a second procedure occurred in 98% of cases after surgical abortion and in 95% after medical abortion. Moreover, no differences in the rates of major complications were observed.[11]

The purpose of the present study was to compare medical and surgical abortion in regard to the incidence and risk factors of immediate (ie, within 42 days after termination of pregnancy) adverse events and complications in a large nationwide cohort. A nationwide cohort with high-quality data derived from national health registries offers the possibility to estimate extensively the risk of adverse events associated with the two methods of early termination of pregnancy. Using this same cohort, we recently reported that the risk of repeat abortion after medical compared with surgical termination of pregnancy depends on various sociodemographic factors but not on the method of abortion.[12]

MATERIALS AND METHODS

This was a cohort study including all women undergoing termination of pregnancy in Finland between January 1, 2000, and December 31, 2006. According to the current law on induced abortions, women need permission with legal indication for termination of pregnancy, but the legislation is interpreted liberally. The Finnish legislation on induced abortion[13] was summarized in our recent study.[12]

The present study was conducted after receiving approval from the ethics committee of the Northern Ostrobothnia Hospital District. The Ministry of Social Affairs and Health and Statistics Finland gave their permission to use the confidential personal-level data from the registries. The Data Protection Ombudsman was notified regarding the data linkage before the analyses as required by the national data-protection legislation.

All women who underwent induced abortion by either medical or surgical methods at a gestational age of 63 days or less were included. The duration of gestation was limited to 63 days because, during the study period of 2000–2006, medical abortions, for the most part, were performed only up to that time.[14] The time of follow-up after abortion was 42 days (6 weeks). Medical abortion was defined as the use of mifepristone alone or in combination with misoprostol or other prostaglandins. Surgical abortion included induced abortions with dilation and curettage or vacuum aspiration. The participants were divided into two arms of the study according to the primary abortion method. For women having more than one abortion, only the first termination of pregnancy during the study period was included.

The study was based on three national registries: the Abortion Registry,[3] the Care Registry for Health Institutions (later renamed the Hospital Registry)[15] complied by the National Institute for Health and Welfare, and the Cause-of-Death Registry of Statistics Finland.[16] The study participants were selected from the Abortion Registry as described in our previous study,[12] after which the other registries were linked with the cohort.

We linked information on the study participants in the Hospital Registry concerning all hospital-inpatient episodes (all hospitals) and outpatient visits (public hospitals) within 42 days after termination of pregnancy to analyze complications related to induced abortion. All of the diagnoses (based on the International Classification of Diseases [ICD]-10, International Statistical Classification of Diseases and Related Health Problems[17]) and codes for surgical procedures (based on the Nordic Classification of Surgical Procedures[18]) found in the cohort were evaluated to select those considered to be of clinical importance.

Complications were divided into seven categories: 1) hemorrhage (all reported hemorrhages), 2) postabortal infections (pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections, and septicemia), 3) incomplete abortion (surgical [re]evacuation, any reported incomplete abortion), 4) injuries or other reasons for surgical operation (all injuries, cervical laceration, uterine perforation, all surgical interventions during the time of follow-up), 5) thromboembolic disease (pulmonary embolism, deep vein thrombosis), 6) psychiatric morbidity (depression, intoxication, psychoses) and 7) death (death from any cause, pregnancy-related death according to the World Health Organization definition). The classification was based on that reported in the Joint Study of

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the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists[19] and modified for the present study.

The Cause-of-Death Register kept by Statistics Finland contains data from death certificates and includes all deaths of Finnish citizens and permanent residents in Finland classified according to ICD-10 codes.[20] All of the early deaths (within 42 days of termination of pregnancy) were classified as direct, indirect, or unrelated. This classification was based on that in an earlier study by Deneux-Tharaux et al.[21]

Differences between the groups were assessed using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. Logistic regression analyses were performed to adjust for the differences in background characteristics in the comparisons of medical and surgical abortions. Furthermore, logistic regression was used to identify risk factors for complications. Variables that showed statistically significant associations with complications in univariable analysis were further entered in multivariable analysis. The estimated risks are presented as odds ratios with 95% confidence intervals. The statistical analyses were performed by using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

The total number of women in the cohort was 42,619. Of these, 22,368 had primary medical and 20,251 primary surgical termination of pregnancy. The characteristics of the women in the cohort are presented in Table 1. The women in the medical-abortion cohort were somewhat younger and more often primigravid, nulliparous, and single. The most notable difference between the groups was the shorter duration of gestation in the cohort undergoing medical abortion; surgical abortions in Finland usually are performed after the 6th week of gestation.

The incidence of various adverse events and complications is shown in Table 2. The most common adverse events were hemorrhage and incomplete abortion, both of which were more common in the medical group. The incidence of infection did not differ between the groups. Injuries requiring operation were rare but were more common in the surgical group. No differences between the two groups were noted in the incidence of thromboembolic disease, psychiatric morbidity, or death, partly because the overall incidence of these events was low. All of the deaths were unrelated to pregnancy: suicide (n=3), homicide (n=1), subarachnoid hemorrhage (n=1), and traffic accident (n=1).

When comparing the numbers of women with adverse events or complications, the difference between the two groups was notable: 20% of women in the medical-abortion group and 5.6% of women in the surgical-abortion group had at least one type of adverse event. When looking at the number of complications per patient, there were fewer multiple complications after surgical abortion (Table 2).

We also analyzed the three most common complications in relation to the duration of gestation (Fig. 1). In the medical-abortion cohort, the proportion of women with hemorrhage decreased with advancing duration of gestation; with surgical abortion it increased, albeit not significantly. In both groups, the incidence of infection and incomplete abortion increased with advancing duration of gestation.

Univariable and multivariable analyses were performed concerning the risk factors for three major classes of complications (hemorrhage, infection, and incomplete abortion) and for surgical (re)evacuation, separately for the medical and surgical abortion cohorts (Table 3), and for the whole cohort combined (Fig. 2). In multivariable analysis, the risk of hemorrhage after medical abortion was increased in the age group of 20–24 years, among parous women, among those of lower socioeconomic status, and among those living in densely populated or rural areas. The risk decreased with advancing duration of gestation. After surgical termination of pregnancy, an increased risk of hemorrhage was seen in the age groups of 20–24, 25–29, 30–34, and 35–39 years when compared with women younger than 20 years. A rural type of residence was associated with a decreased risk of hemorrhage.

Multivariable analysis revealed an increased risk of infection after medical abortion in the age group of 20–24 years and with advanced duration of gestation of 50–56 and 57–63 days. After surgical abortion, an increased risk of infection was found in the age group of 20–24 years, with increasing duration of gestation, and among women of lower socioeconomic class. A decreased risk of infection was associated with parity and with women living in densely populated or rural areas.

The risk factors associated with incomplete medical abortion were age of 20–24 years, parity, previous abortion, being single, living in a densely populated or rural area, and advanced duration of gestation. The risk of experiencing incomplete surgical abortion was associated with previous abortion, cohabiting or being single, and with a duration of gestation of 57–63 days.

In multivariable analysis, the risk of bleeding was almost eightfold higher, the risk of incomplete abor-

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Table 1. Characteristics of the Participants Included in the Study

	Medical Abortion (n=22,368)	Surgical Abortion (n=20,251)	*P*
Age (y)			
Median (mean)	25.0 (26.3)	26.0 (27.3)	<.001
95% confidence interval	26.2–26.4	27.2–27.4	
Age category (y)			
Younger than 20	5,058 (22.6)	4,352 (21.5)	<.001
20–24	5,665 (25.3)	4,337 (21.4)	
25–29	4,098 (18.3)	3,442 (17.0)	
30–34	3,406 (15.2)	3,393 (16.8)	
35–39	2,934 (13.1)	3,130 (15.5)	
40 or older	1,207 (5.4)	1,596 (7.9)	
Parity			
0	12,819 (57.3)	10,171 (50.2)	<.001
1	3,444 (15.4)	3,384 (16.7)	
2	3,897 (17.4)	4,125 (20.4)	
3 or more	2,207 (9.9)	2,570 (12.7)	
Previous abortions			
0	18,626 (83.3)	15,461 (76.4)	<.001
1	2,856 (12.8)	3,471 (17.1)	
2	664 (3.0)	927 (4.6)	
3 or more	221 (1.0)	390 (1.9)	
Marital status			
Married	4,350 (19.5)	4,718 (23.3)	<.001
Cohabiting	3,592 (16.1)	3,113 (15.4)	
Single	14,394 (64.4)	12,412 (61.3)	
Social status			
Upper white-collar worker	1,595 (7.1)	1,497 (7.4)	<.001
Lower white-collar worker	4,799 (21.5)	4,794 (23.7)	
Blue-collar worker	2,691 (12.0)	3,060 (15.1)	
Student	7,598 (34.0)	5,990 (29.6)	
Other	1,072 (4.8)	1,386 (6.8)	
Unknown	4,613 (20.6)	3,524 (17.4)	
Type of residence			
Urban	16,668 (74.5)	15,118 (74.7)	<.001
Densely populated area	2,788 (12.5)	2,286 (11.3)	
Rural	2,912 (13.0)	2,847 (14.1)	
Indication for abortion			
Social reasons	19,691 (88.0)	17,175 (84.8)	<.001
Age 17 y or younger	1,507 (6.7)	1,459 (7.2)	
Age 40 y or older	754 (3.4)	1,076 (5.3)	
Four children or more	366 (1.6)	457 (2.3)	
Other	50 (0.2)	84 (0.4)	
Duration of gestation (d)			<.001
42 or fewer	6,012 (26.9)	1,895 (9.4)	
43–49	7,355 (32.9)	4,724 (23.3)	
50–56	6,014 (26.9)	7,033 (34.7)	
57–63	2,987 (13.4)	6,599 (32.6)	

Data are n (%) unless otherwise specified.

tion was fivefold higher, and the risk of (re)evacuation was twofold higher after medical abortion compared with surgical abortion. The risk of infection, as derived from univariable analysis, was not associated with the method of abortion.

DISCUSSION

In the present study, we found that the two methods of pregnancy termination (medical and surgical) are generally safe. However, the incidence of the two most common adverse events (hemorrhage and incomplete abortion) were notably higher among women undergoing medical abortion, whereas complications requiring surgical treatment, although rare, were more common after surgical abortion. The rates of postabortal infection and serious morbidity (such as thromboembolic events) did not differ between the two groups. There were no pregnancy-related deaths

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Table 2. Incidence of Adverse Events in the Cohort

	Medical Abortion (n=22,368)	Surgical Abortion (n=20,251)	*P**	Adjusted OR† (95% CI)
Hemorrhage	3,487 (15.6)	433 (2.1)	<.001	7.93 (7.15–8.81)
Hemorrhage with surgical (re)evacuation	645 (2.9)	173 (0.9)	<.001	
Infection	383 (1.7)	342 (1.7)	.85	1.15 (0.98–1.34)
Infection with surgical (re)evacuation	172 (0.8)	122 (0.6)	.02	
Incomplete abortion	1,495 (6.7)	323 (1.6)	<.001	5.37 (4.49–6.28)
Incomplete abortion with surgical (re)evacuation	1,320 (5.9)	77 (0.4)	<.001	
Injury	6 (0.03)	122 (0.60)	<.001	NA‡
Thromboembolic disease	18 (0.08)	17 (0.08)	.90	NA
Psychiatric morbidity	2 (0.009)	1 (0.005)	.62	NA
Death	2 (0.009)	4 (0.020)	.35	NA
Women with adverse events	4,479 (20.0)	1,127 (5.6)	<.001	4.23 (3.94–4.54)
Surgical (re)evacuation	1,320 (5.9)	363 (1.8)	<.001	3.58 (3.18–4.03)
Number of adverse events per woman				
0	17,889 (80.0)	19,124 (94.4)	<.001	
1	3,624 (16.2)	1,021 (5.0)		
2	796 (3.6)	97 (0.5)		
3	59 (0.26)	9 (0.04)		

OR, odds ratio; CI, confidence interval; NA, not applicable.
Data are n (%) unless otherwise specified.
* Chi-square test for comparison between medical and surgical cohort.
† Surgical cohort as a reference adjusted for age, parity, previous abortion, social status, marital status, type of residence, and duration of gestation.
† Not applicable owing to small number of patients in one or both groups.

in our data. Because medical abortion is being used increasingly in several countries, it is likely to result in an elevated incidence of overall morbidity related to termination of pregnancy.

The present study covers almost all of the induced abortions performed in Finland during the years 2000–2006 and thus is a unique data source regarding even uncommon adverse events. However, the validity of the data is a potential problem in register-based studies such as the present one. In the Registry of Induced Abortions, 95% of the information has been proven to be identical to that in medical records.[22] However, the reliability of diagnoses and interventions can vary, and underreporting or overreporting by physicians cannot be ruled out. In addition, the Hospital Registry, which was used as a data source, contains data concerning hospital care only. Thus, adverse events dealt with outside the public hospital system, especially those treated in primary health care, will have been missed. Moreover, a single patient may have various diagnoses and complications, such as incomplete abortion and bleeding, and thus may have been registered more than once. The participants, however, each had a unique personal identification number, and we were able to eliminate double counting in our study.

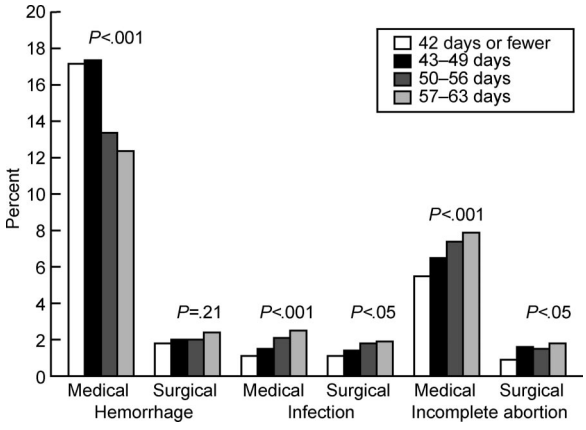

Fig. 1. Complications according to the duration of gestation in the medical and surgical cohorts (%).

Niinimäki. Complications After Medical and Surgical Abortion. Obstet Gynecol 2009.

It is important to note that the severity of the diagnoses found in the Hospital Registry may vary substantially. Thus, another problem in this kind of study is the definition of criteria for complications and adverse events. We evaluated all the ICD-10 diagnoses and codes for surgical procedures included in the Hospital Registry and classified them into seven categories.[19] In addition, women choosing surgical and medical abortion differed subtly in several respects and thus may be prone to different types of adverse events.

The rate of consultation related to a diagnosis of hemorrhage was high and eight times more common after medical termination of pregnancy. Because

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Table 3. Results of the Multivariable Analysis in Three Major Complications and Surgical (Re)Evacuation

	Hemorrhage		Infection	
	Medical	Surgical	Medical	Surgical
Age (y)	1.00 (0.96–1.04)			
Age category (y)				
Younger than 20	1	1	1	1
20–24	1.26 (1.00–1.58)	1.72 (1.25–2.37)	1.37 (1.03–1.83)	1.72 (1.13–2.62)
25–29	1.29 (0.88–1.91)	1.82 (1.30–2.54)	1.31 (0.95–1.80)	1.31 (0.77–2.23)
30–34	1.47 (0.83–2.58)	2.01 (1.45–2.79)	0.82 (0.56–1.19)	1.77 (1.02–3.08)
35–39	1.17 (0.56–2.46)	1.79 (1.28–2.52)	1.10 (0.77–1.58)	1.05 (0.54–2.01)
40 or older	1.01 (0.40–2.56)	0.50 (0.26–0.95)	0.95 (0.56–1.61)	1.54 (0.74–3.20)
Parity				
None	1			1
Yes	1.25 (1.08–1.45)			0.80 (0.56–1.14)
Previous abortion				
None	1			
Yes	1.07 (0.93–1.22)			
Social status				
Upper white-collar worker	1			1
Lower white-collar worker	1.14 (0.92–1.40)			3.21 (1.38–7.46)
Blue-collar worker	1.54 (1.23–1.93)			4.40 (1.87–10.36)
Student	1.50 (1.19–1.88)			3.47 (1.44–8.36)
Other	1.58 (1.20–2.08)			4.50 (1.80–11.27)
Marital status				
Married	1			
Cohabiting	1.12 (0.94–1.34)			
Single	1.05 (0.90–1.22)			
Residence				
Urban	1	1		1
Densely populated	1.43 (1.23–1.66)	0.98 (0.72–1.33)		0.85 (0.55–1.32)
Rural	1.25 (1.07–1.45)	0.71 (0.51–0.98)		0.54 (0.33–0.87)
Duration of gestation (d)				
42 or fewer	1		1	1
43–49	0.93 (0.82–1.05)		1.33 (0.98–1.80)	1.03 (.0.59–1.80)
50–56	0.74 (0.64–0.85)		1.91 (1.42–2.56)	1.15 (0.68–1.94)
57–63	0.63 (0.51–0.76)		2.26 (1.62–3.15)	1.15 (0.68–1.96)

Data are odds ratio (95% confidence interval).
Only those variables that showed a statistically significant association with a complication in univariable analysis (data not shown) were entered in multivariable analysis.

medical abortion is associated with uterine bleeding lasting approximately 2 weeks,[23] the high rate of consultation is not surprising. Uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy. The incidence of such bleeding was relatively low, but it was more common in the medical-abortion group. In earlier studies, an average of 10% of women who underwent medical abortion complained of excessive bleeding.[24]

In line with uterine bleeding, the rate of incomplete abortion was higher in the cohort undergoing medical abortion. Surgical evacuation performed because of incomplete abortion occurred in approximately 6% of women having medical termination of pregnancy. The highest rates of complete medical abortion, reported from centers with extensive experience of the technique, are up to 98%.[11,25] However, it is reassuring to note that a high rate of complete abortion, approaching those reported from centers with extensive experience, was reached in the present national cohort.

One of our key findings was that the rates of infectious morbidity were similar after medical and surgical abortion. In a previous survey, the need for postabortal antibiotics for suspected endometritis was higher after surgical abortion.[26] Moreover, the use of medical abortion previously has been associated with rare cases of severe infectious morbidity and mortality.[27] Reassuringly, only two cases with serious infections (septicemia caused by *Staphylococcus aureus* and *Streptococcus*) occurred in the present cohort, one in

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Incomplete Abortion		Surgical (Re)Evacuation	
Medical	Surgical	Medical	Surgical
1.04 (0.99–1.10)		1.05 (0.99–1.11)	
1		1	
1.14 (0.80–1.62)		1.15 (0.79–1.67)	
1.05 (0.60–1.86)		1.03 (0.56–1.88)	
0.89 (0.40–2.00)		0.89 (0.38–2.09)	
0.66 (0.23–1.88)		0.66 (0.22–2.00)	
0.41 (0.11–1.52)		0.39 (0.10–1.57)	
1		1	
1.65 (1.33–2.03)		1.59 (1.27–1.98)	
1	1	1	
1.34 (1.11–1.60)	1.38 (1.08–1.76)	1.30 (1.08–1.58)	
1		1	
0.97 (0.75–1.24)		0.97 (0.74–1.28)	
0.83 (0.62–1.11)		0.88 (0.65–1.20)	
1.04 (0.77–1.40)		1.02 (0.74–1.40)	
0.74 (0.50–1.08)		0.84 (0.57–1.25)	
1	1	1	
1.07 (0.84–1.35)	1.46 (1.00–2.13)	1.10 (0.86–1.41)	
0.94 (0.76–1.15)	1.46 (1.09–1.97)	0.92 (0.74–1.14)	
1		1	1
1.40 (1.13–1.74)		1.43 (1.14–1.79)	0.75 (0.52–1.08)
1.38 (1.12–1.70)		1.48 (1.19–1.84)	0.68 (0.48–0.96)
1	1	1	1
0.96 (0.78–1.16)	1.64 (0.97–2.75)	1.01 (0.81–1.24)	1.63 (0.97–2.73)
1.34 (1.12–1.66)	1.59 (0.96–2.62)	1.41 (1.14–1.75)	1.92 (1.17–3.15)
1.55 (1.22–1.98)	1.91 (1.16–3.14)	1.77 (1.38–2.28)	2.23 (1.36–3.65)

the medical and one in the surgical group. However, as previously reported, cases of *Clostridium sordellii* septicemia occurred at a rate of 1 per 100,000[27]; even the present cohort is too small to assess the incidence of such a rare infection.

Injuries and surgical interventions for other reasons were relatively rare in both groups. Not surprisingly, the incidence of postabortal surgical intervention was lower among women undergoing medical abortion. Some other serious and rare complications were identified as well. These included thromboembolic and psychiatric complications as well as some deaths. The incidence of thromboembolic complications is in line with earlier reports of an increased risk during pregnancy.[28,29] In a previous register-based study, it was concluded that deaths from external causes of injury and poisoning (including unintentional and intentional injuries, suicides, and homicides) are significantly more common in women after induced abortion compared with nonpregnant women or women after birth.[30] In the present cohort also, five out of six cases of death were the result of external causes. In addition, psychiatric diagnoses, such as depression and psychoses, were identified, but the rates of these complications did not differ between the two cohorts. Similarly, in an earlier, partly randomized study, no differences between women with medically or surgically performed abortions emerged in regard to postabortal anxiety, depression, or self-esteem.[31] Naturally, the present kind of study setting (register-based study) gives only a crude idea of short-term psychiatric morbidity associated with termination of pregnancy.

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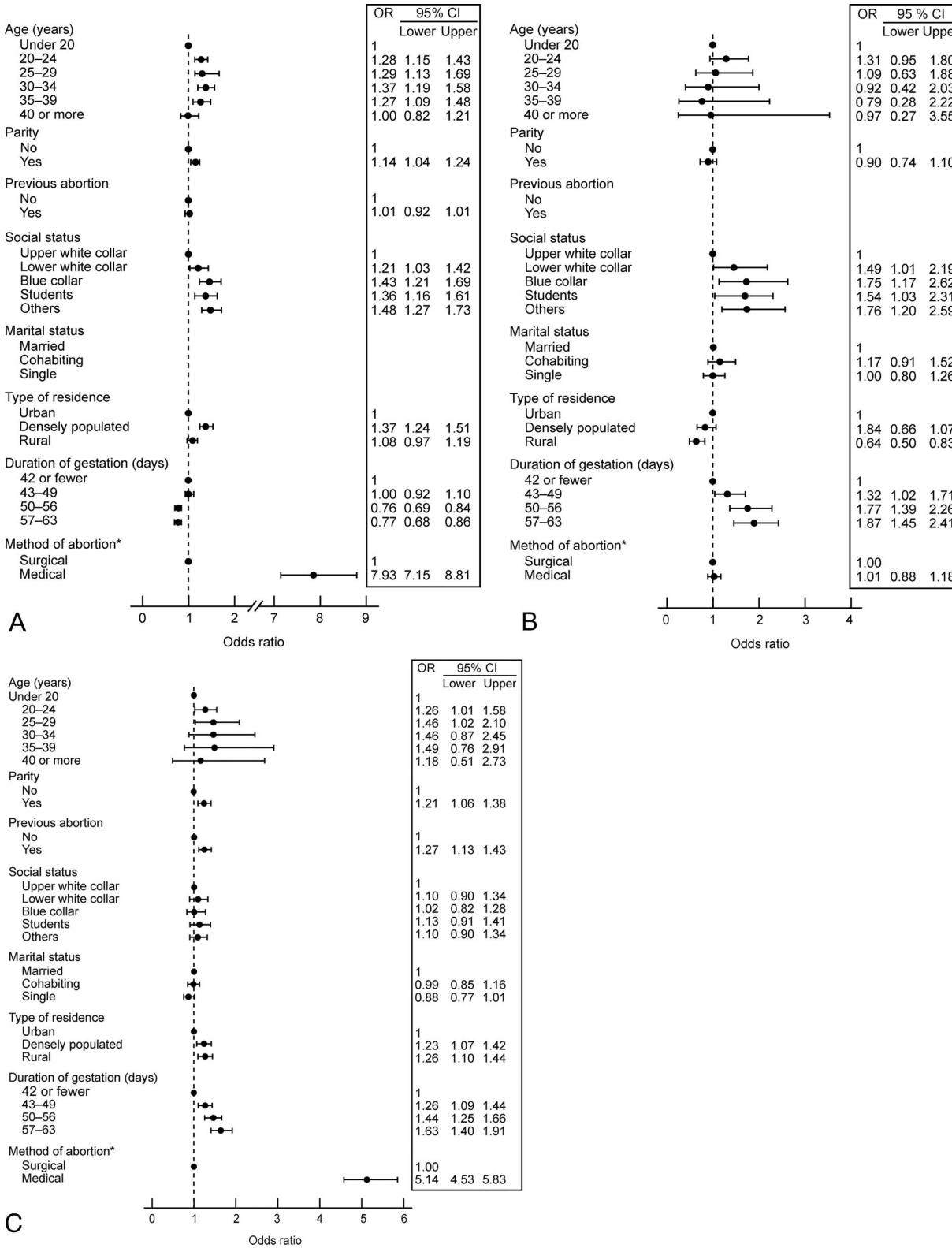

Fig. 2. Risk factors regarding three major complications (bleeding [**A**], infection [**B**], and incomplete abortion [**C**]) among the entire cohort (medical and surgical cohorts combined). OR, odds ratio; CI, confidence interval. *OR for infections is derived from univariable analysis.

Niinimäki. Complications After Medical and Surgical Abortion. Obstet Gynecol 2009.

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The most important risk factor with regard to the two most common adverse events (hemorrhage and incomplete abortion) was the method of abortion. Other risk factors were, for the most part, in line with those reported previously–advanced gestational age, parity, and previous induced abortions.[11,32–34] For unknown reasons, the risk of hemorrhage after medical abortion diminished with advancing duration of gestation. Tolerance of bleeding–a natural part of medical abortion–varies from one woman and physician to another and also depends on preabortion counseling. Other explanations, such as possible bias in reporting the events in the registry, are possible but cannot be verified in the present study. We included all cases requiring consultation in specialized health care because they are registered uniformly in Finland. In addition, every such visit adds to the costs of the health care system. More detailed analysis of all health care costs related to termination of pregnancy and its complications, according to the method, is needed.

In conclusion, termination of pregnancy by means of either medical or surgical methods is associated with a low level of serious complications. On the basis of the present data, however, it appears that medical abortion results in an increased incidence of adverse events.

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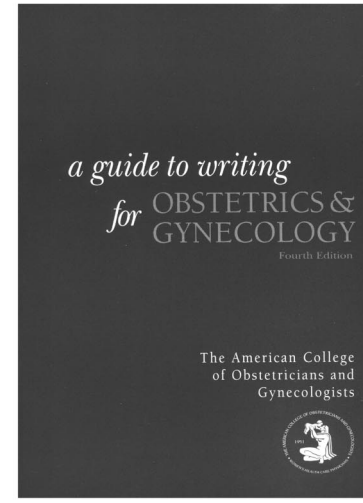

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Exhibit 17

James Studnicki et al., *A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999-2015*, Health Servs. Rsch. & Managerial Epidemiology, Nov. 9, 2021

Original Research

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A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999–2015

James Studnicki[1], Donna J. Harrison[2], Tessa Longbons[1], Ingrid Skop[1], David C. Reardon[3], John W. Fisher[1], Maka Tsulukidze[4], and Christopher Craver[1]

Abstract

Introduction: Existing research on postabortion emergency room visits is sparse and limited by methods which underestimate the incidence of adverse events following abortion. Postabortion emergency room (ER) use since Food and Drug Administration approval of chemical abortion in 2000 can identify trends in the relative morbidity burden of chemical versus surgical procedures.

Objective: To complete the first longitudinal cohort study of postabortion emergency room use following chemical and surgical abortions.

Methods: A population-based longitudinal cohort study of 423 000 confirmed induced abortions and 121,283 subsequent ER visits occurring within 30 days of the procedure, in the years 1999-2015, to Medicaid-eligible women over 13 years of age with at least one pregnancy outcome, in the 17 states which provided public funding for abortion.

Results: ER visits are at greater risk to occur following a chemical rather than a surgical abortion: all ER visits (OR 1.22, CL 1.19-1.24); miscoded spontaneous (OR 1.88, CL 1.81-1.96); and abortion-related (OR 1.53, CL 1.49-1.58). ER visit rates per 1000 abortions grew faster for chemical abortions, and by 2015, chemical versus surgical rates were 354.8 versus 357.9 for all ER visits; 31.5 versus 8.6 for miscoded spontaneous abortion visits; and 51.7 versus 22.0 for abortion-related visits. Abortion-related visits as a percent of total visits are twice as high for chemical abortions, reaching 14.6% by 2015. Miscoded spontaneous abortion visits as a percent of total visits are nearly 4 times as high for chemical abortions, reaching 8.9% of total visits and 60.9% of abortion-related visits by 2015.

Conclusion: The incidence and per-abortion rate of ER visits following any induced abortion are growing, but chemical abortion is consistently and progressively associated with more postabortion ER visit morbidity than surgical abortion. There is also a distinct trend of a growing number of women miscoded as receiving treatment for spontaneous abortion in the ER following a chemical abortion.

Keywords

induced abortion, mifepristone, medical abortion, emergency room, Medicaid

Introduction

Since its fast-track approval by the USA Food and Drug Administration (FDA) in September 2000, induced abortion by the administration of mifepristone and misoprostol (ie, chemical abortion) has grown to over 50% of all induced abortions in the United States and may, in fact, be responsible for ending a long-term decline in the number of induced abortions in the United States[1]

Research on the safety of induced abortion, and particularly those that are chemically induced, continues to be handicapped

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in the United States by the absence of a comprehensive national reporting system of pregnancy outcomes. The Centers for Disease Control and Prevention (CDC) Abortion Surveillance Reports are derived from a profoundly flawed system in which reporting by the states is voluntary, with many states reporting intermittently and some not at all. The reporting of specific data elements is similarly piecemeal and, most disappointing, no event-level data is actually available for any rigorous analytical purposes. Adverse events which may be related to an induced abortion such as a death, incomplete abortion, severe bleeding, or infection are often underreported because there is no certain way to link the adverse event to the precipitating abortion. Further, the FDA's adverse event reporting requirements for mifepristone extend only to deaths.[2] Large population-based record-linkage studies from nations with comprehensive reproductive history data linked to adverse events provide the best opportunity to overcome many of these data limitations and find a much higher overall incidence of adverse events in the chemical compared with the surgical cohort.[3,4] By contrast, USA studies of chemical abortion safety are frequently conducted on opportunity samples of women who have recently undergone an induced abortion. Already limited by the nonrandom nature of patient selection, these studies are frequently subject to design limitations such as the exclusion of an incomplete abortion as a complication, or an unacceptably high percentage of women lost to follow-up.[5,6]

The emergency room (ER) visit is a particularly insightful event by which to assess and compare the relative safety of chemical and surgical abortions for 2 reasons. First, adverse events following a mifepristone abortion are more likely to be experienced at home in the absence of a physician, increasing the likelihood of an ER visit. Second, the ER visit can be for any number of complications and is, therefore, a broad proxy indicator for abortion-related morbidity. One major concern is that ER secondary data describes treatment for a condition (eg, hemorrhage) which may be attributed to a prior event (eg, abortion), but, as we have seen, the prior event is often missed. For example, a study of abortion-related emergency room visits in the United States, using the Nationwide Emergency Department Sample, categorized whether visits were abortion related based only on information taken from the ER visit record. There was no independent confirmation from a different source that an abortion had occurred. Therefore, a woman who was experiencing excessive bleeding following a chemical abortion but did not reveal the abortion to the ER physician would not be identified as an abortion-related visit. Not surprisingly, the study found an extraordinarily low percentage (0.01%) of abortion-related visits among all ER visits to women age 15 to 49.[7] For all the reasons related to data availability and quality, as well as methodological inadequacies, evidence suggests that postabortion complications are substantially underreported.[8,9]

As we have described, research on adverse events following induced abortion varies by procedure, protocols to detect complication, length of follow-up and the sources and quality of data. The emergency room visit as a comprehensive marker for postabortion complications has been infrequently and inadequately utilized in existing research. Therefore, the objective of this research was to complete the first population based longitudinal cohort study of the trajectory of postabortion emergency room utilization following both chemical and surgical abortions in order to test the hypothesis that chemical abortion results in higher emergency room utilization. We selected a longitudinal cohort design because of its superiority to cross-sectional approaches in suggesting causation. Uniquely, our methodology includes first a confirmation of the actual provision of either a chemical or surgical abortion and, only after confirmation, identifies broadly all emergency room utilization before disaggregating abortion-related ER use. In the absence of a national abortion registry, this analysis is intended to provide the most comprehensive view of postabortion-related morbidity in the years following the FDA approval of mifepristone abortion, as well as a glimpse of what we might expect in the future.

Methods

Data were obtained from the enrollee-level Medicaid Analytic eXtract files licensed through the Centers for Medicare and Medicaid Services (CMS) Chronic Condition Data Warehouse's Medicaid data. The analytic dataset is comprised of enrollees from the 17 states whose official policies applied state funds to most abortions not covered by federal Medicaid during the period 1999 through 2015. Not all states funded abortion consistently or to the same extent during the study period. Despite their official policies, Arizona and Illinois funded relatively few abortions during this period, and Alaska experienced a short interruption to its abortion coverage.[10] Not all states had provided claims data through 2015 due to differing reporting timeframes. The latest year of data relative to each state was 2013 for Arkansas, Illinois, Maryland, Montana, and New Mexico; 2014 for Arizona, Hawaii, Massachusetts, and Washington; and 2015 for California, Connecticut, Minnesota, New Jersey, New York, Oregon, Vermont, and West Virginia.

The study population was made up of enrollees over 13 years of age with at least one identifiable pregnancy outcome from 1999 through the latest year of data available for each state. For each beneficiary, all unique pregnancy outcomes were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes. Additionally, Current Procedural Terminology, fourth Edition (CPT4) and Healthcare Common Procedure Coding System (HCPCS) codes were used to confirm pregnancy outcomes.

These codes were used to allocate all pregnancy outcomes into 4 categories: live birth (ICD-9V27.0, V27.2, and V27.5), natural fetal loss (ICD-9V27.1, V27.4, V27.7, 630, 631, 633, 634), induced abortion (ICD-9 635.xx, CPT4 59840, 59841, 59850, 59851, 59852, 59855, 59856, 59857, and HCPCS: S0199, S2260, S2265, S2266, S2267, X7724, X7726, S0190, S0191), and undetermined (ICD-9 636.xx, 637.xx, 638.xx). In order to identify each unique pregnancy, multiple diagnostic or treatment codes within 30 days of a pregnancy loss (natural, induced, or undetermined) or within 180 days of a live birth were counted as a single pregnancy outcome using the first

date associated with that series of Medicaid claims. Twins and higher order gestations that resulted in a combination of live birth and fetal loss were excluded from the analysis.

The analytic strategy was composed of 3 phases. First, we identified every confirmed surgical induced abortion (ICD/CPT codes—CPT4 59840, 59841, 59850, 59851, 59852, 59855, 59856, 59857) and every confirmed chemical induced abortion (HCPCS codes S0190, S0191) in each specific year 1999 to 2015 (index abortion). Codes S0190 and S0191 were added by CMS on January 1, 2001, so chemical abortions prior to that date could have been missed; however, because mifepristone did not receive approval from the FDA until September 28, 2000, the number of mifepristone abortions not captured here is likely minimal. Additionally, as an explanatory variable, we determined whether there was a prior induced abortion or live birth in the 12 months preceding the index abortion procedure. Second, we identified every emergency room visit occurring within thirty days of the index abortion procedure (Place of Service code 23 [emergency room]), including multiple visits for each patient. We further disaggregated ER visits into 3 categories: all-cause, abortion-related codes (ICD-9, 630-639) and spontaneous abortion code (ICD-9, 634). We mapped and adjusted the appropriate codes during the last two quarters of calendar year 2015 to reflect the transition from ICD-9 to ICD-10. The following descriptive metrics were calculated: chemical abortions as a percent of total induced abortions; ER visits following chemical abortions as a percent of total ER visits following total induced abortions; coded abortion-related visits as a percent of total ER visits following an induced abortion; miscoded spontaneous abortion ER visits as a percent of total ER visits following an induced abortion; miscoded spontaneous abortion ER visits as a percent of abortion-related ER visits following an induced abortion; and abortion ER visit rates per 1000 specified induced abortions for all-cause, coded abortion-related, and miscoded spontaneous abortion visit categories. Comparisons of the 1999 to 2015 longitudinal trajectory of these descriptive metrics are displayed in a series of 9 figures.

Third, we performed logistic regression models to identify the association of selected predictor variables with the likelihood of experiencing each of the 3 defined categories of ER visits following an induced abortion. The outcome variable in each equation was the dichotomous indication (yes/no) of the specific type of ER visit. The predictor variables were as follows: surgical abortion; chemical abortion; age at induced abortion; race; months of Medicaid eligibility at induced abortion; prior (within a calendar year of induced abortion) birth; and prior (within a calendar year of induced abortion) induced abortion. The odds ratios were calculated for the entire 17-year study period and, with the disproportional growth of chemical abortions over time, underestimate the current advantage of chemical abortion (vs surgical) in eliciting emergency room visits in the later years of the study observation period.

Summary analytic tables were created using (SAS/STAT) software, version (10) of the SAS system for (Unix). Copyright (2019) SAS Institute Inc. All comparative analyses were completed using Microsoft Excel (version 16).

The study has been exempted from Institutional Review Board (IRB) review pursuant to the USA Department of Health and Human Services Policy for Protection of Human Research Subjects at C.F.R. 46.101(b). See IRB ID: 7269, www.sterlingirb.com.

Findings

From 1999 to 2015, there was a total of 423 000 confirmed induced abortion Medicaid procedures, 361 924 surgical and 61,706 chemical. Surgical abortions increased from 4479 in 1999 to a peak of 36 204 in 2012, declined in 2013 to 2014 to 28 101, and concluded 2015 at 29 558. Chemical abortions had no Medicaid claims in the study population in 1999 to 2000 and only 15 in 2001. From 2002 when there were 352, chemical abortions increased to 8768 in 2012, followed by a 2013 to 2014 decline similar to that experienced by surgical abortion. Following inclusion of California chemical abortions in 2015, the chemical abortion number more than doubled to 15 279. As the result, mifepristone abortions grew from 4.4% of total abortions in 2002 to 34.1% in 2015 (Table 1 and Figure 1).

Similarly, emergency room visits within 30 days of an induced abortion increased during the study observation period for both surgical and chemical abortions. Emergency room visits following chemical abortions grew consistently as a percentage of all ER visits within 30 days of the procedure: 3.5% (36 ÷ [36 + 977]) in 2002; 6.9% (452 ÷ [452 + 6060]) in 2007; 22.0% (3220 ÷ [3220 + 11,401]) in 2012; and 33.9% (5421 ÷ [5421 + 10,578]) in 2015 (Table 1). The steeper growth in total and abortion-related ER visits for mifepristone abortions are apparent in the comparison of Figure 2 (surgical) and Figure 3 (chemical). Total ER visits during the study period totaled 121,283, 99,928 surgical and 21,355 chemical.

There are clear differences for surgical and chemical abortions in terms of the reason for the ER visits following the procedure. Abortion-related visits (ICD-9 630-639) remain stable at 4% to 5% of total ER visits for surgical abortions, reaching a high of 6.2% in 2015. This percentage is 8% to 9% between 2002 and 2013 for chemical abortions, with increases in 2014 to 2015 peaking at 14.6%. Abortion-related ER visits represent a higher percentage of total ER visits for chemical abortions (Figure 4).

ER visits miscoded as a spontaneous abortion following a chemical abortion range between 2% and 3% of total visits from 2003 to 2012, increasing abruptly between 2013 and 2015 reaching 8.9%. ER visits miscoded as a spontaneous abortion following a confirmed surgical abortion averaged less than 1% of all ER visits until 2008, 1.2%-1.3% from 2009 to 2014, and peaked at 2.4% in 2015. Therefore, from 2005 to 2015, visits miscoded for spontaneous abortion treatment in the ER as a percent of all visits, went from 2 to 4 times as likely following a chemical abortion as compared to a surgical abortion (Figure 5).

Table 1. Chemical and Surgical Induced Abortions and ER Visits Within 30 Days, 1999-2015.

	Chemical				Surgical			
Year	Abortions	All ER Visits	630 to 639	634	Abortions	All ER Visits	630 to 639	634
1999	0				4479	351	15	5
2000	0				7248	598	31	11
2001	15	1			9986	732	20	7
2002	352	36	3	0	7729	977	41	10
2003	803	108	6	2	13 012	1792	70	12
2004	1319	198	17	1	18 463	2871	99	14
2005	1360	316	29	9	19 226	4178	170	42
2006	1192	351	23	6	20 558	5042	218	51
2007	1521	452	37	13	21 244	6060	263	53
2008	1988	799	50	14	22 125	6954	313	66
2009	3032	1121	100	27	25 764	7879	358	91
2010	4848	1702	147	48	30 019	8820	386	114
2011	6834	2787	233	99	32 394	10 044	465	104
2012	8768	3220	277	88	36 204	11 401	536	150
2013	6856	2401	219	94	35 814	11 681	558	142
2014	6909	2442	270	117	28 101	9970	466	120
2015	15 279	5421	790	481	29 558	10 578	651	254

As a percent of abortion-related visits (ICD-9, 630-639), visits miscoded for spontaneous abortion treatments (ICD-9, 634) following a confirmed mifepristone abortion averaged approximately 30% between 2003 and 2012 and increased between 2013 and 2015, reaching 60.9%. ER visits miscoded as treatment for spontaneous abortion as a percent of abortion-related visits following a confirmed surgical abortion are a consistently lower percentage than for those following a chemical abortion, peaking at 39% in 2015 (Figure 6). Treatment in the ER miscoded as for spontaneous abortion is consistently and progressively more likely following a chemical abortion than following a surgical abortion.

All-cause ER visit rates within 30 days of an abortion have increased consistently throughout the study period for all types of induced abortion. There were 78.4 all-cause visits per 1000 surgical abortions in 1999 and 357.9 in 2015, an increase of 356% in the rate. Using 2002 as the initial year with sufficient abortion and ER visit counts to calculate a rate, the chemical

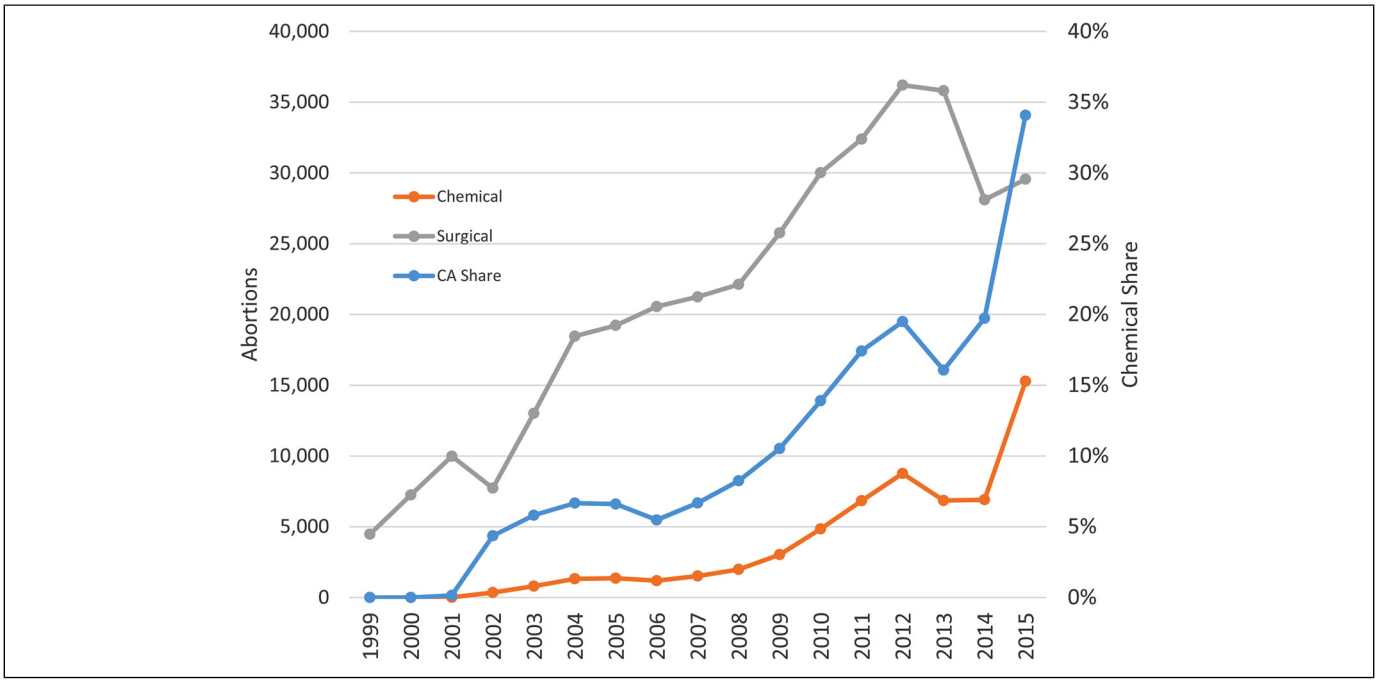

Figure 1. Medicaid abortions (surgical and chemical), 1999–2015, and chemical abortion % total.

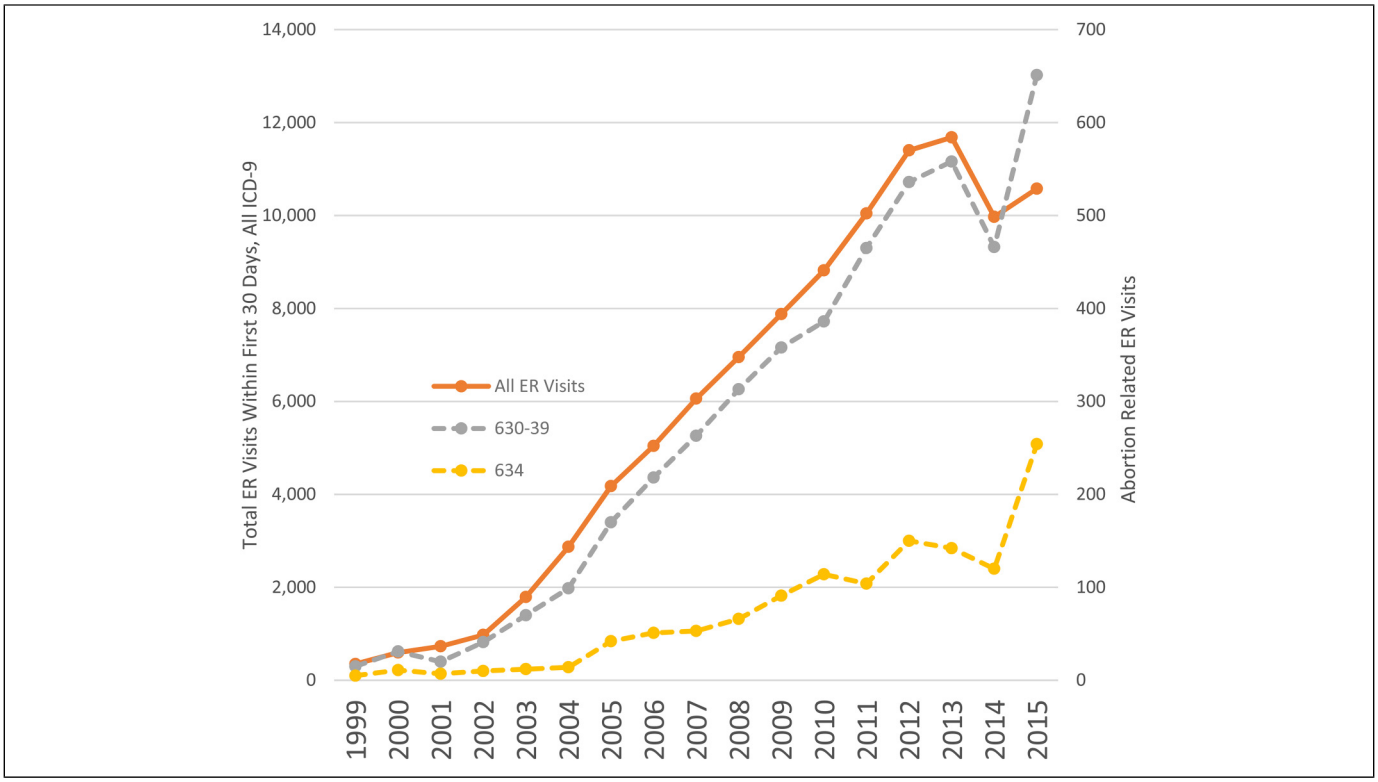

Figure 2. Emergency room (ER) use following surgical abortion, 1999-2015.

abortion rate increased from 102.3 in 2002 to 354.8, a rate increase of 247%. When the surgical rate increase is calculated from 2002 (126.4) and 2015 (357.9), the rate increase is 183%. Both the consistent increase in the rate of ER visits per abortion procedure and the higher chemical rate relative to the surgical rate after 2004 are apparent in Figure 7.

Abortion-related ER visits (ICD-9 630-639) per abortion exhibit a similar upward trend in rates for both surgical and chemical abortions, but, beginning in 2002, a growing divergence by type of abortion is evident. The surgical abortion to abortion-related visit rate increases from 5.3 in 2002 to 22.0 in 2015, an increase of 315%. Chemical abortion visit rates during the same period went from 8.5 to 51.7, an increase of 507% (Figure 8).

ER visit rates miscoded as for spontaneous abortion (ICD-9 634) within 30 days of a surgical abortion show a declining pattern from a peak of 1.5 in 2000 to a low point of 0.8 in 2004, a gradual increase between 2.2 and 4.3 from 2005 to 2014, and a doubling to 8.6 in 2015. By contrast, ER visit rates miscoded as for spontaneous abortion treatment following a chemical abortion show a consistent increase from 8.55 in 2007, the first year ER visits in this category reached double digits, to 31.5 in 2015. Between 2007 and 2015, the ER visit rate miscoded for spontaneous abortion increased 244% following surgical abortion and 268% following chemical abortion (Figure 9). Caution previously noted regarding the coding and classification of these visits is similarly warranted here.

A summary of the logistic regression analyses is in Table 2. All 3 types of ER visits during the study observation period are more likely to occur following a chemical abortion than following a surgical abortion: all-cause (OR 1.22, CL 1.19-1.24); abortion-related (OR 1.53, CL 1.49-1.58); and spontaneous abortion (OR 1.88, CL 1.81-1.96). Prior pregnancy outcomes increase the likelihood of any type of subsequent ER visit. However, an ER visit is significantly more likely to occur following a prior chemical abortion than following a prior surgical abortion: all-cause (OR 2.54, CL 2.38-2.70 vs OR 1.78, CL 1.73-1.82); abortion-related (OR 1.80, CL 1.65-1.97 vs OR 1.35, CL 1.29-1.41); and spontaneous abortion (OR 1.74, CL 1.54-1.96 vs OR 1.43, CL 1.35-1.52). A prior live birth is a lower risk factor for post abortion ER visits than is either a chemical or surgical induced abortion: all-cause (OR 1.52, CL 1.48-1.56); abortion-related (OR 1.09, CL 1.04-1.15); and spontaneous abortion (OR 1.12, CL 1.04-1.20).

Hispanics are slightly more likely than whites to experience any type of post abortion ER visit: all-cause (OR 1.07, CL 1.05-1.10); abortion-related (OR 1.03, CL 1.00-1.07); and spontaneous abortion (OR 1.03, CL 0.98-1.09). Blacks, by contrast, are consistently less likely than whites to experience any type of post abortion ER visit: all-cause (OR 0.59, CL 0.58-0.61); abortion-related (OR 0.68, CL 0.66-0.71); and spontaneous abortion (OR 0.72, CL 0.68-0.76). Age at time of the abortion and years of Medicaid eligibility are not important risk factors in predicting post abortion emergency room use.

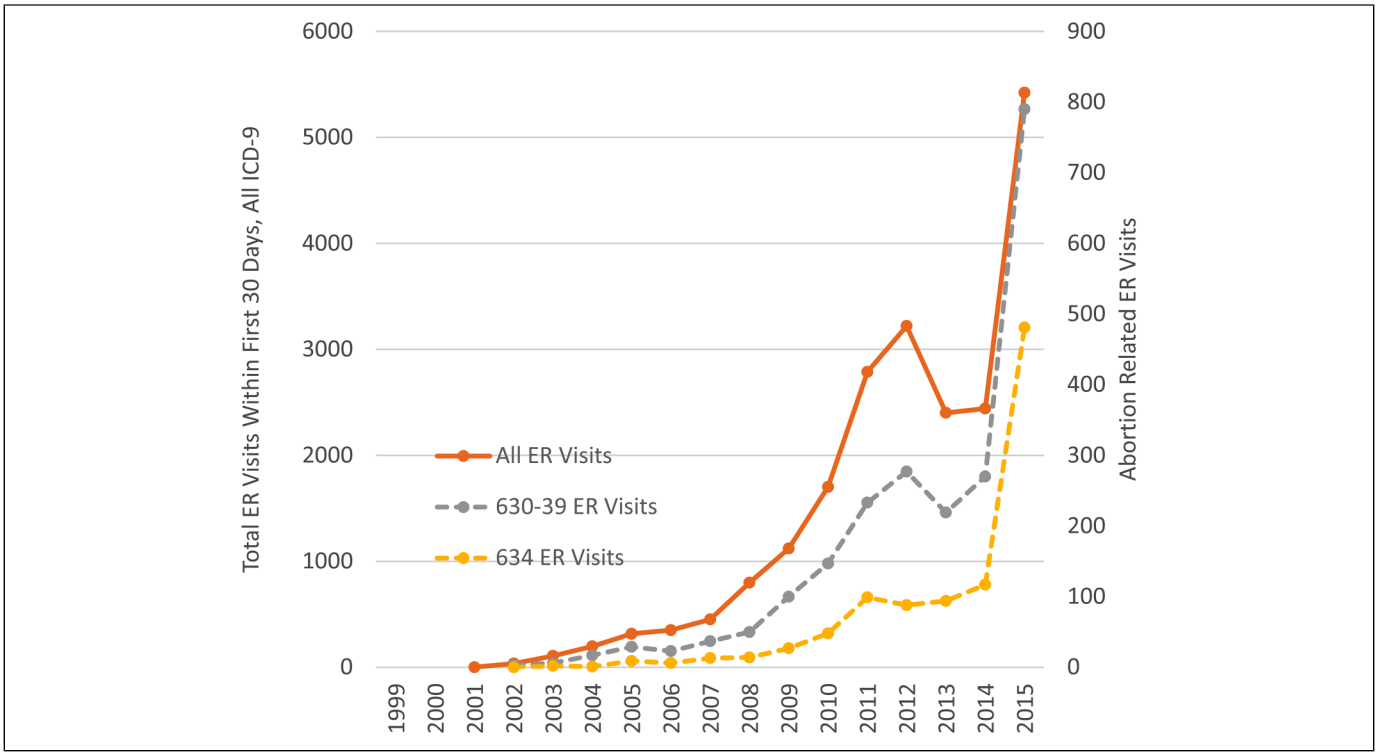

Figure 3. Emergency room (ER) use following chemical abortion, 1999–2015.

Discussion

Regression analysis definitively supports the hypothesis that chemical abortion is associated with more frequent emergency room visits of all kinds for the entire study period. In addition, we found that ER visit rates per 1000 abortion procedures increased consistently throughout the study period following both types of induced abortion, but the rates for mifepristone abortion visits grew faster, especially for abortion-related visits. By 2015, mifepristone versus surgical ER rates were: all visits (354.8 vs 357.9); miscoded spontaneous abortion

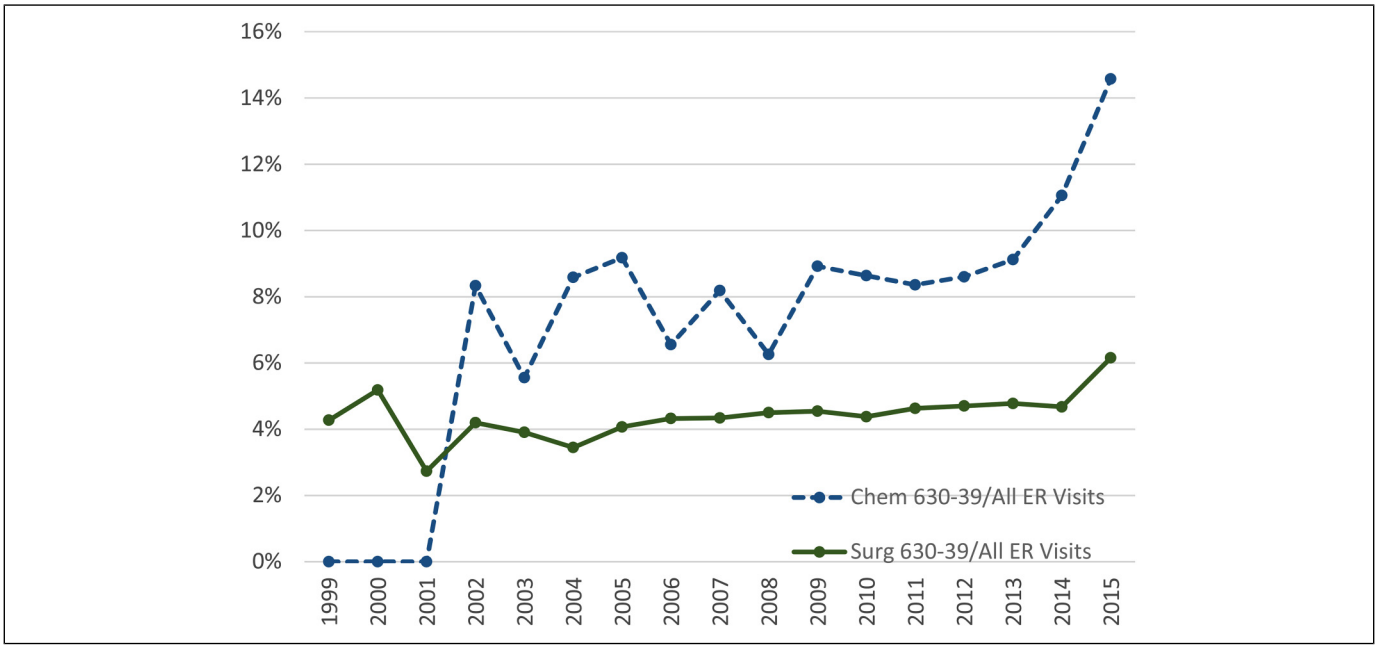

Figure 4. Abortion-related visits as a percent of all emergency room (ER) visits.

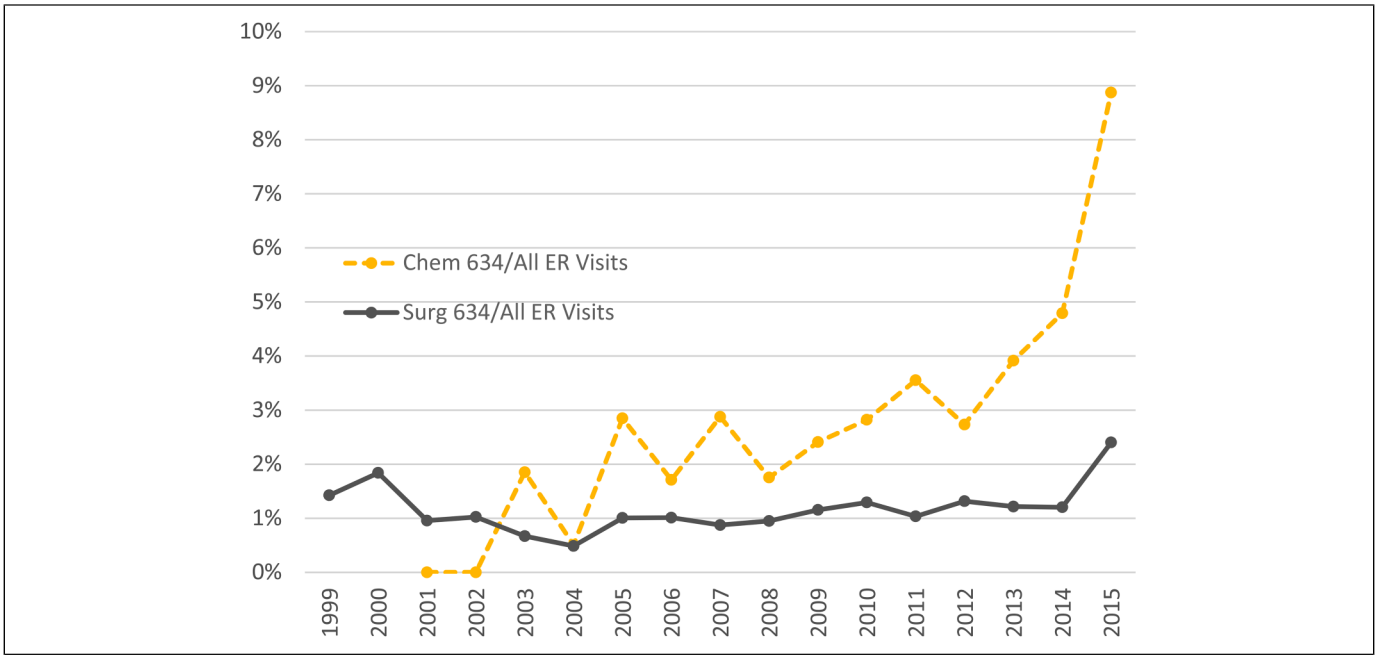

Figure 5. Miscoded spontaneous abortion visits as a percent of all emergency room (ER) visits.

(31.5 vs 8.6); and abortion-related (51.7 vs 22.0). The reasons for the increasing rate of ER visits following mifepristone abortions are not readily apparent but may be influenced by mifepristone abortion providers who are unable or unskilled to handle complications after chemical abortions. This finding would be consistent with an analysis of FDA Adverse Event Reports which showed that abortion providers only managed slightly over half of the dilation and curettage procedures (D&Cs) required for hemorrhage and retained tissue, and the remainder were handled by the emergency room.[11] Further research is needed to delineate whether there is a difference between ER visit utilization after abortions performed by those abortion providers untrained in surgical procedures (ie, midwives, advance practice clinicians, Family Medicine providers and other types of providers). This finding is also of significance when considering the implications of removing a requirement for in-person medical supervision of mifepristone abortion as is currently under consideration by the FDA.[12]

These findings are especially consequential because they are derived directly from all paid medical claims records, unlike most other studies of abortion complications which involve voluntary survey reporting and/or a more limited query of a select set of treatment codes. The more comprehensive examination of all ER codes associated with confirmed abortion events undertaken in this research requires reconsideration of previous findings which now appear to have understated the full range of risks associated with abortion. For example, previous research on only fee-for-service California Medicaid beneficiaries and using only a single code (ICD-9 635.xx) in 2009 to 2010 concluded that 6.4% of all abortions were followed by any ER visit within 6 weeks and 0.87% were followed by an abortion-related visit.[13] Results of our research summarized for the same 2 years found 4.8 times (30.7%) the number of total ER visits and 1.8 times (1.56%) the number of abortion-related visits within our shorter 30-day postabortion observation period. We were able to detect this more accurate number of complications because the women were included in our study based on a CPT code payment for mifepristone abortion, thus eliminating the need for the treating physician to recognize a complication from a chemical abortion.

The finding that many ER visits following known induced abortions are misclassified as postmiscarriage complications is particularly noteworthy. Abortion studies in the United States consistently report lower postabortion complication rates than are documented in the international scientific literature. There are likely multiple reasons for this discrepancy, but among them are the miscoding of abortion-related complications by the provider and the nondisclosure of prior abortion history by the patient. Women obtaining chemical abortions must sign a patient agreement indicating they will bring with them the mifepristone medication guide if seeking emergency care, but some abortion advocates encourage women to withhold information if seeking treatment for an adverse event.[14,15] Our study demonstrated ER visits misclassified or miscoded as spontaneous abortion grew for both types of induced abortion, reaching 39% of abortion-related visits following surgical abortion and 60.9% of visits following chemical abortion in 2015. These mifepristone abortion complications would have been invisible to previous researchers, resulting in a large underestimation of actual mifepristone abortion complications. Our more accurate estimation has significant implications for the evaluation of risks communicated

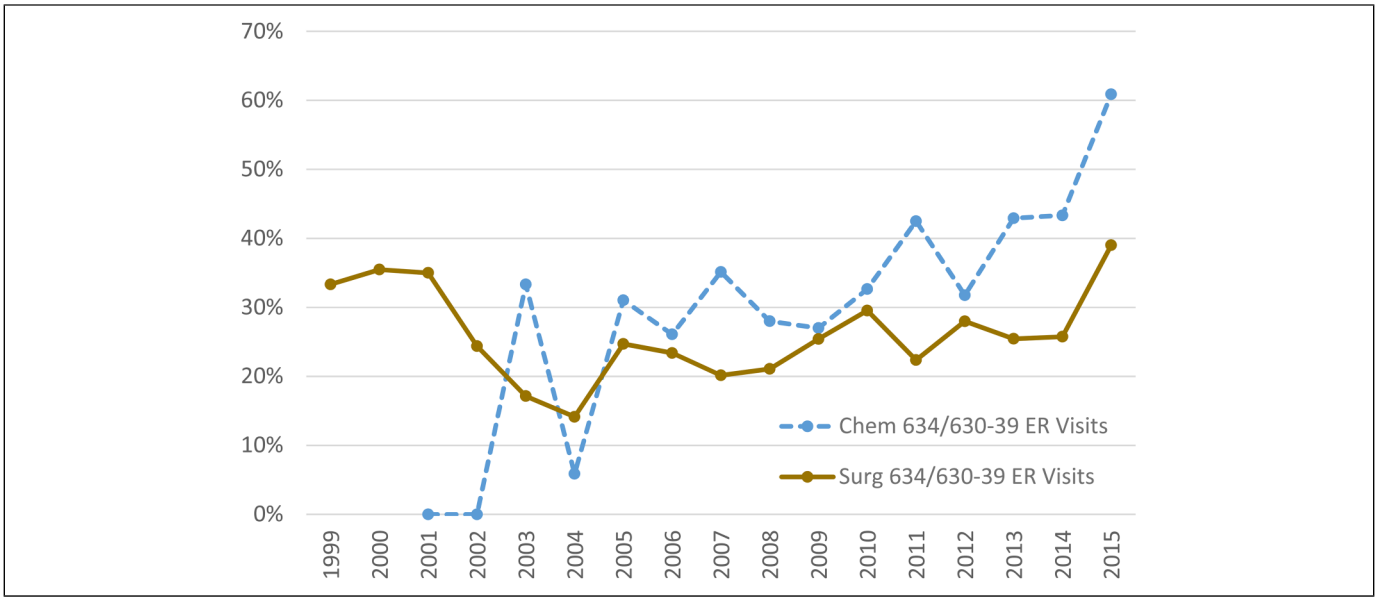

Figure 6. Miscoded spontaneous abortion visits as a percent of abortion-related emergency room (ER) visits.

to women in the process of informed consent prior to abortion, as well as in policy making regarding mifepristone abortion.

Consistent with CDC reports, we found the percentage of abortions performed by means of mifepristone and misoprostol increased from 4.4% of total abortions in 2002 to 34.1% in 2015. Similarly, ER visits following mifepristone abortion grew from 3.6% of all postabortion visits in 2002 to 33.9% of all postabortion visits in 2015. The trend toward increasing use of mifepristone abortion requires all concerned with health care utilization to carefully follow the ramifications of ER utilization.

There are limitations related to the use of Medicaid claims data. Medicaid-eligible beneficiaries are by definition financially disadvantaged and are not representative of all women experiencing abortion. Conversely, a data set composed entirely of low-income women may also be considered an advantage since results are unlikely to be explained by differences in income or other factors strongly associated with income. The lower risk of any ER visit following induced abortion among

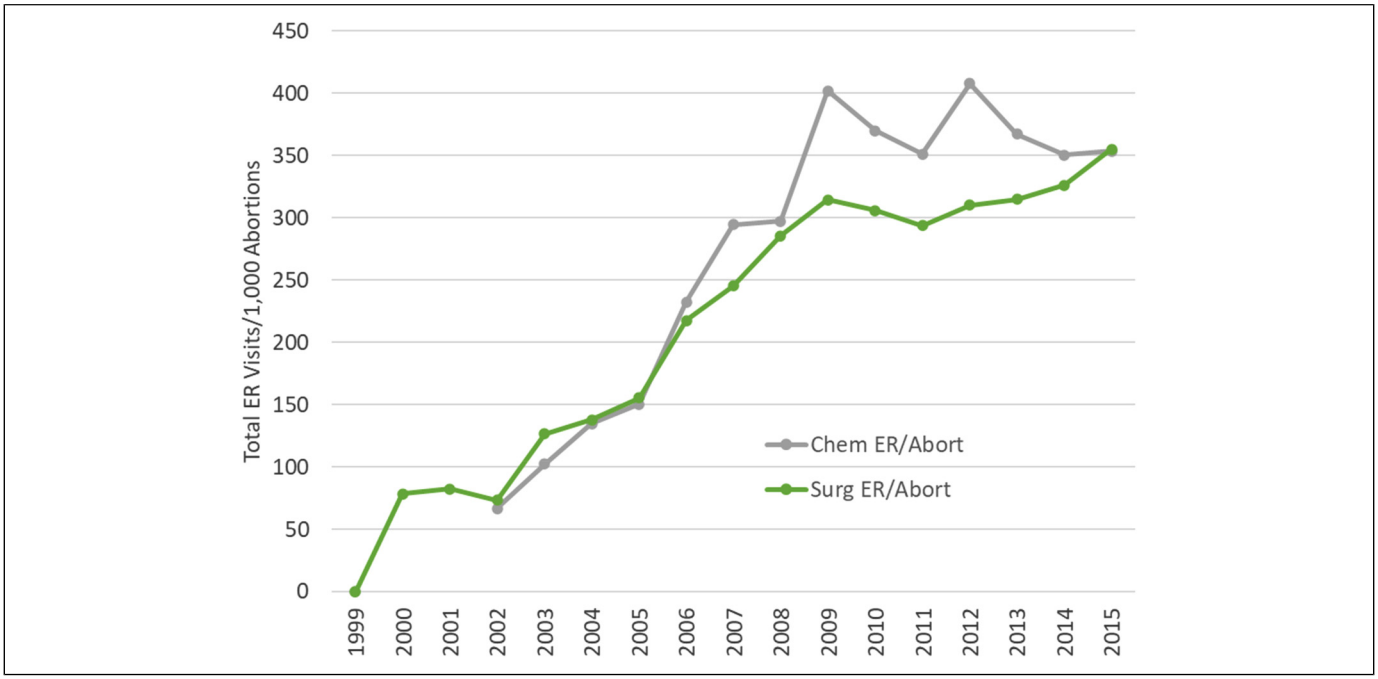

Figure 7. Total emergency room (ER) visits per 1000 abortions.

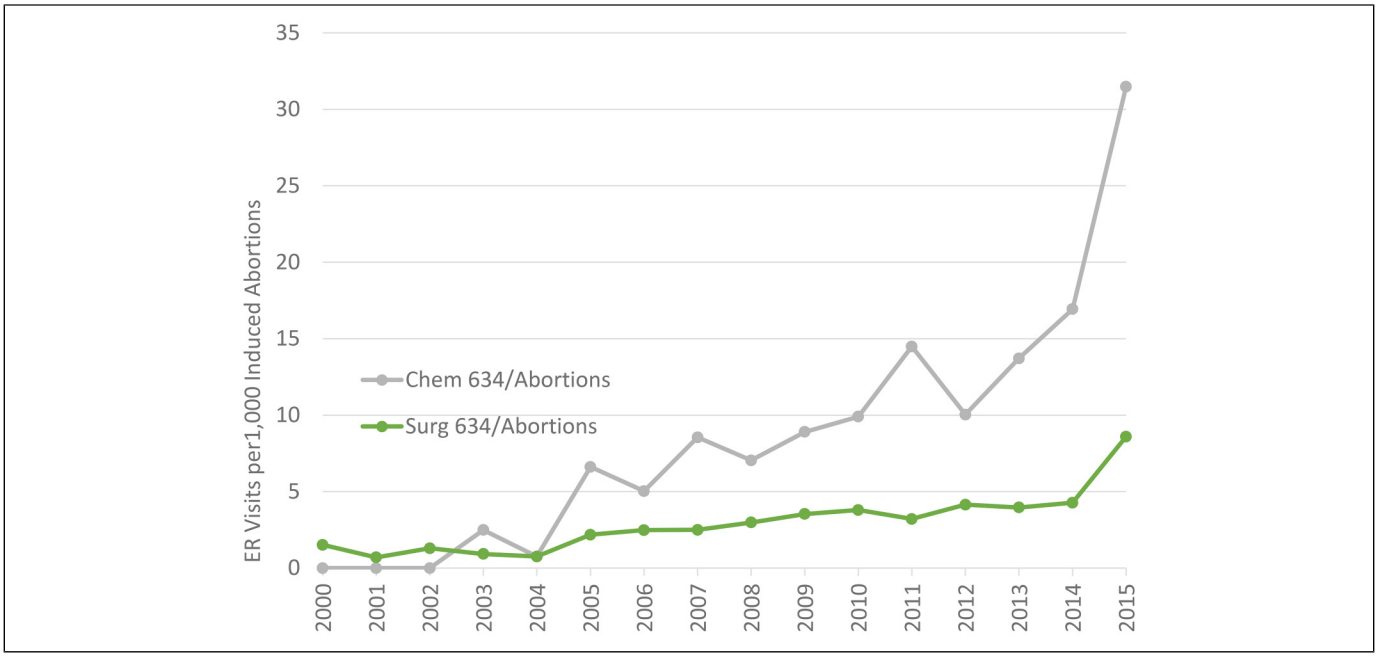

Figure 8. Miscoded spontaneous abortion emergency room (ER) visits per 1000 abortions.

Black women suggests that a more granular analysis of the influence of race is warranted. Services received by eligible women but paid by another source (eg, out of pocket) are not included in the claims data. Services received when the women were not eligible are similarly not included. Administrative data are also subject to limitations regarding coding errors, inconsistent coding, and the exclusion of codes considered nonessential for billing.[16,17] There are inconsistencies in coding which may vary state by state. Our data extraction protocol required both an ICD code and CPT code to

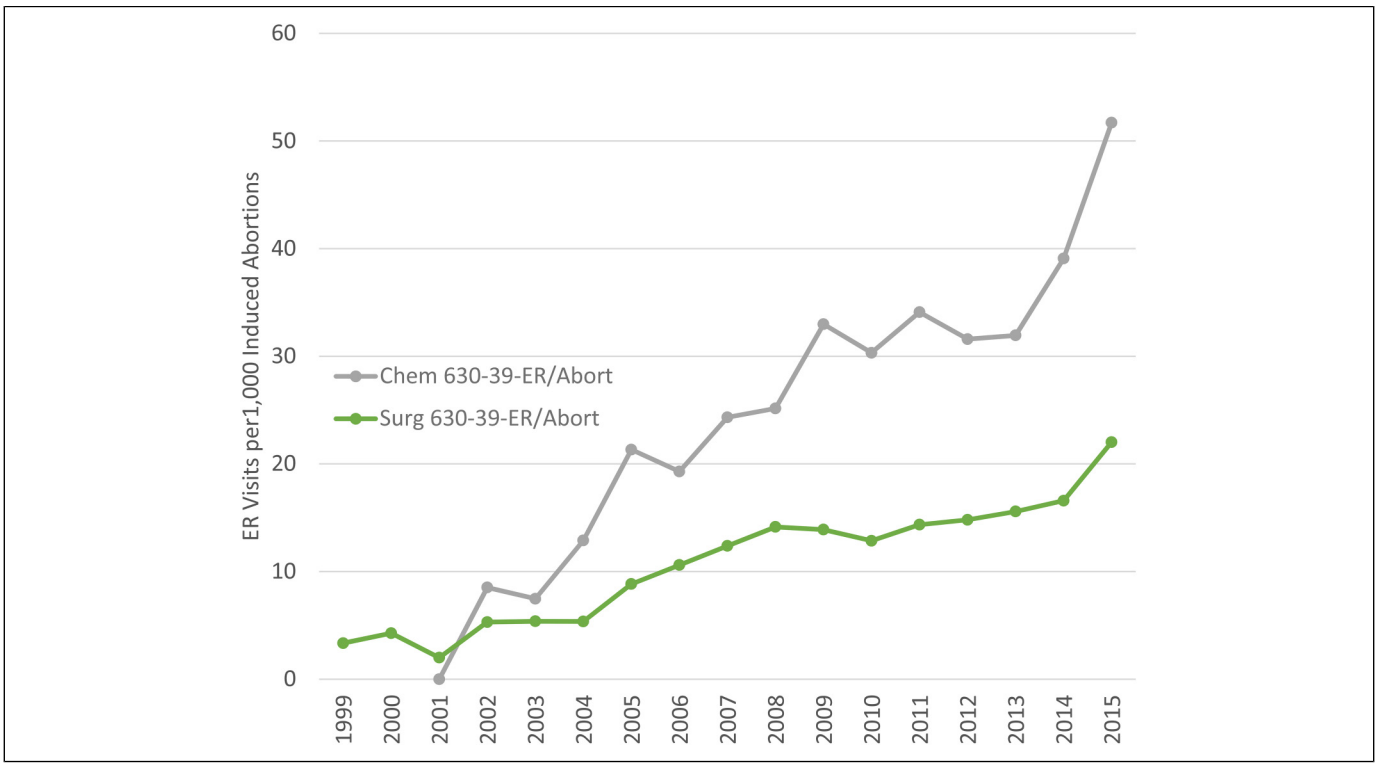

Figure 9. Abortion-related emergency room (ER) visits per 1000 abortions.

Table 2. Logistic Regression Odds Ratio Estimates (OR) and (Wald) Confidence Limits (CLs).

	Any ER Visit		Abortion-Related Visit		Spontaneous Abortion Visit	
	OR	95% CLs	OR	95% CLs	OR	95% CLs
Chemical versus Surgical Abortion	1.22	1.19 to 1.24	1.53	1.49 to 1.58	1.88	1.81 to 1.96
Race						
Black versus White	0.59	0.58 to 0.61	0.68	0.66 to 0.71	0.72	0.68 to 0.76
Hispanic versus White	1.07	1.05 to 1.10	1.03	1.00 to 1.07	1.03	0.98 to 1.09
Other versus White	0.91	0.89 to 0.93	0.88	0.85 to 0.91	0.85	0.81 to 0.89
Pregnancy 365 d prior versus no						
Prior surgical abortion	1.78	1.73 to 1.82	1.35	1.29 to 1.41	1.43	1.35 to 1.52
Prior chemical abortion	2.54	2.38 to 2.70	1.80	1.65 to 1.97	1.74	1.54 to 1.96
Prior live birth	1.52	1.48 to 1.56	1.09	1.04 to 1.15	1.12	1.04 to 1.20
Age	0.993	0.992 to 0.994	1.003	1.001 to 1.004	1.000	0.997 to 1.003
Months Medicaid Eligibility	1.008	1.007 to 1.008	1.006	1.005 to 1.007	1.006	1.006 to 1.006

identify beneficiaries who had an induced abortion. To the extent that some states or individual providers do not code an abortion with an ICD code, our study population may undercount the number of abortions. This undercount would likely be due to a random variation in coding protocols and is unlikely to affect the trends related in our findings.

In summary, mifepristone abortion is consistently and progressively associated with increased morbidity in the form of postabortion emergency room utilization among the population of women with publicly funded abortions. The determination of the causes and potential means of prevention for this burden of illness should have the highest priority of our health agencies and elected officials. Additional research is necessary to investigate the prevalence and type of effects beyond 30 days.

Declaration of Conflicting Interests

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David C. Reardon is the director of Elliot Institute, a biomedical ethicist, and a lead author on numerous studies and books examining the risk factors and effects of pregnancy loss on women and families.

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Maka Tsulukidze, MD, PhD, MPH is an Assistant Professor at the Florida Gulf Coast University, Marieb College of Health & Human Services. Before joining FGCU, she was a Postdoctoral Fellow at the Dartmouth Center for Health Care Delivery Science. She has earned a PhD degree from the University of North Carolina at Charlotte and MD from Tbilisi Medical Academy. Previously she was a UNICEF National Consultant to the Parliament of Georgia, Short-Term Consultant at PAHO/WHO and Senior Expert at the Parliament of Georgia, Committee on Health and Social Issues. She has also worked as a Deputy Chair/Project Manager for the Task Force for Prevention of Micronutrient Malnutrition and Food Fortification Initiatives established under the Parliament of Georgia, Committee on Health and Social Issues.

Christopher Craver is an independent health services researcher affiliated with the Charlotte Lozier Institute focused on the use of secondary healthcare data sources in population based scientific research. He is widely published in many healthcare topics including cancer treatment, rare disease populations, and the efficacy of surgical services.

Exhibit 18

Maarit Niinimaki, et al., *Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study*, BJM, April 20, 2011

BMJ

RESEARCH

Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study

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ABSTRACT

Objective To determine the risks of short term adverse events in adolescent and older women undergoing medical abortion.

Design Population based retrospective cohort study.

Setting Finnish abortion register 2000-6.

Participants All women (n=27 030) undergoing medical abortion during 2000-6, with only the first induced abortion analysed for each woman.

Main outcome measures Incidence of adverse events (haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury, thromboembolic disease, and death) among adolescent (<18 years) and older (≥18 years) women through record linkage of Finnish registries and genital *Chlamydia trachomatis* infections detected concomitantly with abortion and linked with data from the abortion register for 2004-6.

Results During 2000-6, 3024 adolescents and 24 006 adults underwent at least one medical abortion. The rate of chlamydia infections was higher in the adolescent cohort (5.7% *v* 3.7%, P<0.001). The incidence of adverse events among adolescents was similar or lower than that among the adults. The risks of haemorrhage (adjusted odds ratio 0.87, 95% confidence interval 0.77 to 0.99), incomplete abortion (0.69, 0.59 to 0.82), and surgical evacuation (0.78, 0.67 to 0.90) were lower in the adolescent cohort. In subgroup analysis of primigravid women, the risks of incomplete abortion (0.68, 0.56 to 0.81) and surgical evacuation (0.75, 0.64 to 0.88) were lower in the adolescent cohort. In logistic regression, duration of gestation was the most important risk factor for infection, incomplete abortion, and surgical evacuation.

Conclusions The incidence of adverse events after medical abortion was similar or lower among adolescents than among older women. Thus, medical abortion seems to be at least as safe in adolescents as it is in adults.

INTRODUCTION

Pregnancies among teenagers are mostly unplanned and offer a special challenge to family planning services. Most of all such pregnancies (up to 82% in the United States) are unintended.[1] The decision to continue or terminate a pregnancy is strongly associated with age. Besides age, being a student or being single are important factors in young women's decisions on abortion.[2] In the United States, 6% of all abortions are carried out in under 18s.[1] In the United Kingdom, 9.5% of abortions in 2009 were in adolescents.[3] Thus abortions among teenagers are common and are an important public health problem.

The medical termination of pregnancy using the antiprogestin mifepristone and a prostaglandin analogue has been widely established in several countries during the past decade. In 2009, 40% of abortions were medical in the United Kingdom.[3] In Sweden and Finland the corresponding figures were 72% and 76%.[4,5]

Increasing use of medical termination of pregnancy points to a need for appropriate studies to confirm its safety in various target groups. Using nationwide register based data we showed that both medical and surgical abortions are generally safe, with few serious complications when gestation is less than 63 days.[6] The most common adverse events were haemorrhage and incomplete abortion. However, in that study we did not assess the safety of medical abortion among adolescents.

Data on the safety of medical abortion among adolescents are limited. In a small prospective study, medical abortion was found to be highly effective and well tolerated in adolescents aged 14 to 17 when gestation was less than 56 days. Initially, half of the participants experienced stress and fear, but these emotions improved significantly within the month after abortion.[7]

In the present nationwide study we compared the safety of medical abortion between adolescents and adults. To eliminate the possible influence of previous pregnancies on the outcome of termination of pregnancy, we carried out a subgroup analysis among primigravid women. In addition we assessed the impact of a positive *Chlamydia trachomatis* test result at the time of

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abortion on the incidence of infections after abortion—a situation of great clinical relevance to adolescents.

METHODS

From the national abortion register compiled by the National Institute for Health and Welfare we identified all women who had undergone induced abortion in Finland during 2000-6. The study population consisted of women who had had a medical abortion (mifepristone alone or in combination with misoprostol or other prostaglandins) at 20 weeks or less of gestation. We divided the women into two cohorts based on age at the time of abortion: adolescents (<18 years) and adults (≥18 years). To keep the observations independent, we included only the first abortion for women who had more than one during the study period. To assess the potential learning curve in the introduction of medical abortion, we analysed the results in part separately for the first years (2000-3) of its use compared with established use (2004-6). We linked the data with the care register for health institutions (later called the hospital register) and the national infectious diseases register, both compiled by the National Institute for Health and Welfare, and the cause of death register of Statistics Finland. We followed the women for 42 days after the induced abortion and linked all events recorded in the hospital register and cause of death register with the abortion register.

The Finnish national register on induced abortions and sterilisations has been maintained since 1977. In accordance with the current legislation, doctors performing induced abortions are obliged to report cases to the register within one month, using a specific data collection form. In Finland, data on induced abortions are collected from all hospitals and clinics that carry out induced abortions. The register contains data on women having termination of pregnancy. These data include information on pregnancy history, occupation, type of residence, municipality, and marital status. Data on current pregnancy include information on duration of gestation at the time of abortion, indication for abortion, and method of termination.[5]

We have previously described Finnish legislation on induced abortion.[8] Briefly, current legislation permits termination of pregnancy of up to 20 weeks' gestation (24 weeks in cases of a medical condition of the fetus) for social, medical, or ethical reasons. A national guideline on the care of women seeking abortion was published in 2001 and updated in 2007.[9] Based on this guideline all women should be screened for *C trachomatis* and treated if it is present and screened for bacterial vaginosis at the first visit before the termination of pregnancy. Prophylactic antibiotics are not routinely used.

Classification of adverse events

- Haemorrhage—all reported haemorrhage
- Infection—pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections, and septicaemia
- Any reported incomplete abortion
- Surgical evacuation
- Psychiatric morbidity—depression, intoxication, psychoses (ICD-10 codes F10-F48)
- Injury or other reason for surgical operation—all injuries, cervical laceration, uterine perforation, all surgical interventions during follow-up
- Thromboembolic disease—pulmonary embolism, deep vein thrombosis
- Death—death from any cause, pregnancy related death according to the World Health Organization definition

Data collection

All hospitals in Finland are required by law to provide the hospital register with information on inpatient treatment (all hospitals) and outpatient visits (public hospitals). This register contains information on diagnosis (international statistical classification of diseases and related health problems, ICD-10[10]) and treatment (Nordic classification of surgical procedures[11]), as well as the dates of the treatment episodes. To analyse adverse events related to induced abortion we linked information on the study participants in the hospital register for all hospital inpatient episodes and outpatient visits within 42 days after termination of pregnancy with data in the abortion register. We selected diagnoses and codes for surgical procedures in the cohorts for those considered to be of clinical importance.

We divided the complications into eight categories (see box): haemorrhage, infection, incomplete abortion, surgical evacuation, psychiatric morbidity, injury or other reason for surgical operation, thromboembolic disease, and death. The classification was based on that reported in the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists[12] and modified for this and our previous study.[6]

The cause of death register contains data from death certificates and covers all deaths of Finnish citizens and permanent residents in Finland, classified according to ICD-10 codes. All the early deaths (within 42 days of termination of pregnancy) were classified as direct, indirect, or accidental.[13]

The National Department of Infectious Disease Epidemiology and Control at the National Institute for Health and Welfare collects information on cases of detected *C trachomatis* infections. Since 1997 it has been mandatory for laboratories to report all positive cases to the national infectious diseases register based on the Communicable Diseases Act and Decree of 1987.[14] Since 2004, laboratory notifications have included personal identification numbers, enabling linkage of the data with that in other registries. Since 2004 genital *C trachomatis* has been detected by DNA or RNA testing.[14]

Statistical analysis

To assess differences between the groups we used the Mann-Whitney test for age and the χ^2 test for categorical variables. The χ^2 test was also used to calculate the difference in the incidence of adverse events, except for rare ones (psychiatric morbidity, injury, thromboembolic disease, and death) when we used Fisher's

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Table 1 | Characteristics of the two study cohorts. Values are numbers (percentages) unless stated otherwise

Characteristics	Adolescent cohort (<18 years) (n=3024)	Adult cohort (≥18 years) (n=24 006)	P value
Mean (median) age (years), range	16.1 (16.0), 13-17	27.6 (26.0), 18-50	<0.001
Previous pregnancies:			
None	2913 (96.3)	10 474 (43.6)	<0.001
Yes	111 (3.7)	13 532 (56.4)	
Previous deliveries:			
None	2972 (98.3)	12 059 (50.2)	<0.001
Yes	52 (1.7)	11 947 (49.8)	
Previous induced abortions:			
None	3004 (99.3)	19 432 (80.9)	<0.001
Yes	20 (0.7)	4574 (19.1)	
Marital status:			
Married	12 (0.4)	5634 (23.5)	<0.001
Cohabiting	126 (4.2)	4546 (18.9)	
Single	2882 (95.3)	13 785 (57.4)	
Data missing	4 (0.1)	41 (0.2)	
Type of residence:			
Urban	1979 (65.4)	17 977 (74.9)	<0.001
Densely populated	486 (16.1)	2986 (12.4)	
Rural	559 (18.5)	3043 (12.7)	
Duration of gestation (weeks):			
<9	2424 (80.2)	20 143 (83.9)	<0.001
9-12	139 (4.6)	660 (2.7)	
13-16	283 (9.4)	1741 (7.3)	
17-20	171 (5.7)	1151 (4.8)	
Data missing	7 (0.2)	311 (1.3)	
Chlamydia trachomatis positive test result*	99/1749 (5.7)	496/13 547 (3.7)	<0.001

*Data available for 2004-6.

exact test. We used the confidence interval analysis program to calculate the rates of adverse events.[15] For small proportions we used the exact binomial method. The estimated risks of adverse events were determined by logistic regression analyses, and are presented as odds ratios with 95% confidence intervals. Variables that showed statistically significant associations with complications in univariate analysis (type of residence, marital status, duration of gestation, year of abortion, and adolescent or adult cohort) were further entered in multivariate analysis. SPSS 16.0 for Windows was used for the statistical analyses.

RESULTS

During 2000-6, 27 030 women underwent medical abortion between five and 20 weeks of gestation. Of these women, 3024 were younger than 18 (adolescent cohort) and the remaining 24 006 were older (adult cohort). Including only the first induced abortion for each woman during 2000-3, medical abortion was carried out in 1275 (29.3%) adolescents and in 10 459 (31.7%) adults. In 2004-6 the corresponding numbers were 1749 (61.9%) and 13 547 (63.3%).

The two cohorts differed significantly for various characteristics (table 1). The adolescents had fewer previous deliveries and induced abortions and were more often single and living in a non-urban setting. In both groups, most of the medical abortions (over 80%) were performed before nine weeks of gestation, but the mean duration of gestation was more advanced among adolescents. The incidence of *C trachomatis* infections, diagnosed four weeks before to six weeks after abortion, was higher in the adolescent cohort, as calculated for 2004-6.

Table 2 describes the incidence of adverse events among the two cohorts, as well as among the primigravid women. The adult cohort had a significantly higher incidence of haemorrhage (3690 (15.4%) *v* 386 (12.8%), P<0.001), incomplete abortion (2450 (10.2%) *v* 212 (7.0%), P<0.001), and surgical evacuation of retained products of conception (3121 (13.0% *v* 333 (11.0%), P=0.002). Odds ratios were calculated for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation), after adjustment for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion. In the adolescent cohort the adjusted odds ratios were significantly lower for haemorrhage, incomplete abortion, and surgical evacuation than in the adult cohort. In addition, the adult cohort had more participants with adverse events (5535 (23.1%) *v* 575 (19.0%), P<0.001).

In the subgroup analysis carried out among the primigravid women, the proportion of women with haemorrhage (1505 (14.4%) *v* 374 (12.8%), P=0.035), incomplete abortions (887 (8.5%) *v* 201 (6.9%), P=0.006) and a higher overall number of adverse events (2224 (21.1%) *v* 552 (18.9%), P=0.031) was significantly higher in the adult cohort. After adjustment for marital status, type of residence, duration of gestation, and year of abortion, the risks for incomplete abortion and surgical evacuation were lower in the primigravid adolescents than in the primigravid adults (table 2).

The incidence of a psychiatric diagnosis was higher among the adolescents in both the cohort and the primigravid cohort, even though the overall numbers were low. Two deaths were reported during the follow-up period. Both of these occurred in adults and were unrelated to the pregnancy (intracranial trauma and melanoma).

The figure shows the results of logistic regression among the primigravid women for risk of main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation). An increased risk of haemorrhage was associated with living in a densely populated area. The risk of bleeding after medical abortion was higher during 2004-6 than during 2000-3. Gestations of 9-12 or 13-16 weeks were associated with a lower risk of haemorrhage than gestations of less than nine weeks. The risk of haemorrhage was also significantly lower in the adolescent cohort.

Advanced duration of gestation (9-12, 13-16, and 17-20 weeks) was associated with an increased risk of infections after abortion (figure). Additionally, being married or cohabiting compared with being single was associated with an increased risk of infection.

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Table 2 | Incidence of adverse events in study cohorts for all women (3024 adolescents and 24 006 adults) and for primigravid women (2913 adolescents and 10 474 adults)

Adverse events	Adolescent cohort (<18 years)	% (95% CI)	Adult cohort (≥18 years)	% (95% CI)	P value	Adjusted odds ratio (95%CI)*
All women						
Haemorrhage	386	12.8 (11.6 to 14.0)	3690	15.4 (15.0 to 16.0)	<0.001†	0.87 (0.77 to 0.99)†
Infection	60	2.0 (1.5 to 2.6)	489	2.0 (1.9 to 2.2)	0.742	0.97 (0.73 to 1.30)
Incomplete abortion	212	7.0 (6.1 to 8.0)	2450	10.2 (9.8 to 10.6)	<0.001†	0.69 (0.59 to 0.82)†
Surgical evacuation	333	11.0 (9.9 to 12.1)	3121	13.0 (12.6 to 13.4)	0.002†	0.78 (0.67 to 0.90)†
Psychiatric morbidity	3	0.10 (0.02 to 0.29)	2	NA	0.012†	—
Injury	4	0.13 (0.04 to 0.34)	35	0.15 (0.10 to 0.19)	1.000	—
Thromboembolic disease	2	0.07 (0.01 to 0.24)	26	0.11 (0.07 to 0.15)	0.764	—
Death	0	NA	2	NA	0.392	—
No of adverse events per woman:						
0	2449	81.0 (79.6 to 82.4)	18471	76.9 (76.4 to 77.5)	<0.001†	—
1	488	16.1 (14.8 to 17.4)	4456	18.6 (18.1 to 19.1)		—
2	82	2.7 (2.2 to 3.4)	994	4.1 (3.9 to 4.4)		—
3	5	0.17 (0.05 to 0.39)	83	0.35 (0.27 to 0.42)		—
4	0	NA	2	NA		—
Primigravid women						
Haemorrhage	374	12.8 (11.6 to 14.1)	1505	14.4 (13.7 to 15.0)	0.035†	0.88 (0.78 to 1.00)
Infection	57	2.0 (1.5 to 2.5)	227	2.2 (1.9 to 2.5)	0.486	1.01 (0.75 to 1.37)
Incomplete abortion	201	6.9 (6.0 to 7.9)	887	8.5 (7.9 to 9.0)	0.006†	0.68 (0.56 to 0.81)†
Surgical evacuation	311	10.7 (9.6 to 11.8)	1136	10.8 (10.3 to 11.4)	0.794	0.75 (0.64 to 0.88)†
Psychiatric morbidity	3	0.10 (0.02 to 0.30)	1	NA	0.034†	—
Injury	4	0.14 (0.04 to 0.35)	10	0.10 (0.04 to 0.16)	0.521	—
Thromboembolic disease	2	0.07 (0.01 to 0.25)	10	0.10 (0.04 to 0.16)	1.00	—
Death	0	NA	1	NA	0.391	—
No of adverse events per woman:						
0	2361	81.1 (79.6 to 82.5)	8250	78.8 (78.0 to 79.5)	0.031†	—
1	468	16.1 (14.7 to 17.4)	1838	17.5 (16.8 to 18.3)		—
2	79	2.7 (2.2 to 3.4)	356	3.4 (3.1 to 3.8)		—
3	5	0.17 (0.06 to 0.40)	30	0.29 (0.18 to 0.39)		—
4	0	NA	0	NA		—

NA=not applicable owing to small number of women.
*Adult cohort as reference for all women adjusted for parity, previous abortions, marital status, type of residence, duration of gestation, and year of abortion; adult cohort as reference for primigravid women adjusted for marital status, type of residence, duration of gestation, and year of abortion.
†Statistically significant.

Also, the risk was higher in the later period (2004-6) than in 2000-3. The risk of infection was similar between the two cohorts.

Advanced duration of gestation was strongly related to the risk of incomplete abortion and surgical evacuation. The risk of incomplete abortion was lower in adolescents (odds ratio 0.69, 95% confidence interval 0.58 to 0.82) than in adults. The risk of surgical evacuation was increased in women living in rural areas and in those who were married or cohabiting. When abortion was carried out in the later period (2004-6) the risk of surgical evacuation was diminished (figure).

The risk of infections after abortion as a result of concurrent chlamydia infection was assessed among women who underwent abortion during 2004-6. In logistic regression analysis of the whole cohort, the risk of infection after abortion was not associated with concurrent chlamydia infection (1.02, 0.58 to 1.78). Moreover, no significant difference in the rate of infections after abortion emerged between adolescents and those with a positive test result for *C trachomatis* (data not shown).

DISCUSSION

In the present study the rate of adverse events and complications after medical abortion in adolescents was similar to or lower than that in adults. Various characteristics of the two cohorts differed significantly (table 1), but the risk of adverse events was calculated after adjustment for these factors. This study covered almost all abortions carried out in Finland in all regions and hospitals during a seven year period and thus shows reliable national trends. Earlier studies assessing the completeness of the Finnish abortion register found that 99% of abortions were reported to the register and at least 95% of information matched the medical records.[16 17]

One limitation of the study is that the registry based data lack detailed information as the diagnoses were made on clinical grounds, and the severity of adverse

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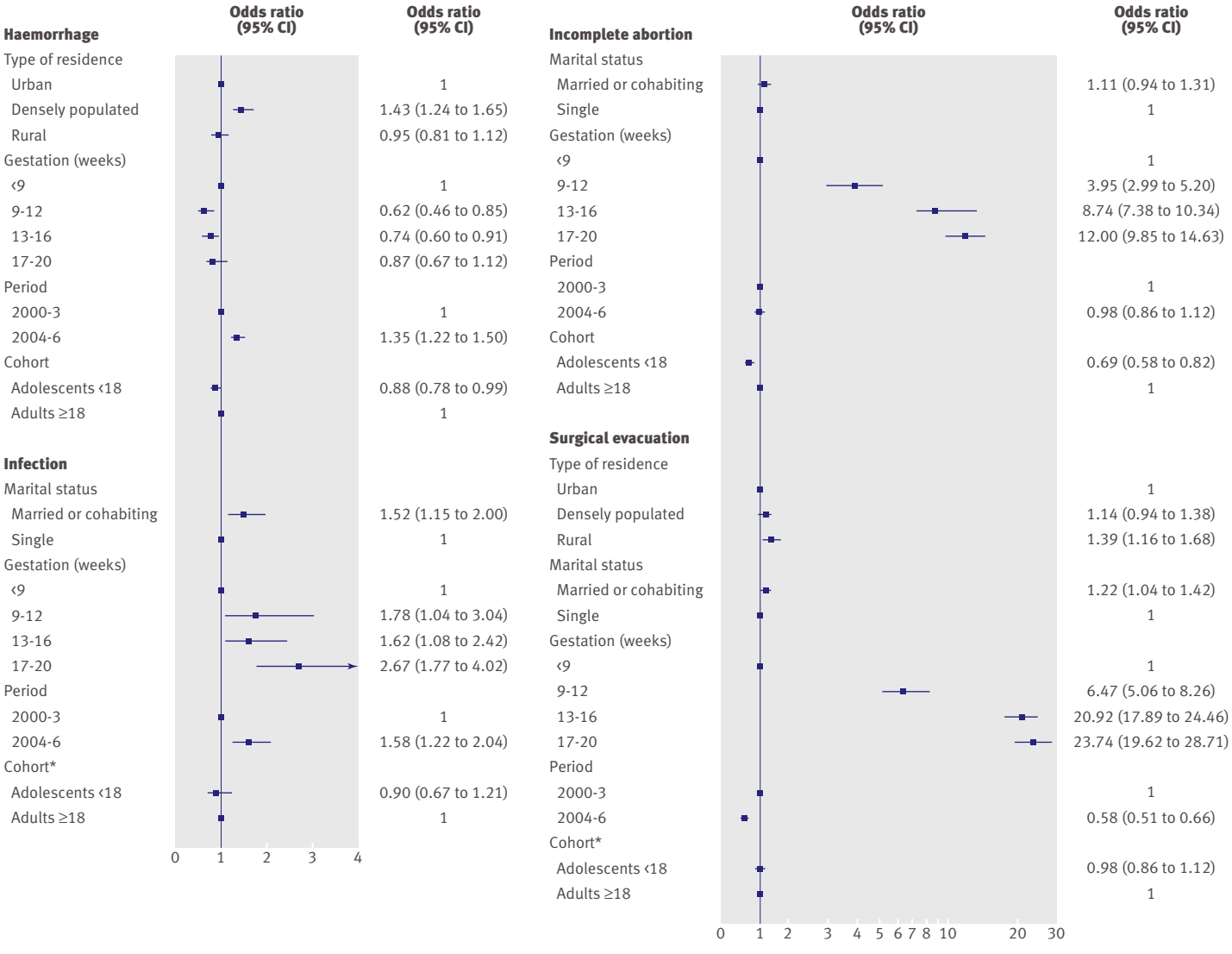

Logistic regression analysis of risk factors for main adverse events (haemorrhage, infection, incomplete abortion, and surgical evacuation) among primigravid women in entire cohort. Results of multivariate analysis are shown unless stated otherwise. Variables showing significance in univariate analysis are included. *Derived from univariate analysis

events may vary substantially. Another drawback is that no conclusions can be made on the effects of abortion beyond the 42 days of follow-up. A further limitation is that data on *C trachomatis* could only be linked with registry data from 2004, when identification numbers were first archived.

More women sought help for bleeding after abortion when gestation was less than nine weeks. This finding parallels that reported in our previous study.[6] This might be explained partly by the fact that medical abortions at nine weeks or more of gestation are carried out by hospitals, and not on an outpatient basis.[9] Moreover, an increasing number of these early abortions are carried out at home using self administered misoprostol.

The risk of surgical evacuation of retained products after medical abortion decreased during 2004-6 compared with 2000-3, whereas the number of incomplete abortions remained the same. These findings probably reflect a learning curve in providing medical abortion. However, the lower number of surgical evacuations occurred at the expense of an increased rate of consultations as a result of uterine bleeding. We took into account the possible bias caused by the differences between the study periods (2000-3 and 2004-6) by adjusting the odds ratios of adverse events by study period.

The rate of infections after abortion was higher (2.0%) than that reported in an earlier review in which medical abortion was assessed (0.9%).[18] The higher figure may in part be a result of the register based nature of the present study—that is, the diagnostic criteria lacked uniformity. In recent reviews, however, the incidence of infections after medical abortion in the second trimester has been estimated to be about 3%.[19,20] Thus in the present study, concerning pregnancies of up to 20 weeks' duration, the incidence of infections was comparable with that reported in the recent

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Teenage pregnancies are mostly unplanned and often result in induced abortion

Medical abortion is increasingly used, albeit its safety has not been properly assessed among adolescents

WHAT THIS STUDY ADDS

The risk of adverse events (haemorrhage, incomplete abortion, infection) after medical abortion is similar or even lower in adolescent (<18 years) compared with adult women

reviews. The risk of infection was increased when the abortion was carried out in the later period (2004-6). The explanation for this is unclear. The incidence of *C trachomatis* infections in the Finnish population did not change at the same time.[14]

C trachomatis is a notable cause of pelvic inflammatory disease. Screening for and treatment of *C trachomatis* can prevent the development of the disease after abortion.[21] To prevent infection after termination of pregnancy both prophylactic antibiotic therapy for all and screen and treat strategies are in use. In a recent study in the United States, routine provision of doxicycin at the time of medical abortion was associated with a significant reduction in the rate of serious infections.[22]

We found no correlation between *C trachomatis* diagnosed at the time of abortion and subsequent infections. In Finland, systematic screening for *C trachomatis* after termination of pregnancy is enforced by national guidelines.[9] In 2004-6 the national incidence of *C trachomatis* among girls and young women aged 10-19 was 1.7% in Finland,[14] whereas a higher rate of 5.7% was detected in the present adolescent cohort. The results of this study do not rule out the possible association with infections after abortions in the cases of untreated *C trachomatis* infections, or with delayed antibiotic treatment. The present study suggests that by timely screening it is possible to treat the infection before the clinical manifestation.

In the present study psychiatric morbidity was significantly more common among adolescents than among adults, although the number of cases was small. Register based studies are not ideal for studying psychiatric disorders, as only some women seek professional help for mental disorders and only some women with mental disorders are treated in specialised healthcare. In a recent register based Danish study, the risk of a psychiatric disorder in women with no such previously detected disorders was not increased after induced abortion in the first trimester.[23] The risk of psychiatric contact was not, however, significantly affected by age. In a US survey, adolescents were not at increased risk for depression or lower self esteem after abortion than the controls during follow-up.[24] The present studies only assessed psychiatric diagnoses during the short follow-up but not possible psychiatric morbidity before abortion. Thus the association of mental disorders and termination of pregnancy among adolescents remains unresolved.

Experience of pain or satisfaction with care could not be studied in the present setting, as these outcomes are not registered in the Finnish abortion register. In a randomised study, women with higher gestational age and first pregnancy seemed to be less satisfied with medical abortion as a result of more pain during the termination.[25] The effective treatment of pain must be taken into account when adolescents, predominantly nulliparous women, undergo induced abortion.

Conclusion

The present population based national study provides evidence that medical abortion is not associated with additional risks of adverse events among adolescents in the short term compared with adult women. The data were derived from one country with a homogeneous population but can be generalised to populations with high quality healthcare and easy access to specialist treatment.

The preliminary results of this study were presented at the International Federation of Obstetrics and Gynecology (FIGO) meeting in Cape Town, South Africa October 2009, and in the International Federation of Professional Abortion and Contraception Associates (FIAPAC) meeting in Seville Spain, October 2010 (MN). We thank Aini Bloigu (National institute for Health and Welfare, Oulu, Finland) for her professional help with the statistics.

Contributors: All authors participated in the design of the study. MN carried out the data analysis, wrote the first draft of the manuscript, and is a guarantor of the study. All authors contributed to the subsequent writing of the paper and gave substantial input into the study. OH obtained funding for the study. MG is in charge of the Finnish reproductive registries (including the abortion register).

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Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: OH has lectured at an educational event organised by Nordic Drugs and has been principal investigator in clinical studies sponsored by the Concept Foundation; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the ethics committee of the Northern Ostrobothnia Hospital District in October 2005 (No 46/2005). The Ministry of Social Affairs and Health, and Statistics Finland gave permission for the use of confidential personal level data from the registries. The data protection ombudsman was notified about the data linkage before the analyses, as required by national data protection legislation.

Data sharing: No additional data available.

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Exhibit 19

James Studnicki et al., *A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization*, Health Servs. Rsch. & Managerial Epidemiology, May 20, 2022

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A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization

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Abstract

Introduction: Previous research indicates that an increasing number of women who go to an emergency room for complications following an induced abortion are treated for a miscarriage, meaning their abortion is miscoded or concealed.

Objective: To determine if the failure to identify a prior induced abortion during an ER visit is a risk factor for higher rates of subsequent hospitalization.

Methods: Post hoc analysis of hospital admissions following an induced abortion and ER visit within 30 days: 4273 following surgical abortion and 408 following chemical abortion; abortion not miscoded versus miscoded or concealed at prior ER visit.

Results: Chemical abortion patients whose abortions are misclassified as miscarriages during an ER visit subsequently experience on average 3.2 hospital admissions within 30 days. 86% of the patients ultimately have surgical removal of retained products of conception (RPOC). Chemical abortions are more likely than surgical abortions (OR 1.80, CL 1.38-2.35) to result in an RPOC admission, and chemical abortions concealed are more likely to result (OR 2.18, CL 1.65-2.88) in a subsequent RPOC admission than abortions without miscoding. Surgical abortions miscoded/concealed are similarly twice as likely to result in hospital admission than those without miscoding.

Conclusion: Patient concealment and/or physician failure to identify a prior abortion during an ER visit is a significant risk factor for a subsequent hospital admission. Patients and ER personnel should be made aware of this risk.

Keywords

induced abortion, medical abortion, emergency room, inpatient admission, retained products of conception, medicaid

Introduction

In a previous study, we found abortion-related emergency room (ER) treatment rates from 2002 2015 increased 315% and 507% following surgical and chemical abortions respectively.[1] During this same period, we also found an increasing number of abortion patients misclassified/miscoded as having post miscarriage complications. A contributory factor to these miscodings may be the advice given to women by some abortion providers to conceal their abortion when seeking care in the ER for adverse events.[2,3] Since 60.9% of abortion-related ER visits following a chemical abortion were being miscoded as miscarriage by 2015, there is concern that this misinformation (ie, miscarriage rather than induced abortion) might result in sub-optimal care and, subsequently, an increased likelihood of hospital admission.[1] We use the risk of hospitalization following one

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or more ER treatments as a proxy for misinformed and suboptimal post abortion care.

Methods

Data were obtained from the enrollee-level Medicaid Analytic eXtract files licensed through the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse. The analytic dataset is comprised of enrollees from the 17 states whose official policies applied state funds to abortions not covered by federal Medicaid during the period 1999 2015. The study population was made up of enrollees over 13 years of age with at least one identifiable pregnancy outcome. For each beneficiary, all unique pregnancy outcomes were identified using International Classification of Diseases, Ninth Revision (ICD-9) codes. Additionally, Current Procedure Terminology, Fourth Edition (CPT4) and Healthcare Common Procedure Coding System (HCPCS) codes were used to confirm pregnancy outcomes. Every emergency room visit occurring within 30 days of the index abortion was identified (Place of Service code 23 emergency room). Emergency room visits within 30 days of a surgical or chemical induced abortion but treated for spontaneous abortion or miscarriage (ICD-9, primary diagnosis 634) are considered miscoded and possible concealment by the patient. Hospital admissions considered for the purpose of surgical removal of retained products of conception (RPOC) comprise ICD-9 procedure codes 690, 694, and 695.

In the original study, between 1999 2015, there were 423 000 confirmed induced abortion Medicaid procedures (361 924 surgical and 61 076 chemical), followed by 121 283 ER visits (99 928 surgical and 21 355 chemical). The exploratory post hoc analysis identified 4273 hospital admissions within 30 days of a surgical abortion and following an ER visit and 408 hospital admissions within 30 days of a chemical abortion and following an ER visit.

Summary analytic tables were created using (SAS/STAT) software, version (10) of the SAS system for (Unix). Copyright (2019) SAS Institute Inc.

The study has been exempted from Institutional Review Board (IRB) review pursuant to the U.S. Department of Health and Human Services Policy for Protection of Human Research Subjects at C.F.R. 46.101(b). See IRB ID: 7269, www.sterlingirb.com.

Results

Women experiencing chemical abortion and a subsequent emergency room (ER) visit within 30 days were less likely (OR 0.81, CL 0.70-0.95) to be hospitalized for any reason in that same time period than women who had experienced surgical abortion. This is true both for women whose prior abortion was concealed by miscoding during the ER visit and those for whom no mistaken miscarriage coding occurred (Table 1). Abortions miscoded in the ER were more likely to result in hospitalization for any reason (OR 1.06, CL 0.87-1.28) than those not miscoded. However, the subset of chemical abortion patients whose abortion was miscoded as miscarriage did exhibit a striking pattern of multiple admissions (3.2 per patient) for those women who were subsequently admitted compared to 1.8 admissions per woman whose abortion was not miscoded. Thus, the number of admissions per patient was 78% higher in women whose chemical abortion was concealed.

Further analysis determined that admissions for surgical RPOC were experienced by 86.3% of the women whose chemical abortion was subsequently miscoded in the ER, 2.5 times the rate of surgical abortion patients (34.2%) whose abortion was similarly miscoded. A very strong contrarian pattern emerges for hospital admissions involving surgical RPOC by aspiration and curettage or dilation and curettage. Chemical abortions are significantly more likely (OR 1.80, CL 1.38-2.35) than surgical abortions to result in an RPOC admission and chemical abortions miscoded in the ER are more likely (OR 2.18, CL 1.65-2.88) than abortions without miscoding to have a subsequent RPOC admission.

Chemical abortion patients whose subsequent ER visit is mistakenly coded as an adverse event related to miscarriage experience multiple hospital admissions within 30 days of the

Table 1. Hospital Admissions (for any Reason and RPOC) Following an Abortion and an Emergency Room Visit: by Type of Abortion with and without Miscoding as a Miscarriage.

	Surgical abortion			Chemical abortion		
Abortion miscoded as miscarriage (ICD 634)	Yes (%)	No (%)	Total	Yes (%)	No (%)	Total
No. patients with ER visits	567 (3.3)	16 671 (96.7)	17 238	366 (11.2)	2912 (88.8)	3278
No. ER patients admitted for any reason	114 (5.9)	1823 (94.1)	1937	22 (10.4)	190 (89.6)	212
% ER patients admitted for any reason	20.1%	10.9%	11.2%	6.0%	6.5%	6.4%
Total no. admissions for any reason	232 (5.4)	4041 (94.6)	4273	71 (17.4)	337 (82.6)	408
Admissions per patient for any reason	2.0	2.2	2.2	3.2	1.8	1.9
No. patients admitted for surgical RPOC	39 (13.0)	262 (87.0)	301	19 (21.6)	69 (78.4)	88
% admitted patients requiring surgical RPOC	34.2%	14.4%	15.5%	86.4%	36.3%	41.5%
No. surgical RPOC admissions	42 (13.3)	274 (86.7)	316	22 (23.7)	71 (76.3)	93
% surgical RPOC admissions of total admissions	18.1%	6.8%	7.4%	31.0%	21.1%	22.8%
Surgical RPOC admissions per patient	1.1	1.0	1.0	1.2	1.0	1.1

abortion and are particularly at risk to experience a hospitalization that involves RPOC.

Discussion

Our research indicates that an ER physician's misclassification of a failed induced abortion as a miscarriage correlated with higher rates of hospitalization and surgical intervention for RPOC. A patient's concealment of a chemical abortion, and/or the ER staffs' failure to identify the failed abortion attempt, are risk factors for multiple hospital admissions and delayed provision of necessary surgical treatment, compared with care for those whose abortion is not miscoded.

One possible explanation is that ER physicians may tolerate a higher level of pain, tenderness, or bleeding if they know they are dealing with an induced abortion patient rather than a spontaneous abortion patient experiencing the same symptoms. It may be that these women were considered sick enough to be admitted, yet surgical care was delayed while alternative treatment options were explored. The percent of admitted women who underwent surgical intervention for RPOC is strikingly higher for women whose induced abortions were misclassified as miscarriages.

It is important for emergency room personnel to obtain an accurate history when faced with an incomplete induced abortion. Additionally, it is inadvisable for abortion providers to tell women that if they present to an ER after the abortion, they can simply say they are having a miscarriage.[2,3]

Abortion providers should advise women that they may be at increased risk of multiple hospitalizations and surgical intervention if they do not inform medical personnel that they are experiencing an abortion complication. As required by the mifepristone Risk Evaluation and Mitigation Strategy, patients should be strongly reminded to bring the Medication Guide when seeking medical care in an emergency room.[4] Further research on adverse events associated with miscoding of induced abortion is warranted.

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Exhibit 20

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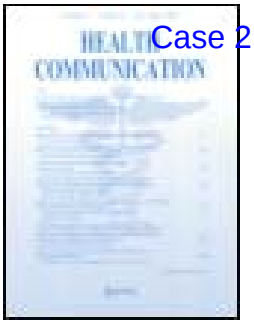

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#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives

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#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives

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ABSTRACT

One out of four women in the United States will have an abortion by age 45. While abortion rates are steadily declining in the United States, the rate of medication abortions continues to increase, with 39% of all abortions being medication abortions. Our study is one of the first to analyze women's narratives after having had a medication abortion. Using relational dialectics theory, we conducted a case study of the nonpartisan website, *Abortion Changes You*. Our contrapuntal analysis rendered four sites of dialectical tension found across women's blog posts: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after abortion, and managing the stigmatizing silence before and after the abortion. We discuss theoretical and practical implications about how the larger politicized discourses prevalent within the abortion debate impact the liminality of women who are contemplating a medication abortion and affect their own narrative construction about the medication abortion experience.

One out of four women will undergo an abortion procedure in the United States by age 45 (R. K. Jones & Jerman, 2017), and 862, 320 reported abortions occur each year (Jones et al., 2019). Despite its frequency, abortion remains a highly contested and stigmatized biopolitical public health issue in the United States (Altshuler et al., 2017). The historic *Roe v. Wade* case has resulted in two nationalized political movements – Right to Life and Right to Choice – that have juxtaposed stances on the legality of abortion. However, the stigma and shame associated with abortion precede and transcend this historic case. Stormer (2010) concluded that a collective memory of secrets and shame has characterized the topic of abortion since Planned Parenthood's 1955 conference, "Abortion in the United States".

While abortion rates are steadily declining in the U.S. (Jones et al., 2019), the rate of medication abortions continues to increase. In 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone to be used in combination with misoprostol as a form of medication abortion. Since then, the annual number of medication abortions has risen steadily: less than 6% of all abortions in 2001 to 39% of all abortions in 2017 (Jones et al., 2019, 2008). Between 2014–2017, the number of medication abortions provided at facilities other than hospitals increased by 25% (Jones et al., 2019). Presently, over one-third of all reported abortions in the U.S. are medication abortions (Jones et al., 2019). In 2016, the FDA protocol expanded provider eligibility for dispensing mifepristone to women. Thus, abortion provision is transitioning from formalized medical procedures conducted in health care settings to a protocol where most of the abortion occurs individually at home with limited clinician assistance (Biggs et al., 2019). Given the privatization of abortion provision, research is needed to examine the distinct experiences of women who have undergone this type of abortion. After all, researchers have found that women often elect to have a medication abortion over a surgical abortion because of more privacy, convenience, and the perception of having more control (Newton et al., 2016). However, medication abortion has been found to have a higher complication rate that results in more emergency department visits post-medication abortion compared to post-surgical abortion (Upadhyay et al., 2015).

Medication abortion practices in the U.S. adhere to the following evidence-based guidelines: using mifepristone in combination with a prostaglandin to carry success rates up to 99% for early pregnancy termination with rare occurrence of serious adverse events. However, the focus of this research is on successful terminations, increases in abortion access, and reductions of in-person clinic visits (H. E. Jones et al., 2017). There remains a dearth of research, particularly in the U.S., that examines women's personal experiences with having this type of abortion procedure (e.g., acknowledging their emotions, understanding their self-efficacy with completing the abortion at home, being aware of whether they are adequately informed about the process). To our knowledge, the only study is from Sweden; researchers used semi-structured telephone interviews with 119 women who had a medication abortion (Hedqvist et al., 2016). They found that almost half (43%) experienced more bleeding than expected, and one-

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fourth (26%) bled for more than four weeks. In addition, one-third (34%) stated that they received insufficient information about what to expect. Women who had never had an abortion nor had gone through childbirth were more likely to feel misinformed.

Scholars know that the medication abortion process is distinct from surgical abortions, with the features of medication abortion (e.g., lack of medical presence, time required for abortion completion, personal experiences with pain and bleeding) influencing women's perception and satisfaction (Newton et al., 2016). Yet, this research on women's satisfaction with medication abortion is often conflicting (Kimport et al., 2012) and limited (Hedqvist et al., 2016). Given that women increasingly prefer medication abortion over surgical abortion (Newton et al., 2016), the need for studying women's experiences post-medication abortion becomes imperative.

Importance of analyzing unsolicited blogging narratives about one's abortion

To understand women's medication abortion experiences, it is important to study platforms where women engage in unsolicited talk. Unsolicited talk is ideal for collecting formative research that can be studied to explore individual and cultural experiences (Baxter, 2011). First, the audience of these texts is a "generalized other" (Mead, 1982), or culture, rather than a specific individual with whom the author has a relationship (Langellier & Peterson, 2004). The absence of a specific audience encourages narrators to provide an unadulterated account of their experience, rather than tailor their story to specific individuals (e.g., a friend who has had a certain stance on the abortion issue). Similarly, anonymity allows for potentially muted or stigmatized groups to post information without fear of sanctioning. In a culture where abortion remains highly contested and talk about having had an abortion is often muted or stigmatized (Altshuler et al., 2017), it is likely that women may prefer to self-disclose their medication abortion experiences online rather than via face-to-face channels. Furthermore, because women traditionally constitute a co-culture who have historically been muted and must strategically use communication to participate in a dominant patriarchal society (M. Orbe, 2005; M. P. Orbe, 1998), scholars must study platforms where women are sharing unsolicited stories in back-channel outlets (e.g., online blogs).

Online blogs as a platform for unsolicited talk

One backchannel platform of unsolicited talk is online blogs. Blogs provide a computer-mediated platform where people can self-disclose their personal thoughts, feelings, and experiences to others online. The proliferation of blogs in the last decade has transformed the way that we, as a society, "share, create, and curate information with individuals and communities" (Becker & Freburg, 2014, p. 415). Blogs often resemble online personal journal entries that enable writers to freely express themselves in ways that may be less face-threatening or stigmatizing (M. Jones & Alony, 2008). One of the many applications and uses of blogs is to share experiences and events through storytelling.

Relational Dialectics Theory (RDT)

Because talking about one's abortion experience remains stigmatized and muted (Cockrill & Nack, 2013), examining women's stories after having had a medication abortion may illuminate the competing discourses surrounding this debated moral and social issue (e.g., largely evident in the two polarized movements: Right to Choice v. Right to Life), as well as some of the larger dominant discourses from the polarized political movements that influence how women tell their own medication abortion story. Given this goal, RDT (Baxter, 2011) is a relevant framework to assess the competing cultural norms and expectations, which are also referred to as discourses. At any given moment, discourses may be dominant/centripetal or marginalized/centrifugal (i.e., anything that deviates from the dominant discourse). Scholars use RDT as a framework to examine the interplay between certain discourses that then construct social meaning and reality for individuals. Within the theory, there are four types of utterances (i.e., speaking chains) from which dialectical tensions (i.e., centripetal vs. centrifugal) may stem: *distal already-spokens* – utterances reflecting the cultural meaning and discourses that cultural members give voice to in their talk; *proximal already-spokens* – utterances conveying past meanings and discourses within a given relationship; *proximal not-yet-spokens* – immediate response from the hearer in the interaction; and *distal not-yet-spokens* – anticipated responses of a generalized other within the culture. The purpose of this paper is to examine how, if at all, these four types of utterance chains are present within women's medication abortion narratives.

A second aspect of RDT (Baxter, 2011) is to understand how social reality is created discursively through power. Power is located in the struggle between marginalized/centrifugal and dominant/centripetal discourses. There are three ways that power can be located within discourses: diachronic separation, synchronic interplay, and discursive transformation. Diachronic separation occurs when discourses emerge in different texts or locations. Synchronic interplay is when discourses negate (total rejection of a competing discourse), counter (offer limited legitimacy to a discourse), and/or entertain (consider multiple worldviews/discourses or general ambivalence toward discourses) one another. Finally, discursive transformations occur when the interplay of competing discourses creates new meanings rather than remaining in opposition to one another (Baxter, 2011). This current study will focus on examining the synchronic interplay among the centripetal and centrifugal discourses.

A case study of women who have experienced medication abortion

To analyze women's personal narratives and the larger discourses influencing their talk about their own medication abortion, we conducted a case study of the website www.abortionchangesyou.com. We selected this website for several reasons: it is not openly politicized, bloggers do not interact with others, bloggers post anonymously, bloggers do not need to create an account in order to post, and the platform is a space for unsolicited stories with no reward or

compensation to those who post. Furthermore, from a strategic storytelling standpoint (Tyler, 2007), it is important to study women's blogs from an organization that recognizes and respects each woman's individual narrative, as opposed to propagating narratives that openly align with the agenda of only one political movement. The woman who created this website has had an abortion herself and openly shares this information on the "About Us" page. The naming of her own abortion experience grounds co-cultural theorizing (M. Orbe, 2005; M. P. Orbe, 1998) such that other women who feel muted may be empowered and capable of finding similar language strategies.

In this case study, we explore the complexity and consequentiality of women's language choices with anonymously telling their own medication abortion story, as well as offer the potential to capture the interplay of individual, organizational, and social discourses surrounding the abortion debate. The current divisiveness surrounding the socio-political climate in the U.S. about abortion provides further exigency and credence for this research. Our critical analysis is rooted in the interpretive paradigm with the purpose of explaining, describing, and illustrating the stories that women share on this website (Tracy, 2013). The following research questions guide our iterative analysis:

RQ1: What topics are women disclosing to the "generalized other" in their blog?

RQ2: What (if any) sites of struggle characterize women's abortion narrative?

Methods

We conducted a case study approach (Arden Ford et al., 2014) of one website, www.abortionchangesyou.com. Case studies are a contextual examination used to understand a phenomenon within a particular context "and with respect to multiple perspectives within that context" (Arden Ford et al., 2014, p. 118). By employing a case study approach, we were able to draw on multiple perspectives (e.g., 98 different blog stories) that were rooted in a specific context. This methodological choice is common in other communication research, where the unit of analysis is an organization and the goals are to provide an in-depth understanding of the unique particulars and complexities of the case within a larger social context (Norander & Brandhorst, 2017).

Our case study included 98 blogs from women who have had a medication abortion and shared their story on the website. We included all blogs posted between October 2007 – February 2018. This date range reflects the time period between the submission of the first medication abortion blog on the website in 2007, and the point at which we extracted our data for analysis in 2018. Women's blogs ranged in length from one paragraph to three pages of text, single-spaced (the average number of words for the 98 blogs was 655 words). All 98 blogs included content about one's own medication abortion; the vast majority (91 women; 93%) also discussed the events and emotions experienced before and after their medication abortion.

Data analysis and synthesis

The case study approach allows for different data analysis strategies (Norander & Brandhorst, 2017). Because the purpose of our case study is to develop a thick description of the case, using an interpretive analytic strategy is most prudent. We selected Baxter's (2011) contrapuntal analysis to study the meanings circulating around individual and relational identities evidenced within the language choices of the women blogging about their own medication abortion. Given the larger competing discourses about the legality of abortion in the U.S., we felt that the struggle of competing and contradictory discourses would likely be apparent in women's personal blogging narratives. Further, contrapuntal analysis (Baxter, 2011) offered a critical perspective to our analysis as we studied the voices of marginalized women (e.g., women who have had a medication abortion) whose perspectives are often muted and stigmatized in society.

To understand the competing discourses and how meaning was constructed through their interplay, we conducted the first stages of thematic analysis to identify the discourses evident within each blog post (Braun & Clarke, 2006). This process required the three coders to independently familiarize themselves with the entire data set: reading the blogs several times and conducting line-by-line coding that captured the essence of the story in each line. Many of the inductive analytic codes applied to the text were descriptive (e.g., uncertainty; not ready), process (e.g., discovering pregnancy, taking the pills), or in vivo codes (e.g., wanted baby; alone; Saldaña, 2013). The coders met regularly for five months to discuss the codes independently applied to each blog post. During this time, codes emerged into themes as processes were identified in the data and repetitively noticed by all three coders (e.g., changing self perception, silence, responsibility, good parenting). Discrepancies in coding were discussed during coding meetings and resolved through group consensus (Strauss & Corbin, 1990).

During the third and fourth months of data analysis, we went back to the data set to identify where discourses competed (e.g., culpability; justification). Here, we paid particular attention to where the bloggers used instances of negating (e.g., claiming another discourse as irrelevant or rejecting it), countering (e.g., offering a particular discursive position in replacement of another), and entertaining (e.g., not completely rejecting a discourse, but instead noting the potential possibilities with different discourses; Baxter, 2011). Women used negating when saying, "can't," "not," "couldn't," and "never." Examples of countering were most apparent when women used the word "but." Entertaining often occurred when women used the words "possibility" and "could have." Finally, we identified where and how competing discourses interpenetrated (Baxter, 2011). Dialogically contractive discursive practices are silenced discourses. Examples of these discursive practices included negating talk, such as: "can't talk about the abortion," or "there was no other choice." In contrast, dialogically expansive discursive practices are discourses that are encouraged and amplified. Women used these discourses when saying things like: "I don't want the procedure, but I don't want the baby" or "hoping for a brighter future now that it is over."

Data were analyzed until the point of theoretical saturation (i.e., no new thematic categories were present in the blog posts; Strauss & Corbin, 1990), which occurred after the 54th blog post. However, we continued to analyze the remaining blog posts in an effort to verify that our analysis of the discourses evident in the 54 posts accurately reflected all of the posts within the entire data set. Further, we wanted to extract the best exemplars from the entire case study and desired that quotations within all posts be considered for representation. Clear and concise exemplars of competing discourses within women's narratives were then selected and agreed upon by all coders.

Trustworthiness and rigor

Evaluation of the quality of case study research should be determined by criteria associated within the naturalistic paradigm (Arden Ford et al., 2014). Trustworthiness is the criterion that assesses the credibility, transferability, dependability, and confirmability of the data collection and analysis processes (Lincoln & Guba, 1985). We upheld these principles when conducting this study by beginning with a careful design that clearly defined its purpose, research questions, and notion of "boundedness" (i.e., establishing the limits and context of the case; Arden Ford et al., 2014). Second, we spent sufficient time developing and analyzing the case: our analysis transpired over five months. Third, we upheld the principles of reflexivity by using inductive coding for all blog posts and writing individual and group memos throughout the entire coding process as a way to remain transparent and keep a data audit. Fourth, we had a team of three female coders, which allowed for the presence of multiple feminine perspectives.

Findings

Our research questions focused on the topics that women discussed in their personal online blogging narrative posted to www.abortionchangesyou.com (RQ1), and what (if any) sites of struggle were evident in these narratives (RQ2). Our contrapuntal analysis (Baxter, 2011) rendered four sites of dialectical tension: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different noteworthy moment within a woman's medication abortion experience: the decision, the medication abortion process, identity after the abortion, and managing the stigmatizing silence before and after the abortion. When recounting their decision to have an abortion, women referenced the struggle of *only choice* vs. *other alternatives*. As women discussed the medication abortion process, the competing discourse of *unprepared* vs. *knowledgeable* was evidenced. Women's narratives about their identity after the abortion indicated the dialectical struggle of *relief* vs. *regret*. Finally, the challenges with managing the tension between *silence* vs. *openness* pervaded women's narratives. Below we discuss each site of struggle using exemplar quotes from women's blogs. Quotes were not edited from their original post.

The decision: Only choice vs. other alternatives

Part of women's narratives included a detailed account of their decision to have a medication abortion. This decision was described as being rife with contradiction, and not a flippant choice. Women enumerated various reasons that were influential in their decision-making process: bad timing, financial instability, relationship problems, lack of family support, not married, too young, too many other children, not prepared to be a parent yet, and/or best decision given the circumstances. After stating one of the aforementioned reasons, 92 women (94%) also explained that abortion was the only or best option given the circumstances. For example, one woman said: "I felt the child growing inside of me. I was rubbing my stomach without me even knowing. I felt the doubt in my heart, but kept telling myself this is the best decision I needed to make" (6–18-17). A different woman recounted:

> "I always leaned more towards keeping the baby and my boyfriend more towards abortion. I knew I could have the baby but it would be difficult. We both work jobs that barely pay over minimum wage and we both were scared to grow up and care for a child" (10-24-17).

Collectively, these exemplars illustrate how any possibility of keeping the baby was negated by one of the reasons that warranted the need for having a medication abortion. Many of the reasons women cited for choosing abortion align with the discourses from the Right to Choice movement: "A pregnancy to a woman is perhaps one of the most determinative aspects of her life. It disrupts her body. It disrupts her education. It disrupts her employment. And it often disrupts her entire family life" (*Roe v. Wade*).

However, the decision to have a medication abortion was not always independently made by the woman. In fact, 52 women (53%) reported that the father to their child or other family members (e.g., parents) negated women's own desires to keep the baby. For example, one woman said:

> "I remember my husband telling me, 'well, don't expect me to be too happy with the idea of having it if you decide to keep it. I won't be too loving.' That was a knife through my heart and I made the tough decision to go through with the abortion" (7-6-12).

Other family members also influenced women's medication abortion decision, albeit her own desires to keep her baby:

> "But my father on the other hand was a different story. He is an old school Puerto Rican who told me that I had to leave if I kept the baby. I had 2 weeks to get an abortion or else he would disown me forever" (3-8-2018).

In both accounts, women communicated their personal choice to have their baby; yet, their choice was negated by family and friends who advocated that abortion was necessary. Centrifugal discourses about others influencing or pressuring women to have an abortion are marginalized discourses.

Finally, when making their decision, 48 women (49%) reported vacillating between keeping their baby and having a medication abortion. Ultimately, outside circumstances or other people influenced their decision to abort. As mentioned earlier, 92 women (94%) shared that abortion was the best or

only option available given the circumstances. In many of these narratives, women did not believe nor realize that other alternatives, besides abortion, were tenable options until after having the abortion. For instance, one woman said:

> "They all tell you 'it's your choice' in the moment, but you don't feel that it is. Being unable to afford it, unable to tell your loved ones, not having the help or feeling unable to support a child. When your partner doesn't want it like you do. All these things push you, blind you to a decision that you don't realize will destroy you" (8-23-17).

Similarly, another woman recounted: "I was kind of excited but I was so scared to tell my family …. I told my mom and her first response was I hope you're getting an abortion. You're going to be a terrible mom" (11-5-17). Both exemplars illustrate the distal and proximal already-spoken discourses that influenced each woman's decision to have a medication abortion. Ultimately, these centripetal discourses (coming from society, the pro-choice movement, other people in their lives, or their own fears) negated the centrifugal discourse that other alternatives (adoption or keeping their baby) were justifiable options available to them.

The medication abortion process: Unprepared vs. knowledgeable

Medication abortions where women undergo most of the process individually at home with limited assistance from a medical provider are becoming more commonplace (Biggs et al., 2019; H. E. Jones et al., 2017). While this process is generally reported to be safe and adhere to evidence-based guidelines (H. E. Jones et al., 2017), little is known about women's personal experiences with having this type of abortion. All women in this case study reported having had a medication abortion. Forty-eight women (49%) provided detailed accounts of their actual medication abortion experience at home. Women said things like: "I felt her come out" (1-8-16). Some women detailed the hardships of this process by saying: "I was in so much pain on the bathroom floor" (3–15-18); "the pills made me vomit, lose control of my bowels, sweat, faint, pass out, and go into full labor" (10-9-09); and "I lay on my bed in the fetal position, holding my stomach" (9-5-15). Other women did not self-report such negative experiences: "The actual process of taking the pill was frightening but not as bad as I imagined" (9-8-15) and "I just popped some pills and got a period" (7-1-15).

In analyzing women's talk about the medication abortion process, a second site of struggle was identified: *knowledgeable vs. unprepared*. In this struggle, women discussed how they were told certain information about the medication abortion process (e.g., when to take the pills, what the pills do, the need to contact a provider if complications arise), but ultimately this information was insufficient, limited, or misleading. Fourteen women (14%) reported being inadequately prepared about what to expect during the medication abortion process. For example, one woman said:

> "They lied to me and said they would give me some pills that would make it just like a late period with a little cramping … The pain of the contractions was so intense I felt like my intestines were pulled out slowly. I collapsed screaming on my bathroom floor, sweat, tears, blood, vomit, and shit all over me" (10-9-09).

Similarly, a different woman recounted:

> "They told me, if you by chance are in pain you can take these pain relievers. If by chance I'm in pain? That sounded like the process would be easy and not so painful. Well NO that was not the case, within 30 minutes I felt really bad cramping. It just kept getting worse and worse. I was crying and moaning from the pain. I literally thought I was dying" (9-2-17).

In both instances, women's personal abortion experiences did not align with the proximal-already-spoken messages (e.g., "it's just a pill") that they were told by their medical providers.

When women's personal experiences contradicted what they were originally told by health care providers, family, or friends women felt deceived. One woman communicated her frustration by saying: "They told me it wouldn't hurt and I wouldn't feel a thing. THAT WAS SUCH A LIE. I felt everything, I heard everything, I seen everything. I ended up blacking out from the pain and puking all over myself" (11-5-17). Similarly, another woman said:

> "We were told we would go back to normal and it won't affect us but they were wrong!!! All I feel is emptiness and hatred. I used to be the happiest most positive girl. All I want is to take it back" (12-15-14).

Even if women did not explicitly report feeling deceived, many women stated that they were inadequately prepared about what to expect. For instance, one woman said: "I knew to expect blood clotting, but nothing could've prepared me for seeing her body. It was the color of my own skin, and was actually starting to look like a person" (1-8-16). Within women's narratives, they expressed a desire for more detailed information about things such as: potential side effects, the intensity of cramping and bleeding, what to do after passing the baby, and potential negative emotions (e.g., fear, uncertainty, sadness, pain) felt after the abortion. When this comprehensive information was not communicated to them prior to taking the pills at home, women reported feeling misled, misinformed, and even deceived. These types of experiences and feelings after having had a medication abortion remain centrifugal discourses that are muted within the abortion debate.

Identity after medication abortion: Relief vs. regret

A third site of dialectical struggle was found in women's talk about their identity after the medication abortion. Most women (N = 81; 83%) reported that their medication abortion changed them, which is not surprising given the name of the website: *Abortion Changes You*. Of noteworthy significance is understanding *how* women talked about these changes and the tension evident in this part of their narrative. Of the 81 women (83%) who stated feeling *changed* after their medication abortion, 75 women (77%) reported being changed in a negative way. Here, women said things like: "I really thought that I could somehow go back to the way things were before finding out I was pregnant. But I cannot. I am not the same person, and my husband is certainly not the same either" (7–11-11). Negative changes often occurred when women's

actual abortion experience did not align with their preconceived ideas about what to expect. These ideas were informed by larger discourses from society, as well as messages from others (e.g., health care providers). Three women indicated a positive change after their abortion by noting something like:

> "Abortion did change my life … As soon as the stomach cramps (only slightly worse than regular menstrual pains) went away, I felt like a whole new person. I couldn't believe how much energy I had again. It was like waking out of a deep depression" (7-1-15).

Positive changes were denoted by experiencing an initial sense of relief with no longer being pregnant. Finally, three women were ambivalent or didn't report their change as positive or negative. One woman said: "I truly believe there is no right and wrong with this situation, it is a life changer but it's your choice" (9-7-10).

Women discussed various issues when talking about change: impact on their emotional health as a result of the abortion, differences in their relationship with their partner/spouse, and new perspectives on their general views of abortion. However, conflicting emotions were evident across all women's blog posts. For instance, one woman said:

> "I went home and confessed to my mother … She helped pull the gigantic blood clots from my body … No one told me it would be like this; the clinic simply gave me what I asked for without telling me what it entailed" (7-20-16).

Similarly, another woman recounted: "I thought maybe after the due date I would feel better, but it doesn't end there. It NEVER ends! The pain and emptiness stays there forever" (4–30-17). In these different accounts, the women alluded to their initial expectations of what the medication abortion would entail or what others told them would happen after their abortion. When a woman's actual medication abortion experience did not align with these messages, women felt disempowered, vulnerable, lost, upset, and sometimes deceived.

When discussing the changes experienced after the abortion, many women talked about emotional changes. One woman said:

> "At first it all seemed like a weight had been lifted and everything was okay then I started to feel really sad and low and now all I do is think about how many weeks pregnant I would have been and what my baby would look like and I miss so much" (4-26-10).

As mentioned, processing one's abortion experience was emotional and took time. Some women wrestled with experiencing negative and difficult emotions after having their abortion. In fact, 37 women (38%) explicitly stated problems with anxiety, depression, drug abuse, and suicidal thoughts as a result of the abortion. For example, one woman said: "I am haunted by the image of my tiny baby. I always will be. I cut myself and even wanted to die" (3–22-13). Another woman recounted: "Looking at my kids thinking of another beautiful child. Couldn't live with myself. Wishing God would take my life" (12–16-11). Collectively, these exemplars illustrate women's emotional changes about processing of their medication abortion.

Finally, 75 women (77%) explicitly stated that they regretted their decision to have an abortion. However, the term regret was rife with contradiction and also included talk about initial relief. For instance, one woman said: "I know I did the right thing for myself and it would be a lot harder for me right now. But I still would give anything to go back in time and keep my baby" (11–19-12). Regret was regarded as a process that was realized over time and through one's life experience. One woman stated: "Had I known how badly I would feel now, I would have kept the baby, even if I had to go through it alone" (10–21-15). Another woman elaborated upon this process by saying:

> "Knowing what I know now at almost a year later I would not have the abortion. That was my child and I should have done what I needed to do to give them a great life. I thought I had no options but I did. I should have put my child first. No matter how early the abortion is its still a growing life and i wish i had done things differently" (4-30-17).

In both accounts, women defined regret as the emotional pain, suffering, remorse, and guilt felt after the medication abortion. Yet, these emotions were often coupled with initial feelings of relief from no longer being pregnant. In sum, the decision to have a medication abortion was significant, transformative, and lifechanging for these women. One woman noted this change by saying: "From the outside, our life looks exactly the same as it would have. But on the inside, everything has changed for me" (10–21-15). Collectively, these accounts expose how the different emotional changes resulted in a lived, dialectical tension between their life before the abortion and their life after the abortion.

Managing the comprehensive stigmatizing silence: Silence vs. openness

Across women's narratives, there existed an overarching dialectical tension of *silence* vs. *openness*, which was difficult for many women to manage when interacting with others. In this struggle, women shared how their medication abortion was often a solo, private experience that was not openly shared with others. Many women decided *not* to inform certain family members about their pregnancy and abortion. Women noted feelings of shame, embarrassment, worry, or fear as some of the reasons for not telling others. Along with stating these emotions, women said things like: "I never told the father and I don't intend to" (8-4-17); "I don't know if I will ever tell my husband and children about what I did" (2–11-12); or "I couldn't talk to my family" (3–16-17). The initial decision to remain silent made it difficult to talk openly with others about their feelings and experiences after their medication abortion. Silence was also experienced in other ways: one woman was glad she was home alone during her abortion so no one could hear her, while a different woman left the abortion clinic and began crying and said, "why is there so much silence here?" as she was taking her pill alone in her bathroom at home.

Even if women did allow certain family members to become privy to their abortion decision, openly discussing their feelings after the abortion remained difficult. When talking with others, one woman said: "I love my husband but it is beyond difficult for me to talk to him about this,

because I know he wants nothing more than to just move on from this" (4–28-18). A different woman recounted: "My close friends know here but I don't really feel I can talk to them about it. I don't feel like i can talk to anyone about it" (2-9-13). Despite these women's desires to talk about their abortion, others (e.g., the baby's father, their husband, family members) refused to engage in conversation with them. As a result, women said things like: "I feel like I have no one to speak to about it since he doesn't think about it the way I do" (9-8-15), and "I try to talk about it with my family and the baby's dad but they all tell me it's in the past" (10–28-17).

Oftentimes, certain dates (such as their child's due date) or friends with other babies who are of similar age to their "would-have-been child" led to triggering events where women desired to express their feelings with others, but felt like they couldn't talk openly. For instance, one woman said: "But I haven't really been able to share the true regret and near constant jealously of my loved ones engagements or pregnancies" (11–21-16). Another woman stated: "I knew I had to have an abortion, but these feelings I have right now I never imagined I'd have. I don't want to go out, I don't want to tell anyone, all I feel like doing is crying" (7-8-18). Thus, the isolation and silence leading up to her own medication abortion continued to pervade after the abortion, creating additional communication challenges with freely expressing her emotions with family and friends.

Silence was often described as being frustrating and challenging. In fact, 59 women (60%) reported feelings of isolation and alienation. As a result, some women personally attacked themselves. For example, one woman said: "I feel like I'm living a lie I get up get ready for work get my family up like normal the days go on like normal but I'm not normal I killed my baby I'm a monster!!" (3–14-17). Similarly, a different woman wrote: "As a mom I feel like a monster and I have to act like nothing happened" (4–18-17). These demeaning language choices (e.g., monster, killer) are present in the distal-already-spoken societal discourses about abortion. Women's awareness of these larger discourses led some women to write about their intentional use of selective language choices when talking about their abortion with others. One woman shared: "I tried to find an OBGYN that could see me ASAP. I went in and told them I had a miscarriage because I was ashamed of the truth of what I did" (3–21-18). Finally, some women reported struggling in silence by saying things like: "I am in desperate need of assistance and I am too embarrassed to attend an in person support group" (11–21-16), and "And when I got home, I had to hold it all in. I was so ashamed of my choice. I couldn't let anyone know" (2–11-11). Even though these women were able to anonymously write about their abortion on this website, they felt muted by their loved ones because of the centripetal discourses of shame and embarrassment associated with abortion.

Discussion

A national study that assessed women's support for and interest in alternative models of abortion provision found that about half of U.S. women are supportive of and nearly one-third are interested in medication abortion (Biggs et al., 2019). The growing interest and practice in this type of abortion provision warrant scholars to understand women's experiences. Our study is the first in the U.S. to conduct a case analysis of women's online blogging narratives about having had a medication abortion. We focused on understanding the discursive dynamics and contradictions that influenced and shaped women's talk about their own experiences. Our analysis rendered four sites of dialectical tension: *only choice* vs. *other alternatives, unprepared* vs. *knowledgeable, relief* vs. *regret*, and *silence* vs. *openness*. Each site of struggle characterized a different stage of women's medication abortion narrative: the decision, the medication abortion process, after-abortion identity, and the general stigmatizing silence associated with abortion.

As other scholars have noted (Kimport & Doty, 2019), we found that women relied upon language choices that aligned with the existing ideological frameworks from both the Right to Life and Right to Choice movements. For instance, some women used the words "fetal tissue," while other women used the word "baby" when referencing their pregnancy. Women also explicitly mentioned distal already-spoken messages from both movements about how they were told "it's just a pill" or "I've killed my baby." Such language choices are not idle linguistic distinctions, but rather indicate a woman's awareness of the different semantics and terminology surrounding the larger cultural narratives about abortion. This awareness was particularly evident when women discussed the overarching silence stigmatizing one's abilities to openly talk with family and friends about their medication abortion experience. Thus, women's talk about their own personal experiences, their justification for having an abortion, and their own sense-making after the medication abortion were shaped by the available heuristics and frames from larger cultural discourses and political movements (Kimport & Doty, 2019).

Cultural narratives of abortion are powerful and construct meaning and truth (Ludlow, 2008). While a woman's personal story about her medication abortion is individual and now occurs in a more private setting (e.g., at home), this experience remains social and political, defined, and reified by larger cultural narratives and semantics (Beynon-Jones, 2017; Cockrill & Nack, 2013). The sexual liberalism script that reflects positive attitudes toward nontraditional sexual behaviors influences individual's attitudes about abortion (Tokunaga et al., 2015), as well as their own narratives about medication abortion. We found evidence of these larger discourses within women's talk about their own medication abortion, and in particular, their rationale for their decision, their description of the medication abortion process, their reflections on their identity after the abortion, and the overall stigmatizing silence resulting in a muted voice and the public illegitimacy of their own narrative. For instance, many of the justifiable reasons recounted by women in this case study for having an abortion align with the centripetal discourses of the Right to Choice movement regarding bodily rights and a woman's freedom of choice. Among women having abortions in the U.S., finances and lack of readiness are the most commonly cited reasons for choosing abortion (Finer et al., 2005).

The presence of larger cultural narratives can result in dialectical tensions as one seeks to construct her own abortion narrative and considers disclosing that narrative to others. In

particular, many women described experiencing both relief and regret after their abortion. Historically, these two emotions have been juxtaposed and positioned as binary emotions that are socially and politically aligned (Ehrlich & Doan, 2019). The Right to Choice movement discourse aligns with the notion that abortion proffers emotional relief, whereas the Right to Life movement discourse positions itself with abortion resulting in regret. This polarized alignment and framing results in both movements speaking different languages and never fully listening nor engaging with the other (Wiederhold, 2014). One proposed origin of this framing dates back to the legal reasoning of the 2007 U.S. Supreme Court case *Gonzales v. Carhart*, where the federal partial-birth abortion ban was upheld. However, our analysis of women's narratives post-medication abortion exposes the complex duality of these two emotions often being experienced in tandem, as opposed to being simplistic binaries. The either-or, unidimensional script from both the Right to Choice and Right to Life movements – abortion provides either relief or results in regret – fueled a sense of tension for many of the women as they processed their identity after the abortion and considered openly disclosing those private experiences with others. Thus, these women's narratives illustrate that one's individual experiences with having had a medication abortion may result in a both/and: initial relief coupled with later regret. A reliance upon political movement discourses to construct one's own narrative may continue to marginalize or invalidate one's own private medication abortion experience when the larger scripts remain politically charged and polarized (LaRoche & Foster, 2018).

The stigma and risk that characterize the topic of abortion are influenced and shaped by the larger centrifugal discourses from both the Right to Choice and Right to Life movements (Beynon-Jones, 2017; Cockrill & Nack, 2013). For example, Cockrill and Nack (2013) found that women seeking an abortion often attempt to manage the stigma of abortion through non-disclosure, stating their reasons for having an abortion as "exceptional" and necessary, or condemning the Right to Life perspectives about abortion. In a different study on Southside Chicago African-American adolescent females, the majority of sexually active teens never talked with their parents about the topic of abortion, and almost 20% expressed fears of harm or eviction if their parent were to learn of an abortion in their past (Sisco et al., 2014). In our case study, we found that women also experienced stigma, silence, and fear that led them to remain private and/or secretive with certain individuals throughout their medication abortion experience. Silence before or during the medication abortion process resulted in women experiencing additional challenges later on with talking openly about one's experiences. Altogether, these findings align with communication scholars who have found that when private health information disclosures are deemed as being threatening or stigmatizing, one's private health information remains concealed (Baxter & Akkoor, 2011; Ebersole & Hernandez, 2016). This is important because secrecy of one's abortion is associated with poorer coping (Major & Gramzow, 1999; Major et al., 1997), and may result in further isolation and lack of social support from others (Cockrill & Biggs, 2017).

Recent movements such as Shout Your Abortion and #YouKnowMe have tried to dispel the stigma and silence surrounding abortion. However, these movements remain politically aligned and purport the "American Dream" abortion narrative: I was able to go to college/graduate/get a good job due to my abortion. These more recent public narratives frame abortion as a restitution or quest experience (Frank, 1995), where women are portrayed as being able to return to normalcy and good health, or regard their abortion story as one part of their personal journey that they were able to overcome. While such discourses were evident in some women's blogs and have been shown to reduce abortion stigma when openly disclosed (Cockrill & Biggs, 2017), many women's narratives within this case study characterized chaos narratives (Frank, 1995) where the abortion experience interrupted their daily lives and left them feeling out of control. Most notably, over 50% of the sample reported that the father to their child or other family members used negating language as a means to justify a woman's need for an abortion, albeit her own desires to keep her baby. In addition, 75 women (77%) regretted their decision, and 37 women (38%) reported struggling with mental illness and suicidal thoughts after the abortion. While previous scholarship has also found evidence of some women experiencing negative outcomes after an abortion due to a lack of decision-making power and limited social support (Kimport et al., 2011), as well as possible significant relationships between abortion and mental health problems (see Fergusson et al., 2013; Reardon, 2018), these centrifugal discourses remain muted and marginalized in the U.S. abortion debate.

Limitations and directions for future research

As with all scholarship there are limitations. Most notably, there is a lack of generalizability due to the limited scope: we only analyzed women's medication abortion narratives anonymously posted to one website. However, it is important to note that the purpose of this project was to make analytic generalizations based on gathering an in-depth descriptive understanding of these women's medication abortion narratives. Second, all qualitative case studies are limited by the sensitivity and integrity of the investigators. We attempted to surmount this obstacle by having three qualitatively trained female researchers who completed independent coding and collectively participated in the contrapuntal analysis process. Third, case study research is criticized for not having a clear set of systematic procedures (Yin, 2014). To address this concern, we sought to clarify and provide transparency with the methodological techniques used. Fourth, the anonymity of women's blog submissions to the website did not allow us to gather and report the social demographics of the women who anonymously shared their abortion narratives, which again hinders the generalizability of our findings. Finally, the population of women who write an anonymous post about their abortion experience may be different from those who do not.

All of these limitations provide avenues for future research. Most importantly, this single case study demonstrates the need for a broader, pluralistic, mixed-method research strategy that

assesses women's medication abortion narratives, particularly given its increased popularity amongst women seeking this type of abortion provision. Such research could interview women who have had a medication abortion, as well as use surveys to assess different variables such as demographic factors, health literacy, and privacy management strategies employed when talking about one's medication abortion.

Conclusion

n sum, our findings show that the medication abortion experience is rife with tension and contradiction. This complexity and duality are not evident in much of the larger cultural discourses and political debates about abortion. Many women in this case study noted that their decision to have a medication abortion was not a flippant decision or an easy choice where women remained unscathed. Women's narratives about their medication abortion experience were complex, and no singular narrative fully encapsulated or defined what women experienced during and after their medication abortion. Therefore, it is critical to transcend the silence in order to expose both sides of the debate and understand how these larger discourses influenced women's personal language choices when constructing their own abortion narrative and anonymously sharing it with others online. The tensions and dialectical struggles experienced after having a medication abortion and attempting to share it with others remain silent from public discourse and debate (Hallgarten, 2018). Presently, this silence positions one's abortion story as an either-or, binary experience that is politically aligned with one movement or another. The larger discourses prevalent within both the Right to Life and Right to Choice movements impact the liminality of women who are contemplating a medication abortion and affect their own narrative reconstruction and sense-making after their private medication abortion.

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Exhibit 21

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 312, 314, and 601

[Docket No. 97N–0165]

RIN 0910–AB20

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing new regulations requiring pediatric studies of certain new and marketed drug and biological products. Most drugs and biologics have not been adequately tested in the pediatric subpopulation. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. This rule will partially address the lack of pediatric use information by requiring that manufacturers of certain products provide sufficient data and information to support directions for pediatric use for the claimed indications.

DATES: *Effective date.* The regulation is effective April 1, 1999.

Compliance dates. Manufacturers must submit any required assessments of pediatric safety and effectiveness 20 months after the effective date of the rule, unless the assessments are waived or deferred by FDA.

FOR FURTHER INFORMATION CONTACT: Khyati N. Roberts, Center for Drug Evaluation and Research (HFD–103), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–6779, or Karen D. Weiss, Center for Biologics Evaluation and Research (HFM–570), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–5093.

SUPPLEMENTARY INFORMATION:

I. Introduction

In the **Federal Register** of August 15, 1997 (62 FR 43900) (hereinafter referred to as the proposal), FDA proposed to require that manufacturers of certain new and marketed drugs and biologics conduct studies to provide adequate labeling for the use of these products in children. As described in the proposal, children are subject to many of the same diseases as adults, and are, by necessity, often treated with the same drugs and biological products as adults. However, many drugs and biological products marketed in the United States that are or could be used in children are inadequately labeled for use in pediatric patients or for use in specific pediatric subgroups (Refs. 1 and 2). Indeed, many of the drugs and biological products that are widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established (Refs. 2 and 3). Safety and effectiveness information for some pediatric age groups is particularly difficult to find. For example, there is almost no information on use in patients under 2 years of age for most drug classes (Ref. 1).

As described in more detail in the proposal, the absence of pediatric labeling information poses significant risks for children. Inadequate dosing information exposes pediatric patients to the risk of adverse reactions that could be avoided with an appropriate pediatric dose. The lack of pediatric safety information in product labeling exposes pediatric patients to the risk of age-specific adverse reactions unexpected from adult experience. The proposal cited reports of injuries and deaths in children resulting from use of drugs that had not been adequately tested in the pediatric population. The absence of pediatric testing and labeling may also expose pediatric patients to ineffective treatment through underdosing, or may deny pediatric patients therapeutic advances because physicians choose to prescribe existing, less effective medications in the face of insufficient pediatric information about a new medication. Failure to develop a pediatric formulation of a drug or biological product, where younger pediatric populations cannot take the adult formulation, may also deny pediatric patients access to important new therapies, or may require pediatric patients to take the drug in extemporaneous formulations that may be poorly or inconsistently bioavailable.

The proposed rule described previous steps taken by FDA in recent years to address the problem of inadequate pediatric testing and inadequate pediatric use information in drug and biological product labeling. FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research have implemented a ''Pediatric Plan'' designed to focus attention on, and encourage voluntary development of, pediatric data both during the drug development process and after marketing. In addition, in the **Federal Register** of December 13, 1994 (59 FR 64240) (hereinafter referred to as the 1994 rule), FDA issued a regulation requiring manufacturers of marketed drugs to survey existing data and determine whether those data were sufficient to support additional pediatric use information in the drug's labeling. Under the 1994 rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the labeling change.

Although the preamble to the 1994 rule recognizes FDA's authority to require drug and biological product manufacturers to conduct pediatric studies on a case-by-case basis, the rule does not impose a general requirement that manufacturers carry out studies when existing information is not sufficient to support pediatric use information. Instead, if there is insufficient information to support a pediatric indication or pediatric use statement, the rule requires the manufacturer to include in the product's labeling the statement: ''Safety and effectiveness in pediatric patients have not been established.''

The response to the 1994 rule has not substantially addressed the lack of adequate pediatric use information for marketed drugs and biological products. Pediatric labeling supplements were submitted for approximately 430 drugs and biologics, a small fraction of the thousands of prescription drug and biological products on the market. Of the supplements submitted, approximately 75 percent did not significantly improve pediatric use information. Over half of the total supplements submitted simply requested the addition of the statement ''Safety and effectiveness in pediatric patients have not been established.'' Others requested minor wording changes or submitted unorganized, unanalyzed collections of possibly relevant data. Approximately 15 percent (approximately 65) of the supplements provided adequate pediatric information for all relevant pediatric age groups, and another 8 percent (approximately 35) provided adequate pediatric information for some but not all relevant age groups.

The absence of adequate pediatric use information remains a problem for new drugs and biologics as well as for marketed products. The proposal presented data from 1988 through the 1990's showing that the percentage of new products entering the marketplace with adequate pediatric safety and effectiveness information has not increased in the last decade.

For example, FDA compared the number of new molecular entities (NME's) approved in 1991 and 1996

with potential usefulness in pediatric patients and looked at the adequacy of pediatric labeling for those drugs. Fifty-six percent (9/17) of the NME's approved in 1991 with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. In 1996, only 37 percent (15/40) of the NME's with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. For both 1991 and 1996, those drugs counted as having pediatric labeling may not have been studied in all age groups in which the drug was potentially useful. The manufacturers of an additional 7 of the 1991 drugs and 17 of the 1996 drugs promised to conduct pediatric studies after approval. Since publication of the proposal, figures for 1997 NME's have become available. In 1997, 39 NME's were approved. Twenty-seven had potential usefulness in pediatric patients, and 33 percent of these (9/27) had some pediatric labeling at the time of approval. Postapproval studies were requested or promised for an additional six. It is uncertain how many of the commitments made for postapproval studies of the 1996 and 1997 drugs will result in pediatric labeling. Of the seven NME's approved in 1991 for which sponsors made commitments to conduct postapproval pediatric studies, pediatric labeling has been added to only one. This figure reflects both studies that resulted in positive labeling, i.e., safety and dosing information, and studies that resulted in warnings against pediatric use. It does not reflect studies that failed to provide any useful information about pediatric use or studies that were completed but the sponsor failed to seek a change in its pediatric use labeling.

These data indicate that voluntary efforts have, thus far, not substantially increased the number of products entering the marketplace with adequate pediatric labeling. FDA has therefore concluded that additional steps are necessary to ensure the safety and effectiveness of drug and biological products for pediatric patients. This rule requires the manufacturers of new and marketed drugs and biological products to evaluate the safety and effectiveness of the products in pediatric patients, if the product is likely to be used in a substantial number of pediatric patients or would provide a meaningful therapeutic benefit to pediatric patients over existing treatments.

In addition to issuing this rule, FDA has initiated other actions that it hopes will encourage the development of adequate pediatric use information. FDA has issued a draft guidance document entitled ''General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products'' (November 30, 1998). FDA also plans to develop additional guidance on how to develop effectiveness, safety, and dosing information to support pediatric labeling. The agency also supported a provision in the reauthorized Prescription Drug User Fee Act (PDUFA) eliminating user fees for pediatric supplements to encourage the submission of these supplements.

Finally, FDA has issued a guidance document entitled ''Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,'' describing the kinds of studies that can support effectiveness in supplemental or original applications. In that document, FDA provides guidance to manufacturers on the circumstances in which FDA may approve an initial or supplemental claim in which substantiation of the results of an adequate and well-controlled trial is provided by information other than a second adequate and well-controlled trial precisely replicating the first trial, or the circumstances in which studies without the extensive documentation ordinarily required could be utilized. This guidance will often be relevant to the data needed to support claims in a pediatric population.

Since the issuance of the proposal, Congress has enacted a bill that has an impact on pediatric studies of certain drugs. The Food and Drug Administration Modernization Act of 1997 (FDAMA) (Pub. L. 105–115) contains provisions that establish economic incentives for conducting pediatric studies on drugs for which exclusivity or patent protection is available under the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98–417) and the Orphan Drug Act (Pub. L. 97–414). These provisions extend by 6 months any existing exclusivity or patent protection on a drug for which FDA has requested pediatric studies and the manufacturer has conducted such studies in accordance with the requirements of FDAMA. FDAMA also specifically recognizes FDA's intention to require pediatric studies by regulation and extends by 6 months any existing exclusivity or patent protection on a drug whose manufacturer submits pediatric studies in compliance with this rule, if the studies meet the completeness, timeliness, and other requirements of section 505A. Under FDAMA, a manufacturer who submits pediatric studies required under this rule may receive a 6-month extension of exclusivity or patent protection granted to the manufacturer for that drug.

Although FDA expects the exclusivity offered by FDAMA to provide a substantial incentive for sponsors to conduct some pediatric studies, the agency nonetheless believes that this final rule is necessary to significantly increase the number of drug and biological products that have adequate labeling. Certain limitations on the scope and effect of the exclusivity offered by FDAMA are likely to leave significant gaps in pediatric labeling. For example, because FDAMA exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act, it provides no incentive to conduct studies on certain categories of products, including most antibiotics, biologics, and off-patent products.

In addition, the voluntary nature of the incentive provided by FDAMA is likely to leave many drugs, age groups, and indications unstudied. Given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies preferentially on those drugs for which the incentives are most valuable, i.e., on drugs with the largest sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. For similar reasons, manufacturers are less likely to seek FDAMA exclusivity by conducting studies on drugs that require studies in neonates, infants, or young children. The youngest pediatric populations are more difficult to study and may require pediatric formulations, making pediatric studies of these groups more expensive, thereby reducing the value of the incentives provided by FDAMA. Thus, where there is a great medical need for data on drugs with relatively small markets or for studies on neonates, infants, or young children, it may be necessary to require the collection of such data, rather than rely on incentives.

Finally, manufacturers are eligible for FDAMA exclusivity when they submit a study to FDA that is consistent with FDA's written request for such a study. The study results are not required to provide useful information on pediatric use (e.g., the results may be inconclusive), and the sponsor is not required to obtain approval of a supplement adding the information gained in the study to the drug's label. Thus, FDAMA provides no guarantee that the studies conducted under the statute will result in improved pediatric labeling.

For these reasons, FDA believes that there remains an important need for this rule. FDA has concluded, however, that with respect to already marketed drugs eligible for exclusivity under FDAMA, the publication of the list required by section 505A(b) and the availability of pediatric exclusivity may diminish the need to exercise the agency's authority to require studies. Under the rule, FDA has discretion whether to require studies of marketed drugs (see § 201.23 (21 CFR 201.23)). FDA believes that, in exercising its discretion under § 201.23, it is appropriate to determine whether manufacturers will undertake the needed studies voluntarily. FDA will therefore allow an adequate opportunity for manufacturers voluntarily to submit studies for drugs listed by FDA as having a high priority. If, following such an opportunity, there remain marketed drugs for which studies are needed and the compelling circumstances described in the rule are met, the agency will consider exercising its authority to require studies. With respect to marketed drugs and biologics that are not eligible for exclusivity under FDAMA, FDA intends to exercise its authority to require studies as of the effective date of the rule in the circumstances described in the regulation. FDA emphasizes that the appearance of a drug or biologic on the list published under section 505A(b) carries no implication that FDA will require studies on that drug or biologic under this rule. FDA intends to reserve its authority to require studies of marketed drugs and biologics to situations in which the compelling circumstances described in the regulation are present.

FDA intends to issue further regulations and guidance implementing the pediatric exclusivity provisions of FDAMA, which will, among other things, provide guidance on the interaction of this rule and FDAMA exclusivity.

II. Highlights of the Final Rule

This final rule is designed to ensure that new drugs and biological products contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The final rule establishes a presumption that all new drugs and biologics will be studied in pediatric patients, but allows manufacturers to obtain a waiver of the requirement if the product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The rule also authorizes FDA to require pediatric studies of those marketed drugs and biological products that: (1) Are used in a substantial number of pediatric patients for the claimed indications, and where the absence of adequate labeling could pose significant risks; or (2) would provide a meaningful therapeutic benefit over existing treatments for pediatric patients, and the absence of adequate labeling could pose significant risks to pediatric patients.

A. Scope of Rule

The proposed rule would have required an application for a drug classified as a ''new chemical entity'' or a new (never-before-approved) biological product to contain safety and effectiveness information on relevant pediatric age groups for the claimed indications. Based upon comments observing that changes in already marketed chemical entities, such as new indications or dosage forms, can have as much or more therapeutic significance for pediatric patients than the original product, the final rule expands the scope of the rule to include new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration for which an applicant seeks approval. The final rule does not, however, require the submission of pediatric data for a drug for an indication or indications for which orphan designation has been granted under section 526 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360bb).

B. Types of Studies Needed

As described in the 1994 final rule, gathering adequate data to establish pediatric safety and effectiveness may not require controlled clinical trials in pediatric patients. Where the course of the disease and the product's effects are similar in adults and pediatric patients, FDA may conclude that pediatric safety and effectiveness can be supported by effectiveness data in adults together with additional data, such as dosing, pharmacokinetic, and safety data in pediatric patients. The rule also does not necessarily require separate studies in pediatric patients. In appropriate cases, adequate data may be gathered by including pediatric patients as well as adults in the original studies conducted on the product.

The specific pediatric information needed in each case will depend on the nature of the application, what is already known about the product in pediatric populations, and the underlying disease or condition being treated. The final rule requires an assessment of safety and effectiveness in pediatric patients only for the indications claimed by the manufacturer. It does not require a manufacturer to study its product for unapproved or unclaimed indications, even if the product is widely used in pediatric patients for those indications. In the proposed rule, the pediatric study requirement for drugs was contained in § 314.50(g) (21 CFR 314.50(g)). In the final rule, the requirement is located in new § 314.55, because § 314.50 does not contain other specific study requirements. The location of the requirement for biological products (§ 601.27 (21 CFR 601.27)) remains unchanged in the final rule.

C. Age Groups

The final rule requires pediatric studies in each age group in which the drug or biological product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients for the indications claimed by the manufacturer. The relevant age groups will, however, be defined flexibly, depending on the pharmacology of the drug or biological product, rather than following the fixed age categories defined in the 1994 rule and identified in the preamble to the proposed rule. For drugs and biological products that offer a meaningful therapeutic benefit, the rule requires manufacturers to develop pediatric formulations, if needed, for those age groups in which studies are required. Manufacturers may, however, avoid this requirement if they demonstrate that reasonable attempts to develop a pediatric formulation have failed.

D. Not-Yet-Approved Products

1. Deferral of Studies Until After Approval

The final rule permits the submission of pediatric information to be deferred until after approval if there is an adequate justification for deferral, e.g., because pediatric studies should not begin until some safety and/or effectiveness information on adults has been collected, or awaiting the completion of pediatric studies would delay the availability of a product to adults. When trials should begin in particular cases, and whether deferral will be necessary, will depend upon the seriousness of the disease for which the drug or biological product is indicated, the need for the product, the amount of safety and effectiveness data available, and what types of pediatric studies are needed.

In general, FDA expects that studies of drugs or biological products for diseases that are life threatening in pediatric patients and that lack adequate

therapy could begin earlier than studies of drugs that are less urgently needed, ordinarily as early as the availability of preliminary safety data in adults (frequently referred to as phase 1 data), even if data from well-controlled studies are not yet available. For less critical drugs and biologics, pediatric studies could ordinarily begin when additional safety and/or effectiveness data from the initial well-controlled trials in adults (frequently referred to as phase 2 data) became available. Of course, studies of products for exclusively pediatric diseases ordinarily need not await the development of adult data. The timing of individual pediatric studies will, however, necessarily depend on the specific information available about the product in question. For example, a study of a noncritical drug in adolescents might begin after the initial safety studies in adults, if all the parties involved agreed that initiation was appropriate in light of the results of the adult and animal safety studies.

In other cases, studies should not begin in pediatric patients until significantly more adult data are collected. For example, FDA does not believe that early study or use in pediatric patients is appropriate for some so-called ''me-too'' drugs that are expected to be widely used but are members of a drug class that already contains an adequate number of approved products with pediatric labeling. Such drugs may not have been shown to provide any benefit over other products in the same class, and may introduce new risks that are not apparent until the drug has been in wide use after marketing. Studies of such drugs will therefore usually be deferred until the safety profiles of the drugs are well established through marketing experience. To encourage use of properly labeled drugs in pediatric patients, FDA may require the pediatric use section of the approved labeling of such a me-too drug to contain a statement recommending preferential use of other drugs that are adequately labeled for pediatric use.

2. Waiver of the Study Requirement

The pediatric study requirement applies to all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration, unless FDA waives the requirement. Under criteria established in the rule, FDA may waive the study requirement for some or all pediatric age groups. The burden is on the sponsor to justify a waiver. A waiver will be granted if the waiver request demonstrates that the product meets both of the following conditions: (1) The product does not represent a meaningful therapeutic benefit for pediatric patients over existing treatments, and (2) the product is not likely to be used in a substantial number of pediatric patients. There was some confusion in the comments on the proposed rule over these waiver criteria. FDA emphasizes that the study requirement applies to a product that offers a meaningful therapeutic benefit even if it is not used in a substantial number of pediatric patients, and vice versa.

In response to comments, FDA has refined its definitions of ''meaningful therapeutic benefit'' and ''substantial number of pediatric patients.'' To define meaningful therapeutic benefit for both drugs and biologics covered by this rule, FDA has relied, in part, on CDER's current administrative definition of a ''Priority'' drug, applied to pediatric populations. The administrative definition of ''Priority'' products for biologics relies on different criteria (Ref. 2). Use of CDER's Priority drug definition to help define ''meaningful therapeutic benefit'' is not intended to affect the administrative definition of a Priority biologic. The Priority classification for drugs is determined based on CDER's estimate, at the time of NDA submission, of a drug's therapeutic, preventive, or diagnostic value. A Priority drug is defined as one that, if approved, would be a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products approved for that use. In establishing meaningful therapeutic benefit for pediatric use, the comparison will be to other products adequately labeled for use in the relevant pediatric population. If there are no such products, a new product would usually be considered to have a meaningful therapeutic benefit. Improvement over existing products labeled for pediatric use can be demonstrated by, for example: (1) Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation. Evidence of improvement over existing therapies need not in all cases come from head-to-head trials.

To help ensure that pediatric patients have a sufficient range of treatments available, a product will also be considered to provide a meaningful therapeutic benefit if it is in a class of products or for an indication for which there is a need for additional therapeutic options, notwithstanding the fact that it might not be a priority drug. In contrast to the range of therapies for a given indication often available to adults, there are relatively few instances in which therapeutic alternatives are studied and labeled for pediatric patients. For some diseases, however, it is therapeutically important to have a range of available treatment options, e.g., because there are frequent treatment failures. The Priority definition would cover the first product labeled for pediatric use, but might not cover the second or third product for a given indication or in a given class, if the subsequent product did not offer an advantage over existing therapies. The specific number of products needed will depend upon such factors as the severity of the disease being treated and the adverse reaction profile of existing therapies. FDA will seek further guidance on applying this criterion from a panel of pediatric experts.

Thus, new products will meet the definition of a meaningful therapeutic benefit if: (1) They provide a significant improvement over existing adequately labeled therapies; or (2) if they are indicated for diseases or conditions, or are in product classes, in which there are currently few products labeled for pediatric use and more therapeutic options are needed. FDA expects that over time, as the number of products adequately labeled for pediatric patients grows, the number of new products meeting the second criterion will diminish. FDA emphasizes that the addition of the second criterion for defining meaningful therapeutic benefit under this final rule is not intended to alter the definition of a Priority drug, and that products meeting the second criterion will not thereby be eligible for Priority status. FDA also notes that the rule's definition of meaningful therapeutic benefit is intended to apply only in the pediatric study context.

FDA has also revised the proposed definition of ''a substantial number of pediatric patients.'' Many comments argued that the number chosen by FDA in the proposal (100,000 prescriptions per year or 100,000 pediatric patients with the disease) was arbitrary. Physician mention data from the IMS National Disease and Therapeutic Index (Ref. 38), which tracks the use of drugs by measuring the number of times physicians mention drugs during outpatient visits, shows that pediatric use of drugs is generally grouped in two distinct ranges. Physician mentions of drugs for pediatric use generally fall either below 15,000 per year or above 100,000 per year. Few drugs fall within the two ranges. Thus, selecting a cut-off

for ''substantial number of pediatric patients'' in the middle of the two ranges will provide a reasonable discrimination between products that are widely used and those that are less commonly used, and the specific number chosen will not arbitrarily include or exclude a significant number of drugs. FDA has therefore chosen 50,000 as the cut-off for a substantial number of pediatric patients. Because the number of pediatric patients with the disease or condition is easier to determine than the number of prescriptions per year, a substantial number of pediatric patients will be defined as 50,000 pediatric patients with the disease or condition for which the drug or biological product is indicated. Although physician mentions per year does not correspond exactly to the number of patients with the disease or condition, they provide a rough approximation and the IMS data show that the number of products included or excluded is relatively insensitive to changes in the cut-off chosen. As proposed, a partial waiver for a particular pediatric age group would be available under this method if 15,000 patients in that age group were affected by the disease or condition. This definition of ''a substantial number of pediatric patients'' has not been codified, however, and FDA may modify it, after consulting with a panel of pediatric experts. Any modification will be issued in a guidance document with an opportunity for comment.

FDA will also waive the pediatric study requirement where: (1) The applicant shows that the required studies on the product are impossible or highly impractical because, for example, the population is too small or geographically dispersed; (2) the product is likely to be unsafe or ineffective in pediatric patients; or (3) reasonable efforts to develop a pediatric formulation (if one is needed) have failed.

To reduce the burden on manufacturers in applying for waivers and deferrals, FDA intends to issue a guidance document providing a format for a request for waiver or deferral.

E. Marketed Products

The final rule is also intended to improve pediatric use information for already marketed drugs and biological products. The rule codifies FDA's authority, discussed in the 1994 rule, to require, in the compelling circumstances described in the regulation, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric-use labeling for the claimed indications. The criteria for requiring studies of marketed products have been revised slightly in response to comments.

F. Early Discussions and Pre- and Postmarket Reports

The final rule contains provisions designed to encourage discussions of the need for pediatric studies early in the drug development process, as well as pre- and postmarketing reporting requirements designed to assist FDA in determining whether pediatric studies are needed for particular products and whether required studies are being carried out with due diligence.

G. Pediatric Committee

Many comments on the proposed rule urged FDA to form a committee of outside experts to assist in various aspects of the implementation of the rule. FDA has concluded that such a panel could provide useful advice and experience. FDA will convene a panel of pediatric experts, including at least one industry representative, and seek its advice on a range of issues related to implementation of the rule, including: (1) The agency's implementation of all aspects of the final rule, including its waiver and deferral decisions; (2) which marketed drugs and biological products meet the criteria for requiring studies; (3) when additional therapeutic options are needed for a given disease or condition occurring in pediatric patients; (4) ethical issues raised by clinical trials in pediatric patients; (5) the design of trials and analysis of data for specific products or classes of products; and (6) issues related to the progress of individual studies.

H. Remedies for Violation of the Rule

For violations of this rule, FDA would ordinarily expect to file an enforcement action for an injunction, asking a Federal court to find that the product is misbranded under section 502 of the act (21 U.S.C. 352) or is an unapproved new drug under section 505(a) of the act (21 U.S.C. 355) or an unlicensed biologic under section 351 of the Public Health Service Act, and to require the company to submit an assessment of pediatric safety and effectiveness for the product. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines. FDA does not intend, except possibly in rare circumstances, to disapprove or withdraw approval of a drug or biological product whose manufacturer violates requirements imposed under this rule.

III. Comments on the Proposed Rule

FDA received 54 written comments on the proposed rule from pediatricians, professional societies, parents, members of the pharmaceutical industry, organizations devoted to specific diseases, and patient groups. A significant majority of the comments, primarily those from pediatricians, professional societies, parents, organizations devoted to specific diseases, and patient groups, supported regulations requiring that drugs and biologics be studied in children. Many of these comments described the problems faced by the pediatric community and parents resulting from inadequate pediatric labeling and the absence of pediatric formulations, and argued that a pediatric study requirement was long overdue. Some comments, primarily those from the pharmaceutical industry, opposed a pediatric study requirement, arguing that existing voluntary measures and incentives were sufficient to ensure adequate pediatric labeling. Finally, a number of comments addressed FDA's legal authority to require pediatric testing of drugs and biologics.

FDA also held a day-long public hearing on October 27, 1997, in Washington, DC, at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties were given an opportunity to discuss the issues raised by the proposed rule. There were three panels, each of which comprised representatives from industry, the pediatric community, organizations devoted to specific diseases, patient groups, and a bioethicist. The panels considered the following three issues: (1) When pediatric studies are needed, (2) what types of studies are needed, and (3) special challenges in testing pediatric patients. Those who spoke were nearly unanimous in their support for some kind of regulation requiring pediatric studies of some drugs and biologics. There was, however, a wide range of views on which drugs and biologics should be the subject of required studies and on how the requirement should be implemented.

Many written and oral comments raised specific issues for consideration by the agency. These comments are addressed below.

A. Purpose of Rule

1. FDA received many comments arguing that this rule is needed to ensure adequate medical care for children. Many comments from pediatricians stated that they regularly must prescribe to young children drugs

that are not labeled for children under 6 or even 12, and for which pediatric dosage forms do not exist. One comment stated that, without adequate testing and labeling, physicians must estimate appropriate pediatric doses, and that even at ''appropriate'' doses, it is not known whether use in children is as safe as use in adults. One comment argued that the absence of pediatric labeling puts children at greater risk for adverse drug reactions (ADR's) and therapeutic failures than adults. According to another comment, most common and severe ADR's in pediatric patients would be eliminated by adequate testing, and that perhaps 2 percent of all pediatric hospitalizations are due to ADR's. One comment concluded that the failure to conduct pediatric studies results in a different standard of care for children and adults in this country.

A comment from a pharmaceutical trade association argued, however, that most of the toxicity problems identified by FDA as caused by inadequate pediatric labeling were from the 1950's and that these ''dated'' examples are not relevant to current practice. As an example, the comment cited chloramphenicol, a drug referred to by FDA in the proposed rule because, when it was used in the 1950's in neonates without adequate testing, it was responsible for many infant deaths (Ref. 4). According to the comment, it is now known that chloramphenicol can be used in neonates if the dose is correct. The comment also stated that practicing physicians have access to adequate dosing information from case reports in the medical literature.

FDA agrees that the absence of adequate pediatric labeling puts pediatric patients at risk for adverse drug reactions and ineffective dosing. FDA believes that the reference to new dosing information that permits use of chloramphenicol in infants illustrates the need for this final rule. Had adequate safety and dosing information been available earlier, many babies' lives could have been saved. Instead, adequately supported dosing information was not available until after the drug had been used in a large number of babies, with tragic consequences. FDA also disagrees with the comment that the remaining reports cited in the proposal of unexpected toxicity in pediatric patients from inadequately tested drugs are ''dated.'' Contrary to the assertion in the comment, a majority of these reports are from the 1980's and 1990's (Refs. 5 through 14).

FDA also does not believe that case reports scattered through the medical literature are an adequate substitute for organized and complete pediatric labeling information. To the extent that published experience is informative and credible, it should be used to improve labeling. The comments received from pediatricians reflect their view that there is often no adequately supported dosing and safety information for the drugs they use routinely in their patients. Even where case reports are available, they describe a limited number of pediatric patients and cannot provide sufficient information to establish the safety profile of a drug in pediatric patients.

2. Some comments argued that pediatric studies are needed because differences between children and adults can make extrapolation from adult data treacherous. One comment pointed out that research on antiarrhythmics in pediatric patients has revealed many surprises in dosing and side effects. For example, drugs that bind to milk may cause safety or effectiveness problems in pediatric patients not detected in adults.

FDA agrees that pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight milligram/kilogram (mg/kg) or body surface area (mg/m^2). There are potentially significant differences in pharmacokinetics, or unique drug-food interactions, that may alter a drug's blood levels in pediatric patients. Moreover, there can be pharmacodynamic differences between adults and pediatric patients.

3. Several comments argued that voluntary measures have not resulted in a significant increase in pediatric labeling, and that new products continue to enter the market without adequate, or any, pediatric labeling. Pediatricians, professional societies, parents, organizations devoted to specific diseases, and patient groups provided many examples of diseases and drug classes for which pediatric labeling was long-delayed, inadequate, or nonexistent. Acquired immune deficiency syndrome (AIDS) drugs were frequently cited as an example of the industry's failure to obtain adequate pediatric labeling at or near the time of approval. One comment pointed to protease inhibitors, which are theoretically most effective in newborns but have not been tested or approved for use in this group. Even for older children, the comment observed that it has taken over a year after adult approval to obtain pediatric labeling for these life-saving drugs. Another comment stated that the absence of drugs for human immunodeficiency virus (HIV) infection that are appropriately labeled and formulated for pediatric patients causes parents to give children inappropriate doses, sometimes giving up part of their own dose if the child's physician will not prescribe it.

Other comments pointed out that epilepsy is considered a pediatric disease but claimed that many new epilepsy drugs are approved without information for use in pediatric patients. These comments urged that anti-epileptic drugs be added to the list of drug classes with inadequate labeling. A comment from a specialist in pulmonary medicine stated that although asthma is a common disease in pediatric patients, adult formulations are often released first, leaving pediatric patients without effective treatments. Other comments observed that not one of the standard immunosuppressive medications used in pediatric patients has been tested in pediatric patients. One comment contended that poor information about the pharmacokinetics of these drugs in pediatric patients has led to inadequate dosing to achieve effectiveness and possibly unnecessary toxicity.

The American Psychiatric Association commented that significant psychiatric diseases are increasingly diagnosed in pediatric patients, who may be treated with drugs despite the lack of pediatric labeling. According to this comment, most psychoactive medications are underutilized in pediatric patients due to the lack of pediatric labeling and to fear of overdosing. In the case of anti-hyperactivity drugs, however, the comment states that as many children are overtreated as undertreated, especially among pre-school age children. A comment from the National Institute of Mental Health (NIMH) stated that the rule was much needed to provide essential data on the safety and effectiveness of psychiatric medications in pediatric patients. This comment attached seven NIMH reviews of the existing data on psychotropic medications for pediatric patients, identifying many critical knowledge gaps that remain to be addressed by pediatric research.

One comment stated that pediatric nephrologists frequently prescribe drugs to pediatric patients for life-threatening conditions, including antihypertensive medications, diuretics, lipid-lowering agents, and immunosuppressive agents, even for pediatric patients less than 2 years of age, without benefit of formal studies. This comment further stated that drug therapy for chronic conditions like kidney failure is currently based only on experience gained from drug usage in children after approval for the indication in adults, and that

discovering ''inadequate dosing or severe side effects by empiric use of these drugs is not desirable or safe.'' Another comment provided the results of a survey of 4,898 pediatric patients with end-stage renal disease on the medications they receive. Ninety-seven percent received prednisone or prednisolone, 91 percent received cyclosporine, and 84 percent received azathioprine. According to the comment, none of these drugs was studied in pediatric patients and no information on the pharmacokinetics of these drugs in pediatric patients is available.

In contrast, several comments from the pharmaceutical industry argued that voluntary measures, the 1994 rule, and the incentives provided by FDAMA are adequate to assure adequate pediatric labeling and that FDA has not given these steps sufficient time to work. Several comments argued that to obtain pediatric studies, FDA should use encouragement and early discussion with sponsors, together with incentives, rather than imposing new requirements. These comments contended that sponsors should make ''phase 4 commitments'' (commitments to conduct pediatric studies after approval) and FDA should track these commitments. According to one comment, these methods have not been systematically used by FDA. According to another comment, FDA did not describe its present experience in getting manufacturers to conduct pediatric studies. Other comments argued that FDA has not allowed the 1994 rule sufficient time to produce results and that the agency should wait until it has reviewed and acted upon all supplements submitted under that rule before imposing new requirements. One comment contended that if the 1994 rule was successful in producing pediatric labeling for marketed drugs, the new rule should apply only to new drugs. One comment argued that incentives, including exclusivity, waiver of user fees, tax credits, and expedited reviews of pediatric supplements, and liability protection for research physicians, Institutional Review Boards (IRB's), universities, pharmaceutical firms, and parents, are the best means of obtaining pediatric labeling. A few comments argued that excessive litigation will follow imposition of this rule.

Two comments argued that the 53 NME's approved in 1996 demonstrate that pediatric labeling efforts by the industry are adequate, and that new requirements are not needed. Although the figures used in the 2 comments do not agree exactly, these comments stated that 20 or 21 of the 53 have potential for pediatric use. According to these comments, of these, 4 have approved pediatric labeling, 14 have planned or ongoing studies, 1 is switching to over-the-counter (OTC) use, and 1 or 2 have no immediate plans for pediatric labeling activities. One comment contended that, between 1990 and 1997, a 28 percent increase occurred in the number of new drugs in development for pediatric uses, but provided no data to support this claim.

FDA believes that the current state of pediatric labeling for drugs and biologics in the United States, as amply illustrated by comments from the pediatric community, is unsatisfactory. The agency's failure to obtain a significant increase in labeling for either new or marketed drugs or biologics through other measures implemented over the last several years demonstrates the need for a requirement that sponsors conduct pediatric studies of drugs and biologics that represent a meaningful therapeutic benefit to pediatric patients or that will be widely used in pediatric patients. As described in section I of this document, the response to the 1994 rule has not produced a significant improvement in pediatric labeling for marketed drugs. FDA received labeling supplements only for a small fraction of the drugs and biologics on the market. Of those supplements it did receive, over half of the submissions merely sought to add a statement to the product's labeling that ''safety and effectiveness in pediatric patients have not been demonstrated,'' and less than a quarter provided adequate pediatric information for some or all relevant age groups.

The agency's experience in attempting to obtain pediatric labeling for new drugs entering the marketplace through voluntary measures has also been disappointing. As described in the proposal, the percentage of NME's with adequate pediatric labeling has not increased since 1991, when the agency began systematic efforts to obtain better pediatric labeling. Although the number of requests by the agency and commitments by sponsors to conduct phase 4 (postapproval) pediatric studies may have increased, these requests and commitments have so far infrequently resulted in pediatric labeling. Table 1 of this document displays the results of commitments or requests to conduct pediatric studies postapproval between 1991 and 1996. FDA notes that the table does not reflect any labeling supplements under review. There are a total of six pediatric labeling supplements currently under review for NME's approved between 1991 and 1996. These supplements may or may not add significant new labeling information; but, in any case, would not substantially increase the number of successfully conducted postapproval studies.

TABLE 1.—PEDIATRIC LABELING

Status of pediatric labeling	1991	1992	1993	1994	1995	1996	Totals
NME's approved	30	25	25	22	28	53	183
Pediatric studies not needed	14	11	11	7	14	13	70
Label includes some pediatric use information or pediatric studies complete at time of approval	9	4	[1]5	[1]6	5	15	44
Postapproval pediatric studies promised or requested	7	10	[2]10	[2,3]10	[2]10	17	64
Pediatric labeling added after approval	1	0	2	4	2	2	11

[1] In one case, pediatric use information provided for one of two approved indications.
[2] In one case, pediatric data requested for second of two approved indications.
[3] In one case, pediatric data requested for additional age groups.

As Table 1 of this document reflects, FDA's figures disagree with those of the comments for the number of 1996 NME's with potential for pediatric use, the number with some pediatric labeling at the time of approval and the number for which commitments or requests for postapproval studies have been made. The comments did not identify specific drugs, so it is not possible to determine why the two sets of figures conflict. Nevertheless, the historical experience reflected in the table suggests that most of the postapproval pediatric studies for which commitments were made for the

1996 NME's will not result in pediatric labeling. Of the 17 commitments to conduct pediatric studies in 1996, there have thus far been only 2 additions of pediatric labeling. Although some additional studies supporting labeling changes may be submitted in the future, the experience reflected in Table 1 of this document suggests that this will not be a large number. For example, the 27 promised or requested studies for the 1991 through 1993 cohorts have resulted in just 3 additions of pediatric labeling 5 to 7 years after approval. Thus, FDA does not agree that the experience with 1996 NME's demonstrates the adequacy of current efforts to obtain pediatric labeling.

None of the comments claiming that the rule will result in excessive litigation provided any evidence suggesting a relationship between pediatric testing and increased litigation or liability. As shown in the number of NME's with pediatric labeling at the time of approval, a significant minority of drug and biologic manufacturers already conducts pediatric testing. FDA is aware of no evidence that excessive litigation has been associated with this testing.

With respect to the argument that the incentives provided by FDAMA will be sufficient to ensure adequate pediatric labeling, FDA believes that a mixture of incentives and requirements is most likely to result in real improvements in pediatric labeling. FDA is hopeful, e.g., that the FDAMA incentives will make more resources available for pediatric studies. As described earlier, FDA does not believe, however, that incentives alone will result in pediatric studies on some of the drugs and biologics where the need is greatest. The incentives provided by FDAMA are available only for drugs already covered by the exclusivity or patent protection provided by sections 505 and 526 of the act. Thus, the FDAMA incentives are not available for many already marketed drugs, or for many antibiotics or biologics. In addition, limited resources available to conduct pediatric studies and fiduciary obligations to shareholders may cause manufacturers to conduct pediatric studies preferentially on those drugs where the incentives are most valuable, rather than on those drugs or biological products where studies are most needed.

4. Two comments argued that the rule is inconsistent with a 1977 FDA document entitled ''General Considerations for the Clinical Evaluation of Drugs in Infants and Children,'' which recommended, among other things, that ''reasonable evidence of efficacy generally * * * be known before infants and children are exposed to [a drug].''

As described in more detail in section III.D of this document under ''Deferral,'' FDA expects that for drugs and biologics other than those for life-threatening diseases without adequate treatment, clinical trials in pediatric patients will ordinarily begin no earlier than when initial data from well-controlled trials in adults (frequently referred to as phase 2 data) become available to ensure that reasonable preliminary evidence of safety and/or effectiveness is available before pediatric patients are exposed to the drug or biological product. How much evidence of safety or effectiveness is ''reasonable evidence'' that should be available before pediatric trials may begin will be determined on a case-by-case basis. Thus, FDA believes that this rule is substantially consistent with the 1977 document.

FDA notes that the 1977 document was based upon a report prepared for FDA under a contract with the American Academy of Pediatrics (AAP). The AAP is currently developing proposed revisions to this document concerning the types of data needed to support pediatric labeling. The 1977 document, which falls under the general category of guidance documents, does not bind FDA or the public, but represents the agency's current thinking on a particular issue. Alternative approaches may be used if the alternative satisfies the requirements of the applicable statute and regulations (62 FR 8961, February 27, 1997) (Good Guidance Practices document). Until such time as an updated guidance on the clinical evaluation of drugs in infants and children is published, sponsors are encouraged to confer with the agency before initiating pediatric studies.

5. Several comments challenged FDA's use of the 1994 IMS National Disease and Therapeutic Index (NDTI) data on the 10 drugs used most frequently in pediatric patients without adequate labeling, arguing that the data incorrectly imply that physicians have no labeling information, when in fact prescribing information is now, or will be, available for most of the 10 drugs listed.

These comments misunderstand the purpose for which FDA cited the 1994 data. Those data provided a snapshot of the labeling information available to physicians for 10 widely used drugs at a given point in time. Even if additional information had been added to the labels of these drugs in the 4 years since the survey was conducted, there was none available during a year in which the drugs, together, were prescribed to pediatric patients over 5 million times. FDA notes, moreover, that, contrary to the suggestion in the comments, adequate labeling has been added for only 1 of the 10 drugs for the age group described in the proposal.

6. Two comments disputed the estimated number of times their products were prescribed to pediatric patients. One manufacturer argued that the total units sold of Auralgan were less than the listed number of prescriptions. Another manufacturer disputed the estimates of Ritalin usage. This manufacturer also complained that it was not contacted by FDA about use of Ritalin despite the statement in the proposal that FDA had contacted the manufacturers of the top 10 drugs used without adequate labeling in pediatric patients.

Limitations on the data used to estimate number of prescriptions may have resulted in the discrepancy noted by the manufacturers of Auralgan or Ritalin. The number of prescriptions is estimated from data provided by IMS America, Ltd. IMS NDTI surveys a sample of physicians (more than 2,940 physicians representing 27 specialities) to determine the number of times that, during patient contacts, physicians mentioned specific drugs for particular age groups. Physician mentions may not correlate exactly with actual usage. In addition, the NDTI numbers taken from the sample of physicians are extrapolated to the nation as a whole, using a given formula. With respect to the claim that FDA has not contacted the manufacturer of Ritalin, FDA notes that it has scheduled meetings with the manufacturer to discuss use of the drug in children, which have been canceled at the manufacturer's request.

7. One comment challenged FDA's use of quinolones as an example of a class of drug that does not need to be studied in pediatric patients. The comment claimed quinolones do need to be studied in pediatric patients because of their important use in cystic fibrosis patients.

FDA agrees that fluoroquinolones may provide important therapeutic benefits to patients with cystic fibrosis. At present, all approved fluoroquinolones are labeled with the following statement: ''Safety and effectiveness in children and adolescents less than 18 years of age have not been established.'' In addition, the label includes a statement advising that the fluoroquinolones cause arthropathy in juvenile animals. Historically, the agency has recognized a potential therapeutic role for the fluoroquinolones in children with cystic fibrosis and hematology/oncology

disorders. Indeed, FDA recently approved ciprofloxacin labeling containing a discussion of cystic fibrosis experience in the pediatric use subsection. These actions show that the agency recognizes that there may be a need to study fluoroquinolones in some pediatric patients.

8. One comment from a pharmaceutical company argued that serious ethical, legal, medical, and technical difficulties often prevent conducting pediatric studies. The comment cited difficulties in enrolling pediatric patients in sufficient numbers, unwillingness of parents to enroll children, and the absence of pediatric patients with the disease near convenient and qualified study centers. According to the comment, studies have been successfully conducted in pediatric patients in the past where there was a medical need for the drug in pediatric patients, but this rule will require pediatric studies of drugs intended for adults that may or may not be administered to pediatric patients. The comment also contended that the rule will necessitate a massive infusion of resources for industry, FDA, and medical speciality organizations, and that the agency should start with a small list of diseases with similar pathophysiology in adults and children, and a small list of drug classes known to have similar metabolism, and plan a graduated approach.

Contrary to the suggestion in the comment, this rule is designed to require studies only in those settings in which there is a significant medical need or where usage among pediatric patients is likely to be substantial. FDA acknowledges the difficulties encountered in some cases, but agrees that where there is a need for studies these difficulties have been overcome and that pediatric studies have been successfully conducted in many situations. FDA believes that the number of such studies already conducted each year, for example of antibiotics, vaccines, and roughly 25 percent of NME's, support the view that such studies are not medically, ethically, or technically impossible. FDA also emphasizes that this rule will not require studies in settings where ethical or medical concerns militate against studies. As with all studies regulated by FDA, no pediatric study may go forward without the approval of an IRB, which is responsible for ensuring that the study is ethical and adequately protects the safety of the subjects. In addition, the deferral provisions of the rule are specifically designed to ensure that no pediatric study begins until there are sufficient safety and effectiveness data to conclude that the study is ethically and medically appropriate.

B. Scope

The proposal would have covered only original applications for those drugs classified as ''new chemical entities,'' including antibiotics, and new biological products that had never been approved for any indication. A ''new chemical entity,'' defined in 21 CFR 314.108(a), is a drug that contains no previously approved active moiety. Under the proposal, chemical modifications that did not change the active moiety, such as the formation of a different salt or ester of the moiety, would not have required further study. New indications or dosage forms of a previously approved moiety also would not have required further studies. FDA sought comment on whether the requirement should apply more broadly, e.g., to applications for minor chemical variations of approved products, new indications, new dosage forms or new routes of administration.

9. A majority of those who commented on the scope of the rule recommended that the final rule cover all new drugs and biologics, including new dosage forms and indications, because modifications in existing drugs may be as therapeutically significant to pediatric patients as the original drug or biologic. These comments included pediatricians, medical societies, one pharmaceutical company, and one disease-specific organization. Several comments, including two companies, an IRB, the AAP, a disease-specific organization, and a professional society recommended including new indications and dosage forms on a case-by-case basis, generally if their inclusion were recommended by an expert panel. Several comments supported the narrow scope of the proposal, including a pharmaceutical trade association, a professional society, and several companies. The pharmaceutical trade association suggested that the rule might also apply to new formulations uniquely suited to pediatric patients.

FDA has reconsidered the scope of the rule in light of the comments and has concluded that, in some cases, the need for pediatric studies is as great for modifications of existing products and new claims as for the original products. A new indication or dosage form for a previously approved drug, e.g., could be far more relevant to pediatric patients than the originally approved product. From a public health standpoint, FDA cannot justify the distinction in the proposal between new chemical entities and never-before approved biologics, on one hand, and significant modifications of those products, on the other hand. Therefore, FDA has revised proposed §§ 314.55 (proposed 314.50(g)) and 601.27(a) to cover applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. The final rule exempts from its coverage any drug for an indication or indications for which orphan designation has been granted under the Orphan Drug Act (21 U.S.C. 360bb). FDA believes this exemption is appropriate because the purpose of the Orphan Drug Act is to encourage the development of drugs for patient populations that are so small as to make the manufacture and sale of the drug unprofitable if not for the incentives offered by the Orphan Drug Act. Imposition of a pediatric study requirement on an orphan drug could conflict with the balance struck by the Orphan Drug Act, by further raising the cost of marketing the drug. This exemption does not apply after marketing under § 201.23 of this final rule.

FDA's decision to expand the scope of the rule does not mean, however, that pediatric studies would always be needed for a new product entering the marketplace, or for a new claim. The waiver criteria will apply equally to modifications of existing drugs and biological products. Thus, FDA will require studies only of those new drugs and biologics that offer a meaningful therapeutic benefit to pediatric patients or that are expected to be used in a substantial number of pediatric patients. In many cases, moreover, new dosage forms might need relatively little pediatric data, such as pharmacokinetic data alone.

10. One comment sought clarification of the applicability of the rule to generic drugs. The comment argued that the collection of pediatric data was unwarranted where a generic manufacturer was copying a drug with an adult dose, and that FDA should require a pediatric bioequivalence study only where the innovator submits a supplement for a new dose or regimen in the pediatric population. Another comment from a generic drug trade association argued that bioequivalence studies in children should never be required to support approval of a generic drug.

This rule does not impose any requirements on studies submitted in support of applications for generic copies of approved drugs that meet the requirements of section 505(j) of the act. FDA also does not currently require bioequivalence studies to be conducted

in children for generic drugs. FDA notes that petitions submitted under section 505(j)(2)(C) for a change in active ingredient, dosage form, or route of administration may be denied if ''investigations must be conducted to show the safety and effectiveness of'' the change. Thus, if a petition is submitted for a change that would require a pediatric study under this rule, the petition may be denied.

C. Required Studies

FDA proposed to amend its regulations related to the content of NDA and biologic license applications (BLA's) to include required information on pediatric studies for certain applications. Under the proposal, an application for a new chemical entity or never before approved biologic would have been required to contain data adequate to assess the safety and effectiveness of the product for all pediatric age groups for the claimed indications, unless FDA granted a deferral or full or partial waiver of the requirement. As described in section III.B of this document under ''Scope'', FDA has revised § 314.55(a) (proposed § 314.50(g)(1)) and § 601.27(a)) to cover applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. Under the final rule, all covered applications will be required to contain data adequate to assess the safety and effectiveness of the product, unless FDA has granted a waiver or deferral of the requirement (see ''Waiver'' and ''Deferred Submission'' in section III.D and E of this document).

Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required, unless reasonable efforts to produce a pediatric formulation had failed (see ''Waiver'' in section III.E of this document). Comments on issues related to formulation are addressed under ''Pediatric Formulations'' in section III.I of this document.

The proposal did not mandate particular types of studies. The proposal recommended that the sponsor consult with FDA on the types of data that would be considered adequate to assess pediatric safety and effectiveness in particular cases.

FDA received several comments on the design and conduct of clinical trials in pediatric patients.

11. One comment asked for clarification of what is meant by ''adequate evidence'' to demonstrate safety and effectiveness. The comment argued that FDA should not require two adequate and well-controlled trials for pediatric studies, and that the amount of evidence required should depend on the ability of the data to be extrapolated from adult to pediatric patients, the seriousness of the illness to be treated, the ability to assess meaningful measures of efficacy in pediatric patients, and the feasibility of conducting adequate trials in relatively uncommon pediatric disease states. Another comment claimed that the ability to extrapolate from adult efficacy data is limited and argued that well-controlled trials in pediatric patients should be the norm. This comment also stated that safety cannot be extrapolated from adult data and recommended studying 300 pediatric patients for an adequate period to identify frequent ADR's. Other comments questioned the appropriateness of extrapolating from adult effectiveness data in a variety of settings. One comment argued that in the area of blood products, in addition to extrapolating from pharmacokinetic data, it may be appropriate to extrapolate from adult data using relative blood volume replacement. Several comments urged reliance on a variety of other sources of data, including published studies and reports, and actual use information. One comment urged FDA to rely on advanced scientific and statistical methods that optimize safety, convenience, and informativeness, while minimizing unnecessary or uninformative clinical trials.

FDA agrees that ''adequate evidence'' of safety and effectiveness for pediatric patients does not necessarily require two adequate and well-controlled trials. One of two central purposes of the 1994 rule was to make it clear that pediatric effectiveness may, in appropriate circumstances, be based on adequate and well-controlled studies in adults with supporting data in pediatric patients that permit extrapolation from the adult data. FDA agrees, however, that extrapolation from adult effectiveness data would not always be appropriate and that it may not be appropriate to extrapolate pediatric safety from adult safety data. FDA has specifically noted, in the FDA guidance document entitled ''Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,'' that if further controlled trial data were needed in a population subset, it would usually be sufficient to conduct a single additional controlled trial. FDA also agrees that useful information can come from data other than adequate and well-controlled trials, and encourages the submission of valid and reliable data from a variety of sources. The type and amount of data required in any particular case will depend upon many factors, including those cited in the comments.

12. One comment urged FDA, in the final rule, to encourage sponsors to use Computer-Assisted Trial Design (CATD), allowing them to reduce number of actual trials in pediatric patients.

FDA encourages the use of any validated scientific method for designing, conducting, or analyzing clinical trials.

13. One comment questioned whether there will be a sufficient pool of pediatric subjects to complete trials, in light of the increase in the number of trials occasioned by the rule.

FDA believes that with appropriate organization, the pool of pediatric patients available for studies should be adequate. The Pediatric Pharmacology Research Units (PPRU's), a network of groups instituted to conduct pediatric research, some of which are located outside of major population centers, have an established record of recruiting pediatric patients and completing valid studies. Even where the number of pediatric patients affected by a disease is small, valid studies have sometimes been successfully conducted. It should also be reemphasized that many of the studies contemplated under the rule are pharmacokinetic studies, dose-response studies with short-term endpoints (pharmacodynamic studies) and safety studies that are likely to impose relatively little burden on individual patients. Where, however, patient recruitment is so difficult as to make the study impossible or highly impractical, the rule permits a waiver of the study requirement (§§ 314.55(c) and 601.27(c)).

14. One comment urged that the final rule include a broader research requirement, and sought to have drug interactions and drug metabolism taken into consideration. Another comment sought to have the final rule codify minimal requirements for studies, such as toxic overdose and pharmacokinetic data. One comment urged FDA not to codify specific requirements for clinical trials, but to establish these requirements in consultation with an expert pediatric committee.

FDA declines to codify specific requirements for pediatric studies. Flexibility is necessary to assure that required studies are appropriate for each product. FDA will, however, consult with a pediatric committee on specific pediatric study issues.

15. One comment from a professional pharmacy organization urged that all protocols for pediatric studies be reviewed by pediatric experts, including a pharmacist knowledgeable about pharmacodynamic factors in each age group.

FDA reviews protocols for pediatric studies submitted in investigational new drug applications (IND's), and its reviewers include experts in pediatrics and pharmacology.

D. Deferred Submission

The proposal recognized that there would be circumstances in which it would be appropriate to permit the submission of pediatric data after approval. Two such circumstances were described in the preamble to the proposal: (1) Where adult safety or effectiveness data need to be collected before the product could be appropriately studied in pediatric patients, and (2) where the product was ready for approval in adults before studies in pediatric patients were completed. Although not included in the text of the proposal, these examples have been added to the final rule. Under the proposal, FDA would have the authority to defer the submission of some or all of the required pediatric data until after approval of the product for adult use, on its own initiative or at the request of the applicant. Under the proposed provisions, if the applicant requested deferral, the request would be required to contain an adequate justification for delaying pediatric studies. If FDA concluded that there were adequate justification for deferring the submission of pediatric use studies, the agency could approve the product for use in adults subject to a requirement that the applicant submit the required pediatric studies within a specified time after approval. It is important to appreciate that deferred submission of pediatric data refers to the date on which the data are submitted, not when the studies are initiated. Thus, deferred studies will generally be initiated before approval, unless it is concluded that the full adult data base or marketing experience are needed before pediatric studies may appropriately begin.

FDA stated in the proposal that it would consult with the sponsor in determining a deadline for the deferred submission, but tentatively concluded that it would require the submission not more than 2 years after the date of the initial approval. To ensure that deferral would not unnecessarily delay the submission of pediatric use information, FDA proposed that a request for deferred submission include a description of the planned or ongoing pediatric studies, and evidence that the studies were being, or would be, conducted: (1) With due diligence, and (2) at the earliest possible time. FDA sought comment on the circumstances in which FDA should permit deferral, and on the factors that should be considered in determining whether a given product was one that should be studied in adults before pediatric patients. FDA received many comments on the deferral provisions in the proposal.

16. A few comments stated that the deferral provisions are an appropriate means of assuring that pediatric patients are not studied before adequate safety data have been gathered. A number of comments from the pharmaceutical industry asserted, however, that the proposal would require concurrent testing in adults and pediatric patients despite medical and ethical reasons for delaying testing pediatric testing. For example, a comment from a pharmaceutical trade association claimed that the rule:

> * * * would require testing of new medical compounds in children before safety in adults has been studied adequately, before effectiveness in adults has been established, and in young children and neonates without adequate information about the effects of the drug in older pediatric patients.

These industry comments appear to have misunderstood the explicit deferral provisions of the rule and perceived them as rare exceptions to a usual requirement that adults and children be studied at the same time. Nothing in the rule requires concurrent testing in adults and pediatric patients, nor testing in infants and neonates before testing in older children. As stated previously and in the proposal, the deferral provisions were specifically included to, among other things, ensure that pediatric studies could be delayed when necessary to assure that appropriate safety and/or effectiveness data were available to support pediatric testing.

17. Most of the comments on deferral focused on whether the need for safety and/or effectiveness data in adults before initiating pediatric studies should be a basis for deferral. Comments from disease-specific organizations, medical societies, including the AAP, and pediatricians argued that deferrals should be granted rarely if at all on this basis. One comment argued that delaying availability of life-saving drugs to children cannot be rationalized scientifically, legally, or ethically, and contended that deferral should not be permitted for serious and life-threatening diseases where there is no substantial difference between the disease or the anticipated effect of the drug in children or adults. Another comment argued that deferral should be used sparingly in all age groups, including infants and neonates, and that its use should be evaluated in the context of the seriousness of the condition to be treated, the therapeutic advance the drug represents, and the likelihood that the drug will be given to children as soon as it is approved. According to this comment, the risks of research in pediatric patients may be outweighed by the risks that the drug will be given to them without data.

One comment argued that pediatric studies of important drugs should be conducted in parallel to adult studies, especially in children under 12. Several comments from the pediatric community, however, supported the development of some adult safety and/or effectiveness data before initiation of pediatric studies. One comment from an organization devoted to pediatric AIDS stated that while the general assumption should be that pediatric studies will be submitted at the same time as adult studies, it may be appropriate to have some testing in adults before children. The AAP stated that it is appropriate to begin studies in pediatric patients after phase 1 and phase 2 studies in adults have defined routes of clearance and metabolic pathways. Thus, the comment urged that pediatric studies be conducted during phases 2 and 3, not 4. A comment from a nephrology organization argued that drugs for organ-specific diseases should be studied in phase 3, as soon as phase 1 and 2 trials have shown safety in adults. This and another comment stated that deferring studies until after approval compromises clinical trial enrollment, citing the experience with recombinant erythropoietin. According to these comments, erythropoietin was not studied in pediatric patients until after its approval for adults, and enrollment was so difficult that pediatric studies were not completed for 5 years.

Several comments from the pediatric community also cited limited circumstances in which they believed deferral to be appropriate. A medical society argued that data should be collected after adult studies only for drugs with narrow therapeutic indices, unusual accumulation in the body, where the drug study requires extensive blood sampling, or where the study design places young patients at risk for limited information gain.

Many comments from the pharmaceutical industry argued, in contrast, that deferral should be the

rule, rather than the exception. Most of these comments contended that it was unethical to begin studying drugs in pediatric patients, other than those that are intended primarily for pediatric patients, until the drugs are shown to be reasonably safe and effective in adult patients. All argued that pediatric studies must not be initiated until substantial data in adults are available, but cited different initiation points, e.g., after phase 2, after safety and effectiveness is established in adults and an approvable letter is received, after approval, after 1 year of marketing.

Although many of these industry comments argued that pediatric studies should be conducted exclusively as phase 4 (postapproval) commitments, a significant number of industry comments acknowledged that pediatric studies could begin before approval, generally after phase 2, and that there were circumstances in which deferral was not appropriate. One comment argued that because early pediatric studies often require pediatric formulations and because up to 50 percent of drugs are abandoned before phase 3, it is wasteful to require companies to manufacture a pediatric formulation and begin studies before the end of phase 2. Another comment argued that no pediatric studies should begin before the decision to proceed to phase 3, except where: (1) The disease affects only pediatric patients; (2) the disease mainly affects pediatric patients, or the natural history or severity of the disease is different in pediatric patients and adults; or (3) the disease affects both pediatric patients and adults and lacks adequate treatment options. One comment urged that the final rule state that ''in most cases, pediatric testing should not begin with any drug or biological product until certain adult safety and/or effectiveness information has been collected.'' According to this comment, there could be exceptions where no other therapy was available and there was a potential for the drug to be lifesaving. A pharmaceutical trade association argued for a presumption that pediatric studies not begin until the end of phase 2 or 3, but listed circumstances in which deferral should not occur: (1) Where the disease is life threatening and there is no alternative therapy, (2) where the drug is intended for a pediatric indication, (3) where the drug presents no major safety issues, (4) where the drug class is well studied in pediatric patients, or (5) where a large amount of ''off-label'' use in pediatric patients is anticipated.

In general, FDA expects that some data on adults will be available before pediatric studies begin, but that less data will usually be required to initiate studies of drugs and biologics for life-threatening diseases without adequate treatment than for less serious diseases. Pediatric studies of drugs and biologics for life-threatening diseases may in some cases be appropriately begun as early as the initial safety data in adults become available, because the urgency of the need for such products may justify early trials despite the relative lack of safety and effectiveness information. In such cases, deferral of submission of pediatric studies until after approval will be unnecessary, unless drug development is unusually rapid and the product is ready for approval in adults before completion of the pediatric studies.

Pediatric studies on products for less serious diseases should generally not begin until more adult data have been collected, ordinarily no earlier than the availability of data from the initial well-controlled studies in adults. As noted earlier in this document, there may occasionally be exceptions to this principle where all parties agree that earlier initiation is appropriate. Whether deferral of submission of the data until after approval will be necessary for such products will depend upon when pediatric studies can scientifically and ethically begin in each case and how difficult the studies are to complete.

In some cases, FDA expects that scientific and ethical considerations will dictate that studies not begin until after approval of the drug or biological product. For example, pediatric studies of ''me-too'' drugs that do not offer a meaningful therapeutic benefit and that are members of a drug class that already contains an adequate number of approved products with pediatric labeling may be deferred until well after approval. In cases where a drug has not been shown to have any benefit over other adequately labeled drugs in the class, the therapeutic need is likely to be low and the risks of exposing pediatric patients to the new product may not be justified until its safety profile is well established in adults through marketing experience. Because the basis for the deferral in such cases will be concern that the drug presents risks to pediatric patients that will not be known until there is widespread marketing experience, without offsetting benefit, FDA may require, in appropriate cases, that such drugs carry labeling statements recommending preferential use in pediatric patients of products that are already adequately labeled. Such a statement might read:

> The safety and effectiveness of this product have not been established in children. There are alternative therapies that have been shown to be safe and effective for use in children with [indicated condition]. Ordinarily, products already labeled for use in children should be used in preference to [name of this product].

FDA labeling regulations at 21 CFR 201.57 express the agency's authority to ensure that drugs are safe for use under the conditions prescribed, recommended, or suggested in their labeling, and to require labeling identifying safety considerations that limit the use of drugs to certain situations. Some drugs with no demonstrated advantage over available therapy can nonetheless be expected to have wide use in pediatric patients. Pediatric studies of such drugs should be initiated relatively early, even if they are not completed at the time of approval.

18. A comment from a pharmaceutical company listed several circumstances in which it argued FDA should permit deferral: (1) The pediatric population is so small that enrollment and completion of trials cannot be accomplished in parallel with adult trials, (2) the natural course of the disease is different in adults and children, (3) analytic tools and clinical methodologies cannot be easily adapted to the pediatric population, (4) the drug has complex pharmacokinetic properties in adults making it hard to extrapolate a pediatric dosage range, (5) the scope and nature of nonclinical studies support only adult clinical studies, (6) two or more attempts to develop a pediatric formulation have failed, or (7) unique drug-drug or drug-food interactions in children confound drug development. Another comment added to this list: (1) Where fewer than 200,000 pediatric patients are affected by the disease being treated, and (2) drugs with a low therapeutic index.

FDA agrees that some of these circumstances could make completion of studies prior to approval in adults difficult, but does not agree that they would make studies impossible or impractical in all cases. The need for deferral must be considered case-by-case. A small pediatric population, e.g., might make completion of controlled trials very slow, but might not prevent obtaining pharmacokinetic data. Simply citing a pediatric population under 200,000 will not be sufficient to justify deferral; a small fraction of this number participating in trials may be sufficient to support timely pediatric studies, depending on the nature of the studies. As an example, over 70 percent of the estimated 6,000 pediatric patients with cancer each year are enrolled in clinical trials (Ref. 15). There does not seem to

be any reason to conclude that deferral is warranted solely because the natural course of the disease is different in adults and children. FDA also disagrees that deferral is necessarily warranted where analytic tools and clinical methodologies cannot be easily adapted to pediatric patients. Deferral may be necessary in some cases where the infants and toddlers are unable to provide subjective outcome data, but it may also be possible to utilize alternative endpoints or to extrapolate effectiveness data from older pediatric age groups, obtaining pharmacokinetic data from the younger age groups to determine an appropriate dose. Drugs with a low therapeutic index that do not fulfill an urgent need should, in general, be studied in pediatric patients later in drug development.

With respect to complex pharmacokinetic properties that prevent extrapolation of adult data to pediatric patients, low-therapeutic index drugs, and unique drug-drug or drug-food interactions in pediatric patients, FDA believes that the need for pediatric studies before approval is even greater where these conditions are present; moreover, none of them represents a significant impediment to studies. Recognizing that drugs and biologics approved for adults are regularly prescribed to pediatric patients despite the absence of adequate dosing and safety data, information positively suggesting that dosing and safety cannot be extrapolated from adult data increases the importance of conducting pediatric studies before the product is widely used in pediatric patients. The absence of supporting nonclinical studies (e.g., studies in young animals) should not usually be a basis for deferral. These studies, if needed, are readily conducted. Moreover, a full adult data base provides pertinent safety information that might make further preclinical data unnecessary. Difficulties in developing an adequate pediatric formulation may, in some cases, justify deferral of studies in young pediatric patients. In other cases, however, it may be appropriate to study a less-than-optimal formulation, e.g., an injection, if one is available, in pediatric patients while awaiting the development of a more desirable pediatric formulation.

19. One comment argued that it was ''unacceptable'' to defer pediatric studies to avoid delaying approval for adult use. Instead, the comment urged FDA to provide a ''limited approval'' for adult use until pediatric data are available and impose a monetary penalty for failure to comply. Another comment argued that permitting deferral to avoid delay in adult marketing could be applied to most applications, creating a de facto situation in which pediatric data were understood to be not required until 2 years after approval. One comment stated that while pediatric dosing schedules are essential, pediatric studies should not delay approval of drugs for a major population, adults.

FDA continues to believe that deferral is appropriate where awaiting the completion of pediatric studies would delay the availability of a safe and effective drug or biological product for adults. Granting a deferral does not automatically mean, however, that pediatric studies need not be submitted for 2 years or that initiating them should be long delayed. The proposal suggested 2 years as the maximum period for a deferral. Where pediatric studies are supposed to be nearing completion at the time a product is ready for approval in adults, FDA expects that the period of deferral would be significantly shorter than 2 years. Where some useful pediatric information, e.g., safety information, is available at the time of approval, even if some required studies are not complete, FDA may require that the pediatric use section of the product's labeling include that information, to the extent consistent with 21 CFR 201.57(f)(9). FDA also notes that it has no authority to impose a monetary penalty for failure to submit a required study of a drug or biological product. FDA must ask a court to impose such a penalty in a contempt proceeding.

20. Several comments argued that pediatric trials should be conducted sequentially, beginning with the oldest pediatric age group, and ending with the youngest. One comment stated that IRB's would question testing a drug in younger children before older children. The AAP argued that there is little defense for studying pediatric patients sequentially from oldest to youngest, and that such a policy will result in approvals without data in neonates. This comment argued that the timing of studies should give consideration to safety, but without consideration of sequence. Another comment argued that FDA should not routinely require that drugs for serious and life-threatening diseases be studied sequentially. In HIV, according to this comment, drug testing should be ''as simultaneous as possible'' because safety and dosing may be initiated in each age group in a dose escalating manner regardless of the results in previously tested groups.

FDA agrees that age-dependent sequential studies are not necessarily appropriate. Particularly were there is urgent need for a product, there may be good reason to study older and younger children at the same time.

21. A few comments objected to FDA's tentative decision to require the submission of studies ordinarily no later than 2 years after the initial approval. One comment stated that deferral of up to 2 years was excessive, citing the ''critical'' need to ensure timely performance of pediatric studies in populations where the drug is likely to be used. Another comment stated that 2 years may be adequate for collecting pharmacokinetic data, but not necessarily for collecting safety data. According to this comment, the size of the clinical data base will be the principal determinant of when data should be submitted. A comment from the American Red Cross stated that the extensive IRB review of studies of blood products involving pediatric patients, and the difficulty in enrolling such patients, makes the 2-year deferral deadline unrealistic for this category of product.

FDA agrees with the comments that the 2-year deadline suggested by the proposal may not be appropriate, and that the length of the deferral should be decided on a case-by-case basis. The timing of the deferred submission will depend upon such factors as the need for the drug or biologic in pediatric patients, when sufficient safety data become available to initiate pediatric trials, the nature and extent of pediatric data required to support pediatric labeling, and substantiated difficulties encountered in enrolling patients and in developing pediatric formulations. FDA may also extend the date for submission of studies at the time of approval, e.g., where other drugs in the class have been approved during the pendency of the NDA and the new drug is no longer needed as a therapeutic option.

E. Waivers

FDA does not intend to require pediatric assessments unless the product represents a meaningful therapeutic benefit over existing treatments or is expected to be used in a substantial number of pediatric patients. FDA also does not intend to require pediatric assessments in other situations where the study or studies necessary to carry out the assessment are impossible or highly impractical or would pose undue risks to pediatric patients. Thus, FDA proposed to add § 314.50(g)(3) (now § 314.55(c)) and § 601.27(c) to authorize FDA to grant a waiver of the pediatric study requirement on its own initiative or at the request of the applicant unless the product represented a meaningful therapeutic benefit over existing

treatments, or was likely to be used in a substantial number of pediatric patients. These provisions also require FDA to grant a waiver if necessary studies were impossible or highly impractical, because, e.g., the number of pediatric patients was very small or patients were geographically dispersed, or there was evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations. If a waiver were granted because there was evidence that the product would be ineffective or unsafe in pediatric patients, this information would be included in the product's labeling.

An applicant could request a full waiver of all pediatric studies if one or more of the grounds for waiver applied to the pediatric population as a whole. A partial waiver permitting the applicant to avoid studies in particular pediatric age groups could be requested if one or more of the grounds for waiver applied to one or more pediatric age groups. In addition to the other grounds for waiver, the proposal would authorize FDA to grant a partial waiver for those age groups for which a pediatric formulation was required (see ''Pediatric Formulations'' in section III.I of this document), if reasonable attempts to produce a pediatric formulation had failed.

The proposal would require the applicant to include in the request for a waiver an adequate justification for not providing pediatric use information for one or more pediatric populations.

FDA would grant the waiver request if the agency found that there was a reasonable basis on which to conclude that any of the grounds for a waiver had been met. If a waiver were granted on the ground that it was not possible to develop a pediatric formulation, the waiver would cover only those pediatric age groups requiring a pediatric formulation.

The agency also proposed two possible methods of determining a ''substantial number of patients.'' The first method would focus on the number of times the drug or biologic was expected to be used in pediatric patients, annually. Under this method, FDA tentatively concluded that 100,000 or more prescriptions or uses per year in all pediatric age groups would be considered a substantial number.

The second proposed method for establishing whether there was a substantial number of pediatric patients would focus on the number of pediatric patients affected by the disease or condition for which the product is intended. Under this method, FDA tentatively concluded that 100,000 pediatric patients affected by the disease or condition for which a product was indicated would be considered a ''substantial number'' of pediatric patients. FDA sought comment on the waiver criteria and on these methods of calculating a substantial number of pediatric patients. FDA also sought comment on whether cost to the manufacturer should justify a waiver.

FDA received many comments on the waiver provisions of the proposal, and has made certain changes in response to the comments, as described below.

22. As proposed, new drugs and biologics are presumptively required to be studied in pediatric patients, unless a waiver is granted. The presumption in the proposal was supported by comments from pediatricians, a pharmacy organization, disease specific organizations, and medical societies, including the AAP. Several industry comments argued, however, that new drugs and biologics should presumptively not be covered by the rule, unless they were specifically identified by FDA as needing to be studied. One of these comments stated that companies should not have to waste the effort of applying for waiver for drugs of no potential benefit to pediatric patients, which the comment estimated as a majority of those developed.

FDA continues to believe that it is appropriate to presume that drugs and biologics should be studied in pediatric patients, and that this presumption should be overcome only if there are clear grounds for concluding that such studies are unnecessary. Pediatric patients are a significant subpopulation, affected by many of the same diseases as adults, and are foreseeable users of new drugs and biologics. The agency has stated, in the context of pediatric studies and other subpopulations, that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug or biological product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409, July 22, 1993). FDA does not believe that the cost of drafting a waiver request will be great, particularly where the basis for the waiver is that the product has no potential use in pediatric patients. To assist sponsors in preparing such waivers, FDA has included in this document a partial list of diseases that are unlikely to occur in pediatric patients and for which waiver requests need include only reference to this document.

23. FDA received many comments on the proposed criteria for waiving pediatric studies. A few comments supported the proposed criteria. Many comments from pediatricians, medical societies, and disease-specific organizations argued that the proposed grounds for waiver were too broad. Several of these stated that the rule should apply to drugs for all conditions that affect pediatric patients unless there is a special reason not to do so. One comment argued that waivers should be available only for drugs known to be extremely toxic in pediatric patients or to have no anticipated use in pediatric patients.

Other comments from the pharmaceutical industry argued that the waiver provisions were too narrow. One comment from a generic trade association urged that pediatric studies be required only when there is a significant public health concern with respect to the safety of a drug product in pediatric patients or to the availability of adequate pharmacological intervention for pediatric patients for the indication. Another comment stated that the criteria in the proposal ''do not begin to address the complexities associated with moving forward on a clinical development plan'' and argued that additional criteria should include: (1) The lack of correlative safety evidence, (2) liability concerns, and (3) prohibitive cost (but the sponsor, not FDA, should be allowed to determine the importance of cost).

FDA believes that the criteria for waiver in the final rule strike a careful balance. On the one hand, requiring studies for all new products would have potentially severe resource implications for manufacturers and the agency. On the other hand, obtaining studies only where the studies impose no burden on the sponsor would continue to expose millions of pediatric patients to unnecessary risks and ineffective treatment. Requiring pediatric studies only of those drugs or biologics that offer a meaningful therapeutic benefit or that are expected to be used in a substantial number of pediatric patients focuses limited resources on those products that are most critically needed for the care of pediatric patients.

24. Several comments addressed the definition of ''meaningful therapeutic benefit.'' Some comments from the pharmaceutical industry stated that ''meaningful therapeutic benefit'' should be defined as it is used in 21 CFR 314.500. (That regulation applies to drugs ''that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).'') One of these comments

suggested that analogous cases in the pediatric context would be: (1) Where the drug treats a pediatric disease for which no other treatments exist; (2) where the drug treats patients who are unresponsive to or intolerant of other drugs; or (3) where the drug produces a superior response over other treatments. One industry comment argued that the agency should consult with the sponsor, and the pediatric investigators involved to assess whether the drug will provide a ''meaningful therapeutic benefit.'' According to the comment, the assessment should include the likely use of the product in a specific pediatric population, the likely benefit without increased risk to patients versus existing treatments, a ''definitive need'' for a new therapy in very serious or life-threatening illnesses, and the cost and feasibility of developing the necessary formulations and of conducting studies. Another comment from a disease-specific organization argued that ''meaningful therapeutic benefit'' should be a relative term, depending on the severity of the illness, the potential risk posed by the drug, and the availability of alternative treatments. One comment from a medical society devoted to the treatment of psychiatric disorders contended that ''meaningful therapeutic benefit'' should mean that the product enables a child to function better, and participate in age-appropriate activities, such as playing and going to school, without undue pain and suffering from the disease or disorder. Another comment argued that ''meaningful therapeutic benefit'' should mean better response or ability to treat nonresponsive patients. Another comment maintained that the presumption should be that a product represents a meaningful therapeutic benefit in pediatric patients if it is expected to provide a meaningful therapeutic benefit in adults.

Several comments from the pharmaceutical industry contended that it is not possible to define meaningful therapeutic benefit before approval or that FDA should not be responsible for defining it. A pharmaceutical trade association argued that meaningful therapeutic benefit is the decision of the sponsor, not FDA, and that it is not possible to determine meaningful therapeutic benefit until a drug has been used for some period of time. Another comment maintained that FDA must first have adult data to reach the conclusion that a drug offers a meaningful therapeutic benefit. The same comment also argued that a rigorous determination of meaningful therapeutic benefit would require randomized, controlled trials in pediatric patients.

FDA disagrees that it is impossible or beyond FDA's expertise to reach a conclusion before approval about whether a product has the potential to offer a meaningful therapeutic benefit. FDA routinely estimates the therapeutic benefit of new drugs and biologics at the time applications are first submitted, in order to determine whether to assign ''Priority'' (expedited) status to the review of the application. In assigning Priority status to new drug applications, CDER determines whether the product, if approved, ''would be a significant improvement compared to'' marketed (or approved, if such is required) products, including nondrug products or therapies. ''Improvement can be demonstrated by, for example: (1) Evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation'' (Ref. 16). These criteria are similar to many of the criteria suggested in the comments. FDA notes that demonstration of an advantage over existing products may come from evidence other than head-to-head comparisons of the new product and existing products. For example, in some cases a new product could be shown to lack an adverse effect associated with an existing product, or to have an effect on a different outcome or on a different stage of disease than an existing product, without a direct comparison of the two products.

FDA has concluded that in determining whether a product offers a meaningful therapeutic benefit, it will use the Priority definition, with some modifications. First, in determining whether a product is expected to be an improvement over other products, the comparison will be made only to other products that are already adequately labeled for use in the relevant pediatric population. Second, it is often therapeutically necessary to have two or more therapeutic options available, because some patients will be unresponsive to a given therapy. Because the Priority definition would not cover more than the first or second product for a given indication or in a given class (unless the product offered an advantage over others for the indication or in the class), a drug or biologic will also be considered to provide a meaningful therapeutic benefit if it is in a class of drugs and for an indication for which there is a need for additional therapeutic options. The specific number of products needed will depend upon such factors as the severity of the disease being treated, and the adverse reaction profile of existing therapies. FDA has added this definition of meaningful therapeutic benefit to §§ 314.55(c)(5) and 601.27(c)(5). This rule's definition of meaningful therapeutic benefit is intended to apply only in the pediatric study context and is not intended to alter the definition of a Priority drug.

25. Several comments addressed the definition of ''a substantial number of pediatric patients.'' A few comments argued that it would be difficult to estimate product use until after marketing. Several comments argued that FDA should not base waivers on the number of patients or prescriptions. Many other comments claimed that the proposed numerical cut-offs are arbitrary. These comments maintained that waivers should be decided on a case-by-case basis. Several comments urged that FDA consult with an expert panel in deciding whether pediatric use was substantial.

Comments from the pediatric community contended that the numerical cut-offs in the proposal were too high, and would preclude studies of many serious diseases affecting fewer than 100,000 pediatric patients. One comment, for example, voiced concern that pediatric patients with less common seizure types may not benefit from the regulations because the use is not sufficiently widespread. Another comment argued that numerical cut-offs should not apply to drugs for serious and life-threatening diseases, unless the number of pediatric patients was so low as to make clinical study impossible. Another comment suggested that studies be required not only for uses greater than 100,000 prescriptions, but for ''drugs used chronically for a defined, though smaller group of pediatric patients, usually for organ-specific diseases, such as kidney failure or hypertension.''

Comments from the pharmaceutical industry argued that the numerical cut-offs proposed by FDA were too low. Some of these comments argued that 100,000 prescriptions per year translates to fewer than 100,000 patients, and that the resulting population could be so small that it would be difficult to study. Several of these comments urged that cut-off for substantial use be 200,000 patients with the disease, the threshold established by the Orphan Drug Act for identifying rare diseases.

FDA has decided to revise its proposed method of defining a substantial number of patients, in light of the comments. Physician mention

data from the IMS National Disease and Therapeutic Index (Ref. 38), which tracks the use of drugs by measuring the number of times physicians mention drugs during outpatient visits, shows that pediatric use of drugs is generally grouped in two distinct ranges. Physician mentions of drugs for pediatric use generally fall either below 15,000 per year or above 100,000 per year. Few drugs fall within the two ranges. Thus, selecting a cut-off for ''substantial number of pediatric patients'' in the middle of the two ranges will provide a reasonable discrimination between products that are widely used and those that are less commonly used, and the specific number chosen will not arbitrarily include or exclude a significant number of drugs. FDA has therefore chosen 50,000 as the cut-off for a substantial number of pediatric patients. Because the number of pediatric patients with the disease is easier to determine than the number of prescriptions per year, a substantial number of pediatric patients will be defined as 50,000 pediatric patients with the disease for which the drug or biological product is indicated. Although physician mentions per year does not correspond exactly to the number of patients with the disease, they provide a rough approximation and the IMS data show that the number of products included or excluded is relatively insensitive to changes in the cut-off chosen. As proposed, a partial waiver for a particular pediatric age group would be available under this method if 15,000 patients in that age group were affected by the disease or condition. This definition of ''a substantial number of pediatric patients'' has not been codified, however, and FDA may modify it, after consulting with the pediatric panel discussed in section III.M of this document (''Pediatric Committee''). Any modification will be issued as a guidance document.

In response to those comments that voiced concern that this definition would exclude a number of serious diseases, FDA emphasizes that the definition of ''meaningful therapeutic benefit'' assures that drugs and biologics will be covered by the rule if they are medically needed as therapeutic options because there are insufficient products adequately labeled for pediatric patients for that indication or in that drug class. Until there are enough adequately labeled products available, many new drugs and biologics for serious and life-threatening diseases will be considered to offer a meaningful therapeutic benefit and thus will be required to be studied, even if the products are not also used in a substantial number of pediatric patients. This will be particularly true during the first few years after implementation of this rule when few drugs and biologics will yet be adequately labeled for use in pediatric patients, and a larger proportion of new entrants into the marketplace will be considered to be medically necessary therapeutic options.

In response to the comments arguing that FDA's proposed numerical cut-off is too low and will result in too many pediatric studies, FDA expects to defer until after approval many of the studies of products that will be used in a substantial number of pediatric patients but that do not offer a meaningful therapeutic benefit. As described previously in response to comments on the deferral provisions, studies of new drugs and biologics that do not offer a meaningful therapeutic benefit and are members of a class that is already adequately labeled for pediatric patients are likely to be deferred until well after approval of the product for adults.

26. A few comments addressed the provisions that would permit waiver if pediatric trials were impossible or impractical. One comment argued that the provision authorizing waiver if the proposed population was ''too small or geographically dispersed'' was too broad. This comment urged that tests should be waived only if ''significant efforts to recruit patients fail.'' The comment also argued that the unsupported suggestion that tests are ''impractical'' should not be accepted, and that evidence of due diligence should be required. Another comment argued that waivers should never be granted because the population is too small or dispersed. According to this comment, many safety and pharmacokinetic studies are already performed in dispersed populations, and the comment maintained that no experimental drug should be administered to a child with a serious or life-threatening disease without requiring that some safety data and pharmacokinetics data be obtained. Another comment observed that although only 600 renal transplants are performed each year in pediatric patients, pediatric academic centers have been creative in forming collaborative efforts to study these small groups. One comment from an organization devoted to children with HIV stated that the ''impossible or highly impractical'' standard must be narrowly interpreted, and that a manufacturer should show that all reasonable efforts to recruit patients have failed. According to this comment HIV/AIDS drugs should be a benchmark of when a waiver should not be granted: Any group as big or bigger than the pediatric AIDS population should be considered big enough to study.

Another comment argued that because of special difficulties encountered in recruiting pediatric patients into studies of blood products, such as parental fear of disease transmission, the inability to obtain a sufficient number of test subjects should be added to the criteria for waiver or to the definition of ''highly impractical.''

FDA agrees with those comments urging that this ground for waiver be interpreted narrowly and that unsupported assertions be rejected as a basis for waiver. Although the number of patients necessary to permit a study must be decided on a case-by-case basis, FDA agrees that there are methods available to conduct adequate studies in very small populations. Moreover, where only safety or pharmacokinetic studies are required to support pediatric labeling, the size of the population or geographic dispersion would only rarely be a sufficient basis to consider trials impossible or highly impractical. Because of the speed and efficiency of modern communications tools, geographic dispersion will justify a waiver only in extraordinary circumstances and will generally have to be coupled with very small population size. FDA is not persuaded that inability to recruit patients because of parental fears associated with administration of the drug is an adequate basis to conclude that studies are impractical where there is also evidence that similar products are regularly prescribed to pediatric patients outside of clinical trials.

27. Several comments responded to the request for comment on whether cost should justify a waiver. Comments from the pediatric community argued that cost to the manufacturer should never or rarely justify a waiver. Two of these comments stated that the cost of failure to study is always higher than the cost of research. Another comment stated that cost may be a factor, but FDA must be careful not to allow studies to be waived automatically because they ''cost too much.'' Two comments from a pharmaceutical company and a pharmaceutical trade association argued that FDA should not have responsibility for assessing the costs of a study.

In light of the comments, FDA has concluded that it does not have an appropriate basis to evaluate and weigh cost in granting or declining to grant a waiver. Therefore, cost will not ordinarily be a factor in determining whether a waiver should be granted.

28. One comment claimed that the proposal lacks adequate regulatory procedures for timely processing of waiver requests and will result in a new layer of bureaucracy.

As described previously in response to comments on the deferral provisions, preliminary decisions on whether to grant waivers will be provided to the sponsor at the end of phase 1 for drugs and biologics for life-threatening diseases and at the end of phase 2 for other products. FDA does not agree that processing of waiver requests will result in a new layer of bureaucracy. The decisions will be made by the division responsible for reviewing the NDA or BLA. FDA intends to ensure that the process is timely and fair. To reduce the burden on manufacturers in applying for waivers and deferrals, FDA intends to issue a guidance document providing a format for a request for waiver or deferral.

29. One comment asked that the rule clarify that the onus is on the manufacturer to justify waivers. Another comment argued that the proposed standard for granting a waiver (''reasonable basis'') places an inadequate burden of proof on manufacturers. According to this comment, manufacturers should be required to present ''persuasive proof,'' and FDA should have to find that the grounds for waiver have ''in fact'' been met.

FDA agrees that the burden is on the manufacturer to justify waivers, but believes that the rule already adequately imposes that burden. The rule requires both a certification from the manufacturer that the grounds for waiver have been met and an adequate justification for the waiver request. FDA believes that it would be inappropriate to require ''proof'' that the grounds for waiver have ''in fact'' been met because each ground requires a degree of speculation about the safety and effectiveness of, or the ability to test, a product, in a population in which it has not yet been tested.

30. Many comments from pediatricians, disease-specific organizations, a pharmacists' organization, a medical society, several companies, a pharmaceutical trade association, and the AAP urged that the decision to require pediatric studies be reviewed by a panel of outside pediatric experts. Some of the comments recommended that the panel include industry representatives. The comments were divided on whether the panel would review only waiver requests or would be responsible for identifying, in the first instance, those drugs that need study. Some of these comments believed that the rule should include no criteria for granting waivers and that the decision should be made on a case-by-case basis in consultation with the expert panel.

As described later in this document, FDA intends to convene a panel of pediatric experts, which will include one or more industry representatives, to assist the agency in implementing this rule. FDA will bring before that panel some issues related to waivers. FDA does not believe, however, that it is reasonable to bring every product undergoing clinical studies before the panel for a decision on whether pediatric studies are required. Because many dozens of drugs and biologics reach the end of phase 1 and phase 2 each year, and the panel could not realistically meet more than once every few months, insisting that each product be brought before the panel would introduce substantial delay into the development and review of drugs and biologics. Moreover, many waiver decisions will be straightforward and noncontroversial.

FDA does, however, agree that it would be beneficial to have the advice of pediatric experts on its administration of the waiver provisions of the rule. FDA will therefore ask the panel, at least on an annual basis for the first several years, to review the agency's waiver decisions and provide advice on whether it believes that the criteria used in making those decisions were appropriate. FDA will use the advice it receives to modify future waiver decisions. FDA also expects to consult with individual members of the panel on difficult waiver decisions in their fields of expertise.

31. One comment suggested that FDA identify diseases that are not likely to occur in pediatric patients, such as prostate cancer, and classes of drugs not likely to be used in pediatric patients, and grant blanket waivers. Another comment listed the following product classes as having no applicability to pediatric patients: Alcohol abuse agents, Alzheimer's agents, Amyotrophic lateral sclerosis agents, antifibrosis therapy, antiparkinsonian agents, fertility agents, gout preparations, multiple sclerosis drugs, oral hypoglycemics, osteoporosis agents, oxytocics, tremor preparations, uterine relaxants, and vasodilators (including cerebral vasodilators).

FDA agrees that there are some disease and drug classes that have extremely limited applicability to pediatric patients and that waiver is appropriate for these. The decision to grant a waiver in such cases would be based on a conclusion that a disease does not have sufficient significance in the pediatric population (either because of frequency or severity) to constitute a meaningful therapeutic benefit for pediatric patients or to be used in a substantial number of pediatric patients. FDA emphasizes that this decision would not be intended to prevent or impede studies of these diseases or drug classes in the pediatric population, should a sponsor wish to conduct them.

The agency has identified the diseases following for which waivers will be likely to be granted. Some of the diseases listed in the comment are included in FDA's list. Others, such as osteoporosis, gout, multiple sclerosis, and tremors can develop in children, and are not included in FDA's list. Waiver decisions on products for the listed diseases are expected to be straightforward and noncontroversial. FDA may add to or revise this list in the future by issuing guidance documents. An applicant who wishes to obtain a waiver because the product is indicated for a disease on the list may refer in the waiver request to this **Federal Register** notice, or to any guidance document modifying this notice. FDA's list follows:

1. Alzheimer's disease.
2. Age-related macular degeneration.
3. Prostate cancer.
4. Breast cancer.
5. Non-germ cell ovarian cancer.
6. Renal cell cancer.
7. Hairy cell Leukemia.
8. Uterine cancer.
9. Lung cancer.
10. Squamous cell cancers of the oropharynx.
11. Pancreatic cancer.
12. Colorectal cancer.
13. Basal cell and squamous cell cancer.
14. Endometrial cancer.
15. Osteoarthritis.
16. Parkinson's disease.
17. Amyotrophic lateral sclerosis.
18. Arteriosclerosis.
19. Infertility.
20. Symptoms of the menopause.

F. Pediatric Use Section of Application

FDA proposed to add § 314.50(d)(7), under which applicants would be required to include in their applications a section summarizing and analyzing the data supporting pediatric use information for the indications being sought. FDA received no comments on this provision. The new pediatric use section will be required to contain only brief summaries of the studies together with a reference to the full description of each provided elsewhere in the application.

G. Planning and Tracking Pediatric Studies

1. Sections 312.23(a)(3)(v), 312.47 (b)(1)(i), (b)(1)(iv) and (b)(2), and 312.82—Early Discussion of Plans for Pediatric Studies

In the proposal, FDA identified several critical points in the drug development process, before submission of an NDA or BLA, during which the sponsor and FDA should focus on the sponsor's plans to assess pediatric safety and effectiveness. These time points include: Any pre-IND meeting or ''end-of-phase 1'' meeting for a drug designated under subpart E of part 312 (21 CFR part 312), the IND submission, the IND annual report, any ''end-of-phase 2'' meeting, the presentation of the IND to an FDA drug advisory committee, and any pre-NDA or pre-BLA meeting. Of these, the pre-IND meeting, the ''end-of-phase 1'' meeting, the IND submission, the IND annual report, the ''end-of-phase 2'' meeting, and the pre-NDA/pre-BLA meeting are codified in part 312, FDA's regulations governing IND's.

In a separate rulemaking, FDA has already amended the IND annual report requirement to include discussion of pediatric patients entered in trials (63 FR 6854, February 11, 1998). In the proposal, FDA proposed to amend §§ 312.23(a)(3)(v), 312.47 (b)(1)(i) and (b)(2), and 312.82 (a) and (b) to specify that these meetings and reports should include discussion of the assessment of pediatric safety and effectiveness. To assist manufacturers in planning for studies that may be required under this proposal, FDA also proposed to inform manufacturers, at the ''end-of-phase 2'' meeting, of the agency's best judgment, at that time, of whether pediatric studies would be required for the product and when any such studies should be submitted. The proposal also stated that, in addition to the discussions of pediatric testing codified in the proposal, FDA would assist manufacturers by providing early consultations on chemistry and formulation issues raised by requirements under this rule.

Because, as described previously, studies of drugs and biologics for life-threatening diseases may begin as early as the end of phase 1, FDA will, at the end-of-phase 1 meeting, provide the sponsor of such a product the agency's best judgment, at that time, whether pediatric studies will be waived or deferred. Section 312.82(b) has been revised to include this requirement. Because studies of other products may begin as early as the end of phase 2, FDA will, at the end-of-phase 2 meeting, provide the agency's best judgment, at that time, whether waiver or deferral is appropriate. Although a formal request for deferral or waiver is not required until submission of the NDA or BLA, FDA has revised § 312.47(b)(1)(iv) to state that a manufacturer who plans to seek a waiver or deferral should provide information related to the waiver or deferral in the advance submission required before the end-of-phase 1 or end-of-phase 2 meeting, as appropriate.

As described earlier, a pediatric study required under this rule may be eligible for exclusivity under FDAMA, if such study ''meets the completeness, timeliness, and other requirements of [section 505A].'' (See 21 U.S.C. 355A(i).) Among other requirements, a pediatric study must, to be eligible for exclusivity, be responsive to a written request for the study from FDA. To obtain a written request, a manufacturer may submit a proposed written request to FDA that contains the information described in a guidance document issued by FDA entitled, ''Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act.'' A manufacturer who has been told in the end-of-phase 1 or end-of-phase 2 meeting that it is FDA's best judgment at that time that it does not intend to waive the study requirement may submit a proposed written request at any time thereafter. FDA will issue a written request for a study required under this rule promptly after an adequate proposed written request is submitted.

FDA also sought comment on the types of evidence that FDA should examine to ensure that deferred pediatric studies are carried out in a timely fashion. In response to comments, FDA has revised §§ 312.47 (b)(1)(iv) and (b)(2) to require submission of information about planned and ongoing pediatric studies.

32. One comment supported the proposed provisions and the need for early consultation with sponsors, stating that discussions should take place as early as possible in drug development. The comment urged that proposed § 312.47(b)(1) be revised to acknowledge the possibility that studies could already be underway.

FDA agrees with this comment and has revised § 312.47(b)(1) as suggested in the comment.

33. Several comments provided suggestions on how to assure that deferred studies are carried out expeditiously. One comment urged that the criteria to ensure deferred studies are carried out in a timely fashion be modeled on the AIDS Clinical Trials Group (ACTG) system of National Institute of Allergy and Infectious Diseases (NIAID). Another comment recommended that evidence demonstrating that the required studies were underway be submitted to FDA within 6 months of approval. This comment suggested that the evidence should include: (1) A finalized protocol, (2) evidence of sufficient entry of patients to address the objective of the protocol, and (3) a time line for data analysis and submission to FDA. Another comment argued that the burden should be on manufacturers to provide evidence that studies are being conducted with due diligence through submission of protocols, progress reports and certifications by researchers. To hold manufacturers accountable, this comment suggested that nonproprietary information related to deferrals be made available to the public, including deferral requests, FDA action, postmarketing status reports, and the time line for deferred studies. One comment argued that FDA's current procedures are adequate to track the timeliness of pediatric studies. A pharmaceutical trade association argued that FDA should institute an adequate tracking system and meet periodically with the sponsor to discuss the progress of the studies, but that no new rules are needed.

FDA agrees that an adequate system for ensuring that studies, both deferred and nondeferred, are carried out in a timely manner requires the submission of plans and progress reports from the sponsor at defined intervals. As described previously, FDA will provide sponsors with a preliminary decision on whether pediatric studies will be required and their timing at the end-of-phase 1 meeting, for drugs and biologics for life-threatening diseases, and at the end-of-phase 2 meeting, for other products. FDA has revised § 312.47(b)(1)(iv) to state that sponsors should submit, in the advance submission for the end-of-Phase 2 meeting, a proposed time line for protocol finalization, enrollment, completion, data analysis, and submission of pediatric studies, or, in the alternative, information to support a planned request for waiver or deferral. For drugs and biologics for life-threatening diseases, the submission should be made in advance of the end-of-Phase 1 meeting. FDA has also revised § 312.47(b)(2)(iii) to state that sponsors should submit, in the submission in advance of the pre-NDA or pre-BLA meeting, information on the status of needed and ongoing pediatric studies. The proposed language of § 312.47 has been slightly modified to

seek information on ''needed'' and ongoing studies rather than ''planned'' and ongoing studies. This change has been made because not every sponsor elects to have an end-of-phase 1 or end-of-phase 2 meeting. In those cases, the need for a pediatric study may be discussed for the first time at the pre-NDA or pre-BLA meeting. FDA has also revised the title of § 312.47(b)(2) from '' 'Pre-NDA' meetings'' to '' 'Pre-NDA' and 'pre-BLA' meetings.'' This is merely a clarification, because part 312 is expressly applicable to products subject to the licensing provisions of the Public Health Service Act, as well to products subject to section 505 of the act and 21 CFR 312.2(a).

2. Sections 314.81(b)(2) and 601.37—Postmarketing Reports

To permit FDA to monitor the conduct of postapproval studies to ensure that they are carried out with due diligence, FDA proposed to amend § 314.81(b)(2) of the postmarketing report requirements to require applicants to include in their annual reports: (1) A summary briefly stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated; (2) where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population; (3) an analysis of available safety and efficacy data in the pediatric population and changes proposed in the label based on this information; (4) an assessment of data needed to ensure appropriate labeling for the pediatric population; and (5) whether the sponsor has been required to conduct postmarket pediatric studies and, if so, a report on the status of those studies. (Additional postmarketing reporting requirements are described under ''Remedies'' in section III.L of this document.) Although the proposal was intended to cover both drugs and biological products, the proposal inadvertently omitted a postmarketing reports requirement specifically applicable to biological products. In the final rule, FDA has corrected this oversight and included an identical postmarketing reports requirement in § 601.37.

FDA notes that FDAMA includes a provision requiring reports of postmarketing studies in a form prescribed by the Secretary of Health and Human Services (the Secretary) in regulations. (Section 506 of the act (21 U.S.C. 356B).) At such time as regulations implementing this provision are issued, FDA may modify or withdraw §§ 314.81(b)(2) and 601.37 for consistency with the implementing regulations.

34. Three comments from the pharmaceutical industry agreed that it was appropriate to require postmarketing reports on the progress of postapproval pediatric studies. One comment argued, however, that collection of this information along with an adequate system to track pediatric studies could preclude the need to finalize the rule. Another comment argued that the required analyses of pediatric data ''may lead to exposure of a larger number of children to an unapproved product.'' This comment also contended that estimates of patient exposure are difficult to obtain and unreliable.

FDA disagrees that postmarket reports and a tracking system are an adequate means of assuring that drugs and biologics are appropriately labeled for pediatric use. As shown above, even postmarket commitments to conduct pediatric studies have infrequently resulted in pediatric labeling submissions. FDA also disagrees that the analyses required under § 314.81(b)(2) require exposure of any new patients. The analyses referred to in the provision are of already collected data. Finally, the rule requires estimates of patient exposure ''where possible.'' If there are no data on which to make such estimates, the estimates are not required. FDA notes, however, that there are commercial data bases designed to estimate use of marketed drugs.

35. One comment argued that FDA should require postmarket surveillance of approved drugs that do not have pediatric labeling, to generate helpful comparative information and provide additional information useful for analysis of adverse event profiles.

The provisions of the final rule require manufacturers of approved drugs without pediatric labeling to conduct postmarket surveillance on their products and provide an analysis of available safety and efficacy data in the pediatric population.

H. Studies in Different Pediatric Age Groups

Because the pharmacokinetics and pharmacodynamics of a drug or biological product may be different in different pediatric age groups or stages of development, FDA proposed to require an assessment of safety and effectiveness in each pediatric age group for which a waiver was not granted. The following age categories for the pediatric population were distinguished in the proposal: (1) Neonates (birth to 1 month); (2) infants (1 month to 2 years); (3) children (2 years to 12 years), and (4) adolescents (12 years to 16 years). The proposal stated that the need for studies in more than one age group would depend on whether the drug or biological product was likely to be used or offered meaningful therapeutic benefit in each age group (see ''Waivers'' section III.E of this document), the metabolism and elimination of the drug, and whether safety and effectiveness in one age group could be extrapolated to other age groups. The proposal further stated that it would not ordinarily be necessary to establish effectiveness in each age group, but there would generally need to be pharmacokinetic data in each group to allow dosing adjustments. The proposal recognized that studies in neonates and young infants present special problems, and sought comment on whether it is appropriate to require the assessment of safety and effectiveness in this age group.

36. Several comments addressed the requirement that all relevant age groups be studied. Some comments opposed studies in more than one age group. One comment contended that requiring safety data in each pediatric group may place an unnecessary burden on the sponsor, and that FDA should require safety data only in one group, presumably that with the highest potential use. Another comment claimed that requiring studies in all four age groups would almost never be justified. In most cases, according to this comment, it should be possible to study a single subgroup and extrapolate. Other comments argued that studies in more than one age group could be necessary depending on the pharmacokinetics of the drug, the disease, and expected use of the drug. Most of these comments stated that the type and extent of studies in different age groups must be decided on a case-by-case basis. Several comments contended that drugs should be studied in each age group in which they are expected to be used. One comment stated that studies in toddlers are especially needed. A comment from an organization devoted to pediatric AIDS argued that all age groups should be studied unless the manufacturer provides compelling evidence that it would be impossible or virtually impossible to study that group.

FDA continues to believe that studies in more than one age group may be necessary, depending on expected therapeutic benefit and use in each age group, and on whether data from one age group can be extrapolated to other age groups.

37. Many comments argued that the pediatric subgroups identified in the proposal were arbitrary and that FDA should be flexible in determining which age ranges or stages of development need to be studied. A comment from a pharmaceutical trade association contended that rigid age divisions for required studies were inappropriate, and that the method by which the compound is cleared from the body must be considered in light of what is known about physical development. The AAP stated that the groups identified in the proposal provide acceptable guidelines, but should not be adhered to rigidly. One comment argued that the definition of pediatric patients should include all subgroups of growth and development from 0 to 21 years.

FDA agrees that the age ranges identified in the proposal may be inappropriate in some instances and that it will be reasonable in some cases to define subgroups for study using other methods, such as stage of development. FDA has deleted the references in the rule to specific age ranges.

38. Several comments addressed inclusion of neonates in studies. One comment maintained that because neonates are a special challenge, they should not ordinarily be included in studies under this rule. Another comment described the difficulties in conducting studies in infants and neonates and recommended that before studies in this group there be an assessment of ''the expected extent of use and potential benefit in this patient population'' and an evaluation of safety data in adults and older pediatric patients. One comment contended that there are not many instances in which the benefit will outweigh the risk of exposing neonates and young infants to drugs. This and another comment also argued that it is not always possible to extrapolate from data in older pediatric patients. A pharmaceutical trade association maintained that validated end-points and ability to assess these by age should determine which age groups to include, and that it may not be possible to study certain end-points in very young pediatric patients. One comment argued that early research on neonates raises special ethical issues. Citing the 1977 FDA guideline, this comment asserted that testing in neonates should occur only when substantial evidence of benefit or superiority over accepted agents has been demonstrated in older pediatric patients and adults.

Other comments argued that neonates should not be excluded from studies. According to one comment, study designs will be appropriate and necessary ethical issues will be addressed if neonatologists are included in the review of studies. Another comment stated that neonates represent the greatest disparity in drug disposition compared to adults, and that, on a scientific and ethical basis, they must therefore be included in drug studies. The AAP stated that premature infants, newborns, and infants are more difficult to study, but that the difficulties do not outweigh the importance of studying them. According to this comment, inadequate study of neonates has led to frequent and severe toxicity. This comment agreed that it is inappropriate to extrapolate from older pediatric patients to the youngest age group.

FDA agrees that the benefits and risks to premature infants, neonates, and infants must be carefully weighed before these pediatric patients are included in pediatric studies. Although the agency believes that studies in these groups may be frequently waived or deferred until adequate safety data have been collected, there will be cases in which the drug or biologic is important and expected to be used in these groups. In such cases, it will be appropriate to require studies in these groups. To exclude them from study would be to subject the most vulnerable patients to the risks of the drugs in clinical use without adequate information about safety or dosing. FDA agrees that studies in neonates and young infants raise special ethical issues, but once these issues are addressed in each case, the studies should proceed.

I. Pediatric Formulations

As described in the proposal, testing of a product in pediatric patients could require the development of a pediatric formulation. Many young children are unable to swallow pills and may require a liquid, chewable or injectable form of the product. A standardized pediatric formulation also ensures bioavailability and consistency of dosing, compared to alternatives such as mixing ground-up tablets with food, and permits meaningful testing of safety and effectiveness. FDA proposed in §§ 201.23, 314.50(g)(1) (now 314.55(a)) and 601.27(a) to require a manufacturer to produce a pediatric formulation, if one were necessary, only in those cases where a new drug or new biological product provided a meaningful therapeutic benefit over existing treatments, and where the study requirement had not been waived in the age group requiring the pediatric formulation. The proposal recognized that the difficulty and cost of producing a pediatric formulation may vary greatly depending upon such factors as solubility of the compound and taste. FDA proposed to waive the requirement for pediatric studies (see ''Waivers'' in section III.E of this document) in age groups requiring a pediatric formulation, if the manufacturer provided evidence that reasonable attempts to produce a pediatric formulation had failed.

FDA sought comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation, on whether the cost of developing a pediatric formulation should ever justify a waiver of the pediatric study requirement, and on how to define ''reasonable attempts'' to develop a pediatric formulation.

39. Many comments from the pediatric community argued that it is appropriate to require manufacturers to produce pediatric formulations. Several comments from pediatricians and parents described the difficulties and uncertainties in attempting to administer adult formulations to pediatric patients, and argued that pediatric formulations are essential to assure bioavailability, accurate dosing, and patient compliance, and to avoid wasting medications. The AAP argued that FDA should require development of an appropriate formulation for each age group for which the drug will be used, taking into account ease of administration and ability to dose accurately.

Comments from the pharmaceutical industry described technical problems in producing pediatric formulations, including stability, taste and palatability, and claimed that FDA underestimated these difficulties. Some of these comments maintained that requiring development of pediatric formulations during the investigational phase will necessitate diversion of resources, increase the cost of the adult formulation, and create a disincentive to produce drugs with pediatric uses. One comment argued that it would be wasteful to require development of a pediatric formulation before some evidence of effectiveness has been collected and dose selection has been achieved, because before that time the drug could be abandoned because of lack of safety or effectiveness. A pharmaceutical trade association opposed a pediatric formulation requirement, arguing that the government has no right to tell manufacturers what products to market. This comment stated that only if FDA successfully demonstrated that ''all attempts to develop a voluntary solution have failed'' might the industry consider other options. One comment stated that

a single drug could require more than one pediatric formulation for different pediatric age group, such as a chewable tablet, a nonalcohol containing liquid, and sprinkles. Counting failed attempts, this comment claimed that producing a pediatric formulations may cost millions of dollars.

FDA believes that for drugs and biologics that offer a meaningful therapeutic benefit to pediatric patients, it is essential to provide pediatric formulations that ensure bioavailability and accurate dosing. FDA disagrees that it is inappropriate for the government to require manufacturers to produce pediatric formulations. As many comments demonstrated, adult formulations of these drugs are frequently used in pediatric patients because there is no other choice. Drug manufacturers profit from these uses, but do not take responsibility for them. Where a product is commonly being used in a subpopulation for an indication recommended by the manufacturer, it is appropriate to require the manufacturer to take steps to ensure that the use is safe and effective.

FDA agrees that producing a pediatric formulation can be difficult or, rarely, impossible and has attempted to account for this problem by permitting waiver of the pediatric study requirement where reasonable attempts to produce a pediatric formulation have failed. FDA notes that the pharmaceutical industry did not respond to FDA's request to help define what should constitute such ''reasonable attempts.''

To permit pediatric studies that may begin, for products for life-threatening diseases, at the end of phase 1, or, for other products, at the end of phase 2, it may be necessary to begin development of a pediatric formulation before initiation of clinical trials. FDA does not agree that it is wasteful to begin development of a pediatric formulation at this stage. This rule is premised on the view that for drugs and biologics that will have important use in pediatric patients, it is the responsibility of the manufacturer to ensure that use is safe and effective. Although some such products may ultimately prove to be unsafe or ineffective, work on pediatric formulations of such products is not necessarily more wasteful than work on adult formulations. FDA does not agree that manufacturers will be required to develop several pediatric formulations for different age groups. Even for a drug that was to be used in all pediatric age groups, a liquid formulation, e.g., might be usable in all age groups.

FDA has no basis to conclude that producing pediatric formulations will increase the cost of adult formulations or create disincentives for producing drugs and biologics with pediatric uses. No evidence was submitted to support either of these assertions.

40. Several comments discussed how to define ''reasonable attempts'' to produce a pediatric formulation. The AAP argued that difficulty in producing a pediatric formulation should be a basis for waiver only if the sponsor provides data showing that formulation experts encountered insurmountable problems of solubility, stability, compatibility, or palatability using accepted methods, and that cost be given only limited consideration. The AAP urged that such an assertion be corroborated by a panel of pediatric experts and FDA as well as formulation experts. Another comment agreed that formulations appropriate for younger age groups should be developed unless the manufacturer shows it would be virtually impossible. This comment argued that if a manufacturer wants to show that the cost is prohibitive, it should provide information allowing the financial and other costs of development to be seen in terms of the entire drug development process. Another comment argued that waivers should not be based on whether reasonable efforts to develop a pediatric formulation have failed because this ground for a waiver would permit small companies to avoid producing pediatric formulations on cost grounds. This comment urged that waivers be allowed only if a pediatric formulation cannot be produced for scientific or technological reasons. One comment argued that even if producing a pediatric formulation is impossible, the manufacturer should be required to study the adult formulation in pediatric patients, because it will be used in pediatric patients.

One industry comment urged that the decision to require a pediatric formulation be made on a case-by-case basis. Another comment argued that pediatric formulations should be required only if a panel of pediatric experts concludes that there is a genuine pediatric need and substantial benefit.

FDA agrees that the burden should be on the manufacturer to provide evidence that experts in formulation chemistry had encountered unusually difficult technological problems in the development of a pediatric formulation. In determining whether those problems were sufficiently severe to warrant a waiver of pediatric studies, FDA will consider the potential importance of the product for pediatric patients. The more important the product, the more efforts should be made to develop a pediatric formulation. FDA will also, at its discretion, take to the Advisory Committee for Pharmaceutical Sciences questions about whether ''reasonable attempts'' have been made to produce pediatric formulations in particular cases. Although FDA believes that it is appropriate to consider the cost to the manufacturer in determining whether attempts to produce a pediatric formulation have been reasonable, the agency received no helpful guidance on how to assess whether the costs of producing a pediatric formulation were unreasonable. In addition to any informative cost information provided by the manufacturer, FDA will take into account whether a product is still under patent or exclusivity protection. FDA will assume that manufacturers can incur greater costs for products that have significant patent life or exclusivity remaining.

41. One comment contended that FDA chemistry requirements have increased over the last 10 years. Another comment urged that FDA be more flexible in its review of formulations, e.g., by permitting generally recognized as safe (GRAS) substances in pediatric formulations.

FDA recently held a conference on pediatric formulations at which the agency sought input from industry on identifying the regulatory issues that affect the development of pediatric formulations for both new and approved marketed drugs. At this meeting, FDA also requested proposals for solutions to facilitate the development and approval of pediatric formulations. FDA is committed to removing unnecessary burdens on the review and approval of pediatric formulations.

42. Two comments urged manufacturers to provide formulas in product labeling for extemporaneous pediatric formulations made by pharmacists. These comments stated that the current practice among hospital pharmacies is to use unvalidated formulas, resulting in a lack of consistency from one hospital to another, no stability testing, and, in some cases, reluctance to produce pediatric formulations at all because of the lack of guidance. One comment stated that information on extemporaneous formulations should be provided only where: (1) A commercial formulation is not possible or (2) the drug has extremely limited use in pediatric patients.

FDA is concerned that the availability of this approach may undermine efforts to produce standardized pediatric formulations. There are, however, one or two examples in which approved labeling carries directions for producing

extemporaneous pediatric formulations. FDA will consider, on a case-by-case basis whether such an approach is appropriate, e.g., where it has not been possible to develop a stable commercial formulation.

J. Marketed Drug and Biological Products

FDA proposed in § 201.23 to codify its authority to require, in certain circumstances, a manufacturer of a marketed drug or biological product to submit an application containing data evaluating the safety and effectiveness of the product in pediatric populations. FDA proposed to impose such a requirement only where the agency made one of two findings: (1) That the product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the product was indicated for a very significant or life-threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Before requiring a study under this section, FDA proposed to consult with the manufacturer on the type of studies needed and on the length of time necessary to complete them, and would notify the manufacturer, by letter, of the agency's tentative conclusion that such a study was needed and provide the manufacturer an opportunity to provide a written response and to have a meeting with the agency. At the agency's discretion, such a meeting could be an advisory committee meeting. If, after reviewing any written response and conducting any requested meeting, FDA determined that additional pediatric use information was necessary, FDA proposed to issue an order requiring the manufacturer to submit a supplemental application containing pediatric safety and effectiveness data within a specified time. The proposal referred to the order in one place as a letter. FDA has clarified the final rule by stating that the manufacturer will receive ''an order, in the form of a letter.'' A few other minor clarifying revisions have also been made in this section.

FDA sought comment on whether it should codify its authority to require the manufacturers of marketed drugs and biologics to conduct pediatric studies, and, if so, on the circumstances in which the agency should exercise that authority.

43. Many comments from the pediatric community agreed that FDA should codify its authority to require pediatric studies on marketed drugs. Several comments from the pharmaceutical industry argued that FDA lacked authority to require studies of marketed drugs and that the 1994 rule sufficiently addressed pediatric labeling for marketed drugs. Some comments argued that adding pediatric labeling for indications applicable to pediatric patients should be at the sponsor's discretion. Others claimed that incentives are better than requirements. One comment contended that the proposed requirement forces manufacturers ''to take on unwanted liabilities in order to maintain an asset which was created and earned under a different set of rules.'' Other comments maintained that companies should not be required to conduct new studies, and that pediatric labeling should be based on existing data, such as marketing experience and dosing regimens generally accepted by experts. A comment from a pharmaceutical trade association argued that studies should not be required but that FDA should work with industry and others to ''develop creative ways to obtain the needed labeling information'' for marketed drugs.

FDA believes that it has ample authority to require pediatric studies of marketed drugs and biologics, as described in the preamble to the 1994 rule (59 FR 64240 at 64243) and in ''Legal Authority'' section IV of this document. FDA has also concluded, as described previously, that the response to the 1994 rule and other voluntary measures have not produced a significant improvement in pediatric labeling for many marketed drugs and biologics. In addition, as one pharmaceutical company conceded, manufacturers are unlikely to initiate clinical research on marketed drugs whose patents have expired, or are about to expire. FDA has therefore concluded that where pediatric information is critical to patient care, it is necessary to require that pediatric studies be carried out. FDA notes that new requirements are sometimes imposed on already marketed consumer products when such requirements are necessary to protect the public health. FDA emphasizes, however, that it will require studies of marketed products only in the compelling circumstances described in the regulation.

44. FDA received many comments on the grounds for requiring studies of marketed products. Comments from medical societies, pediatricians, and disease-specific organizations argued that the proposed grounds were too narrow. One comment stated that pediatric studies should be required of any marketed drug that is likely to be used in pediatric patients. Several comments argued that the phrase ''very significant illness'' was ill-defined. One comment stated that it was ''so open-ended and subjective as to be impossible for use as a regulatory standard.'' Another comment suggested that any definition of ''very significant illness'' would be arbitrary and overbroad. Several comments urged that the same criteria that are applied to not-yet-approved drugs be applied to marketed drugs. One of these comments argued that even if the criteria remain as proposed, ''widely used'' and ''significant risk'' should be defined in terms of the severity of the illness. According to this comment, if the consequences of no treatment are serious, the absence of labeling should be more readily found to present a significant risk. One industry comment maintained that the requirement should apply to marketed drugs only where there is a ''compelling need'' for pediatric data. One comment argued that the requirement should apply to all marketed drugs unless an expert panel concluded that studies were not required, while other comments urged that FDA utilize an expert panel to affirmatively identify and prioritize marketed drugs that should be studied in pediatric patients. Some of these comments suggested that there be no criteria and that the panel should determine which drugs should be studied on a case-by-case basis. One comment suggested that the list should be prioritized using the number of pediatric prescriptions.

FDA believes that criteria are necessary to assure consistency and fairness in deciding which marketed drugs and biologics are studied. FDA has reviewed the grounds for requiring pediatric studies of marketed drugs and biologics and has revised them in light of the comments. FDA has concluded that the phrase ''very significant illness'' is not sufficiently defined and agrees that it would be less confusing to use the same concepts that are used in defining which new products will be subject to the pediatric study requirement. FDA has therefore replaced the concept of ''very significant illness'' and replaced it with ''meaningful therapeutic benefit.'' However, to ensure that this authority is reserved for cases in which there is a compelling need for studies, FDA has added the requirement (already present in the first criterion) that FDA also find that the absence of adequate labeling could pose significant risks for pediatric patients. The second criterion will now read:

* * * there is reason to believe that the drug product would represent a meaningful therapeutic benefit over existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

FDA has also revised the first criterion to conform more closely to the criteria for requiring studies in not-yet-approved drugs and biologics, replacing ''widely used'' with ''used in a substantial number of pediatric patients.'' FDA will use the same definition of ''substantial number'' for both marketed and not-yet-approved drugs and biologics. The first criterion will, however, continue to include the requirement that ''the absence of adequate labeling could pose significant risks to patients.'' FDA believes that the pediatric study requirement may impose greater burdens on the manufacturers of marketed drugs and biologics than the manufacturers of not-yet-approved products, and that it is appropriate to require such studies only in the compelling circumstances described in the regulation. In determining which marketed products ''could pose significant risks to patients,'' FDA will consider such factors as the severity of the illness and the consequences of inadequate treatment, the number of pediatric prescriptions, and any available information on adverse events associated with use of the product.

FDA emphasizes that it intends to exercise its authority under § 201.23 only in compelling circumstances. FDA has estimated that it will require studies of approximately two marketed drugs per year.

FDA agrees that an expert panel can provide useful experience and guidance in developing a prioritized list of marketed drugs and biologics that meet the criteria for required studies. FDA intends to seek advice on developing such a list from a pediatric panel, as described in section III.M of this document (''Pediatric Committee'').

FDA also notes that FDAMA requires the agency to publish a list of marketed drugs for which ''additional pediatric information may produce health benefits in the pediatric population.'' FDA published this list within 180 days of the enactment of FDAMA, as required by that statute. Although the products on the list designated as high priority may be appropriate candidates for required studies under this rule, the list of high priority products is not necessarily exhaustive. Other products that might be subject to a requirement under this rule might not appear on the list. FDA also emphasizes that there is no implication that the agency will require studies of any particular product on the list. As noted in the Introduction to this preamble, before imposing any requirements under § 201.23, FDA intends to allow manufacturers eligible for FDAMA incentives an adequate opportunity to voluntarily conduct studies of marketed drugs in response to those incentives. If, following such an opportunity, there remain marketed drugs for which studies are needed and the compelling circumstances described in the rule are met, the agency will consider exercising its authority to require studies.

45. One comment claimed that the proposal requires studies only from manufacturers of innovator drugs (sponsors of the original application for the drug), while the major market share for many of these drugs is now held by generic manufacturers. This comment argued that a waiver should be granted if ANDA holders fail to share the costs of required studies. Another comment argued that the pediatric study requirement should apply only to the sponsor of the original application.

Where the agency requires pediatric studies on a multi-source marketed drug, each manufacturer of that drug, whether innovator or generic, will be responsible for satisfying the study requirement. To avoid duplication of research, FDA will encourage all the manufacturers to jointly fund an appropriate study. If, however, a joint study is not agreed to, each manufacturer will be responsible for submitting adequate studies.

K. Ethical Issues

In the proposal, FDA noted that because pediatric patients represent a vulnerable population, special protections are needed to protect their rights and to shield them from undue risk. To address ethical concerns in research on pediatric patients, both the AAP (Ref. 17) and the Department of Health and Human Services (DHHS), 45 CFR part 46, subpart D, have developed guidelines for the ethical conduct of clinical studies in pediatric patients. FDA advised in the proposal that sponsors should adhere to these guidelines for pediatric studies conducted under this rule. The agency also sought comment on ethical issues raised by the proposal.

46. A few comments addressed appropriate ethical guidelines for pediatric studies. Several comments said that existing ethical guidelines provide an adequate framework for pediatric studies. A comment from the AAP stated that ethical conduct should be guided by the DHHS and AAP guidelines, and that IRB approval that explicitly ensures protection of vulnerable subjects should be obtained. This comment also stated that the AAP guidelines provide a means to ensure ethical conduct of studies without impeding pediatric research. One comment said that DHHS ethics regulations may not provide sufficient protection for pediatric patients and suggested incorporating AAP guidelines for ethical conduct of pediatric studies into FDA's human subjects protections regulations. Another comment contended that pediatric studies should strictly adhere to regulations currently in effect for studies of human subjects who are unable to give consent, and urged FDA to further define requirements for investigation in vulnerable populations.

FDA believes that adherence to the DHHS and AAP guidelines will provide sufficient protection to pediatric patients from the risks of research. FDA will, however, seek advice from a panel of pediatric experts on whether additional protections are necessary.

47. Several comments addressed the ethics of requiring pediatric studies as described in the proposal. Two comments asserted that children are overmedicated and that administering drugs to children is unacceptable and ''ungodly.'' Comments from the pharmaceutical industry claimed that the rule as drafted would result in unethical testing of pediatric patients. One comment maintained that the regulations do not adequately protect pediatric patients from the risks of research because they impose a ''general rule that a deferral of testing in pediatrics will only be granted in narrow and limited circumstances.''

In contrast, comments from the pediatric community maintained that far more serious ethical concerns are raised by using untested drugs in pediatric patients than by conducting pediatric research. A comment from the AAP stated that there is no greater ethical dilemma than whether to give a drug with insufficient safety and effectiveness data to a child, or to withhold treatment and let the disease progress unabated.

Some comments suggested specific points in drug development at which pediatric testing becomes ethical. One comment argued that testing in pediatric patients before efficacy is demonstrated in adults may unnecessarily expose pediatric patients to a product's risks before its benefits are established. Another comment contended that it is unethical to begin studying drugs in pediatric patients that are not intended primarily for pediatric patients until the drug is adequately characterized in

adult patients, including choice of appropriate adult dose and establishment of reasonable evidence of safety and efficacy with an acceptable therapeutic margin. A pharmaceutical trade association argued that it is unethical to begin trials in pediatric patients until enough adult safety and effectiveness data have been gathered to conclude that the drug ''is likely to be approved for use in adults.''

FDA believes that some of the comments from the pharmaceutical industry misstate the application of the rule. As described fully previously, deferral of pediatric studies is specifically permitted in those cases where data should be collected in adults before exposing pediatric patients to the agent. There is no suggestion in either the proposed or final rule that deferral will be granted only in ''narrow and limited circumstances.'' FDA believes that, as drafted, the deferral provisions of the rule permit ethical pediatric testing that does not expose pediatric patients to inappropriate risks.

48. A few comments urged that placebo-controlled trials in pediatric patients be used rarely if at all. The AAP stated that placebo controls should not be used where that design would impose a substantial increase in risk to the child or would impede the ability to perform useful clinical trials. This comment urged that alternatives to placebo controls be used wherever possible and that where placebo controls are used, the study design should incorporate safeguards to avoid undue risk.

The question of appropriate control group arises only when there is a need for controlled trials to establish efficacy in the pediatric population. FDA agrees that alternatives to placebo-controlled trials should be used wherever they can provide sufficient information to establish effectiveness. FDA often accepts data from active control studies for certain therapeutic classes, such as anti-infectives and oncologic drugs. (See 21 CFR 314.126.) In some cases, new treatments can also be studied against a placebo together with a background of existing therapy, i.e., studied in ''add-on'' trials.

49. One comment argued that parents should not be given money or equivalent compensation for participation in drug studies. This comment suggested that any compensation could be put in the child's IRA.

The IRB overseeing a research study, rather than FDA, is responsible for determining whether compensation offered to the subjects of the study is ethically appropriate.

L. Remedies

If a manufacturer failed, in the time allowed, to submit adequate studies to evaluate pediatric safety and effectiveness required under proposed § 201.23(c) or § 314.55 (proposed § 314.50(g)), FDA proposed to consider the product misbranded under section 502 of the act or an unapproved new drug under section 505(a) of the act (see ''Legal Authority,'' in section IV of this document). Although proposed § 201.23 expressly covered both drugs and biologics, FDA inadvertently omitted in that section a reference to actions against biologics that have not obtained a license under section 351 of the Public Health Service Act. Such a reference has been added in the final rule. When a product is misbranded or an unapproved new drug, sections 302, 303, and 304 of the act (21 U.S.C. 332, 333, 334) authorize injunction, prosecution or seizure. FDA may also seek an injunction or bring a prosecution under the Public Health Service Act. In the proposal, FDA advised that it would bring an enforcement action for injunctive relief for failure to submit a required assessment of pediatric safety or effectiveness. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines. As noted in the proposal, FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies, except possibly in rare circumstances, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product. Such circumstances might arise where the predominant use of the product was in pediatric patients rather than adults, and there were life-threatening risks associated with use of the product in pediatric patients when used without proper dosing and safety information in the labeling.

To assist FDA in determining whether pediatric assessments are needed or are being carried out with due diligence, FDA proposed to amend § 314.81(b)(2) (21 CFR 314.81(b)(2)) (annual postmarketing reports) to require that annual reports filed by the manufacturer contain information on labeling changes that have been initiated in response to new pediatric data, analysis of clinical data that have been gathered on pediatric use, assessment of data needed to ensure appropriate labeling for the pediatric population, and information on the status of ongoing pediatric studies. FDA also proposed to require that, where possible, the annual report contain an estimate of patient exposure to the drug product, with special reference to the pediatric population.

50. Several comments agreed with the agency that withdrawal or denial of approval is infeasible and supported the use of injunctive remedies. One comment argued that if FDA provides no incentives, disincentives to avoid pediatric trials must be strong, and that withdrawal and denial of approval must therefore be used as a remedy.

FDA continues to believe that refusal to approve or removal from the market is generally an unsatisfactory remedy from a public health perspective because it denies adequately studied populations access to safe and effective medicines.

51. Several comments supported the imposition of monetary fines. One comment urged that fines be imposed in the amount of a percentage of the profits to ensure that large and small companies had an equal disincentive. Several comments argued that fines should be used by FDA to fund pediatric studies carried out by government or private agencies. One comment contended that monetary penalties, such as fines or shortening of exclusivity, are the only practical remedy because industry and government are economically driven, but that injunctions are too costly.

Although FDA continues to believe that court-imposed fines are an appropriate remedy for failure to submit pediatric assessments, the agency has no authority itself to impose fines for violation of this rule, to set the amount of such fines, or to take the fines and direct them to specific activities.

52. Two comments opposed treating violative products as ''misbranded'' because this could limit access to the drugs or could delay availability of the products for adult use. According to one comment, FDA should consider a misbranding charge only if the sponsor failed to meet a phase 4 commitment. Another comment argued that injunction or prosecution are appropriate only as a final response, and that other, unspecified means are more efficient to elicit compliance. This comment also argued that seizure would serve only to deprive patients of safe and effective drugs.

The comments arguing that a misbranding charge could limit access or delay approval provided no basis for concluding that these results would occur, and FDA is aware of none. FDA agrees that injunction and prosecution are appropriate remedies only after the sponsor has been given an adequate opportunity to meet its obligations under the rule. FDA emphasizes, however, that providing adequate

pediatric labeling cannot be long-delayed without putting the health of pediatric patients at risk and that the agency will not accept unwarranted delays in submitting required studies. FDA also notes that it does not intend ordinarily to use seizure as a remedy for failure to conduct required studies.

53. Some comments offered additional or alternative remedies for failure to conduct required studies. One comment urged that failure to provide information to support pediatric labeling result in highly visible warnings on prescription and OTC labels that the drug has not been approved by FDA for pediatric use. Two comments argued that the label should disclose the status of pediatric studies, whether waivers or deferrals had been requested or granted, and the timetable for full compliance. Another comment contended that incentives are more effective than penalties, and that FDA discussions with sponsors during drug development will achieve the results sought in the proposal.

FDA agrees that publicity can sometimes be a useful tool for encouraging compliance. FDA does not believe, however, that it is feasible to include in labeling detailed information on the status of pediatric trials, because that information could change frequently. As described in section III.M of this document, FDA will, in appropriate cases, bring issues related to the progress of pediatric studies before a panel of pediatric experts, and may utilize other forms of publicity to provide the public with information about the status of required pediatric studies. FDA notes, e.g., that FDAMA contains provisions concerning disclosure of information on the status of postmarketing studies. FDA may also consider the use of prominent warnings about the absence of data on pediatric use, if necessary in particular cases.

M. Pediatric Committee

A large number of comments recommended that FDA form a panel of pediatric experts to provide advice on a range of topics related to implementation of this rule. Two comments recommended that an expert panel give advice on all facets of the rule. Several comments suggested more specific roles for the panel. For example, the AAP recommended that the panel provide advice on waiver requests, which marketed drugs require study, whether a drug is ''widely used,'' whether to accept a manufacturer's failure to develop a pediatric formulation, relevant age groups for study, the appropriateness of deferral, and appropriate timetables for completion of deferred studies. A disease-specific organization urged that a pediatric committee assist in establishing ''pediatric guidelines and practice,'' including a list of drugs for which studies would be required, protocol design, formulations, and age ranges. Two industry comments recommended that the panel review which drugs require testing and labeling, at what phase of drug development pediatric patients should be exposed, when waivers should be granted, what methods should be used to evaluate safety and effectiveness, the economic burdens on industry, and liability issues. Several comments, including comments from a pharmaceutical trade association, a disease-specific organization, a medical society, and pediatricians, recommended that the panel give advice on which drugs should be studied in pediatric patients. One comment suggested that FDA appoint a pediatric pharmacology expert to each of the existing drug advisory committees, except possibly the Fertility and Maternal Health Advisory Committee.

FDA has concluded that a panel of pediatric experts could provide useful advice and experience on several aspects of the implementation of the rule. FDA will therefore convene a panel of pediatric experts, including at least one industry representative, and seek its advice on a range of issues. Such a panel may be composed of pediatric experts appointed to each of FDA's existing drug advisory committees. As described in section III.E of this document under ''Waivers,'' FDA does not believe that it would be practical to ask such a committee to review every waiver or deferral request. However, the agency will ask the panel to provide annual oversight of the agency's implementation of the final rule, including the agency's record of granting or refusing waivers and deferrals. FDA will also seek the advice of the panel in identifying specific marketed drugs and biological products that should be studied in pediatric patients, and the age groups in which they should be studied. FDA will also ask for advice on assessing when additional therapeutic options are needed in treating specific diseases and conditions occurring in pediatric patients. As described previously, FDA will seek the panel's advice on ethical issues raised by clinical trials in pediatric patients, and whether additional rules should be implemented in this area. Where a manufacturer is not carrying out required studies according to the agreed upon timetable, FDA may seek the advice of the panel on whether the manufacturer is acting with due diligence. In addition, FDA may bring before the panel other issues that arise in the implementation of the rule, including the design of trials and analysis of data for specific products and classes of products.

N. Other Comments

54. Several comments suggested various forms of oversight for the implementation of the rule. One comment suggested that FDA establish a plan to prospectively evaluate these regulations, including their effect on the cost of drug development and on the time to new drug approval, and the number and success of pediatric studies actually performed. Another comment urged FDA to appoint a ''Children's Studies Ombudsman.'' One comment asked that the rule include an appeals mechanism to resolve disputes between sponsors and agency reviewers.

As described previously, FDA intends to convene a panel of pediatric experts, including at least one representative of the pharmaceutical industry, to, among other things, review the agency's implementation of the rule. FDA notes that it already has procedures for resolution of disputes between sponsors and FDA reviewing divisions, 21 CFR 312.48 and 314.103, and that these procedures will be available for disputes that arise under this rule.

55. Several comments contended that the rule is inconsistent with requirements in Canada, Europe, and Japan for pediatric studies. These comments argued that the rule was at odds with harmonization efforts and urged FDA to harmonize its requirements with those of other countries. One comment recommended that the United States, the European Union (EU), and Japan adopt pediatric drug development as a topic for global discussion and harmonization.

Although FDA is not required to harmonize its labeling regulations and enforcement with those of our International Conference on Harmonization (ICH) partners, harmonization is a goal that the agency strives to achieve. FDA intends to work through the ICH process to harmonize methods for conducting pediatric studies.

56. A few comments sought additional incentives for pediatric studies. One industry comment suggested that FDA should provide: (1) Priority reviews for applications containing pediatric data or ongoing studies; (2) waiver of user fees for pediatric effectiveness supplements; and (3) application of the subpart E

regulations (21 CFR part 312, subpart E) to pediatric development of new drugs and biological products, to address the issues associated with small sample size and therapeutic need.

Since the publication of the proposal, two significant new incentives have become available for pediatric research. First, as described elsewhere in this document, FDAMA provides 6 months of exclusive marketing to certain applicants who conduct pediatric studies. Second, as a result of changes made during the reauthorization of the PDUFA, user fees are no longer required for supplements that are solely for the purpose of adding a new indication for use in pediatric populations.

IV. Legal Authority

In the proposal, FDA cited as authority for the requirements in the rule sections 502(a), 502(f), 505(d)(7) of the act, and § 201.5 (21 CFR 201.5), which require adequate directions for use and prohibit false or misleading labeling; section 201(n) of the act, which defines as misleading labeling that fails to reveal material facts related to consequences of the customary or usual use of a drug; sections 201(p), 301(a) and (d) (21 U.S.C. 331(a) and (d)), and 505(a) of the act, which subject a drug to enforcement action if it is not recognized as safe and effective or approved for the conditions prescribed, recommended, or suggested in the labeling; section 502(j) of the act, which prohibits drugs that are dangerous to health when used in the manner suggested in their labeling; sections 505(i) and 505(k) of the act, which authorize FDA to impose conditions on the investigation of new drugs, including conditions related to the ethics of an investigation, and to require postmarketing reports; section 701(a) of the act, which authorizes FDA to issue regulations for the efficient enforcement of the act; and section 351 of the Public Health Service Act, which formerly required biological products to meet standards designed to insure their ''continued safety, purity, and potency.'' FDA notes that section 351 was amended by FDAMA, and now requires biological products to be ''safe, pure, and potent.''

FDA has authority under section 302 of the act and under the Public Health Service Act to seek an injunction requiring studies of certain marketed drugs on the grounds that the absence of pediatric safety and effectiveness information in the labeling renders the product misbranded or an unapproved new drug. The act also authorizes seizures of misbranded or unapproved drugs under section 304 of the act. Misbranding drugs and introducing unapproved new drugs into interstate commerce are prohibited acts under sections 301(a), (d), and (k) of the act. The statutory definition of ''drug'' is set out at section 201(g) of the act.

57. Several comments agreed that FDA has authority to require pediatric testing of drugs and biological products. One comment argued that the act already gives FDA the authority to require that all drugs be tested in pediatric patients, and that the rule, which permits waivers and deferred testing in some cases, weakens the agency's existing statutory authority. One comment contended a provision of FDAMA granting exclusivity to ''any pediatric study [that] is required pursuant to regulations promulgated by the Secretary [and that meets certain other requirements]'' shows that Congress agrees that FDA has authority to require pediatric studies. This comment also argued that, to the extent that FDA's position on its authority to require pediatric studies has changed, the change in position is justified because the proposal articulates a reasoned basis for the change.

FDA agrees that it has the authority to require pediatric testing of drugs and biologics. For the reasons cited in the preamble to the proposed and final rules, FDA has concluded that the requirements in the rule appropriately balance the need for adequate pediatric labeling and the limitations on resources available for pediatric testing and agency review. FDA also agrees that the reference in FDAMA, which was enacted after the proposal was issued, to pediatric studies required by FDA, demonstrate that Congress is aware of FDA's position that it has the authority to issue this rule and agrees that the agency has such authority. Finally, FDA agrees that it has articulated a reasoned basis for its position that the agency has authority to require pediatric studies, but notes that FDA previously stated its position that it has the authority to require pediatric studies in 1994 (59 FR 64240 at 64243).

58. Several comments argued that FDA lacks authority to require pediatric studies of drugs. A few comments cited remarks by former Commissioner David Kessler during a 1992 speech. In that speech, David Kessler stated his opinion that FDA does not have ''the authority to require manufacturers to seek approval for indications which they have not studied.'' Other comments argued that FDA has no authority to require the study of any indications or populations other than those proposed by the manufacturer. One comment challenged FDA's reliance on section 201(n) of the act for not-yet-approved drugs, claiming that the agency cannot know what will be the ''customary or usual uses'' of an unmarketed drug. A few comments argued that the agency's legal theory would authorize the agency to require studies of all off-label indications.

FDA disagrees that any of these arguments show that FDA lacks authority to issue this rule. Under FDA's longstanding policy, statements made in speeches, even by Commissioners, are informal expressions of opinion and do not constitute a formal agency position on a matter. As such they are not binding on the agency. (See, e.g., 21 CFR 10.85(k).)

FDA also disagrees that it has no authority to require a drug or biologic to be studied in a population that is expected to use the product for the claimed indication, or that this is a new position. The agency has repeatedly stated that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given the product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409). The agency has also previously asserted its authority to require studies in pediatric patients and in other subpopulations for both not-yet-approved products and marketed products. In the preamble to the 1994 rule, FDA made the following statement:

> If FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric populations, and the drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric use information.
>
> If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as an unapproved new drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262.)
>
> (59 FR 64240 at 64248; see also 58 FR 39406 at 39409)

The act and implementing regulations require drugs to be adequately labeled for their intended uses. See sections 502(f) of the act and § 201.5. ''Intended uses'' encompass more than the uses explicitly included in the manufacturer's proposed labeling. *Id.*, 21 CFR 201.128. In determining the intended uses of a drug for which it must be adequately labeled, FDA may consider both the uses for which it is expressly labeled and those for which the drug is commonly used, § 201.5.

FDA may also consider the actual uses of the drug of which the manufacturer has, or should have, notice, even if those uses are not promoted by the manufacturer, 21 CFR 201.128. Section 201(n) of the act defines labeling as misleading if it fails to include material facts about the consequences of ''use of the [drug] * * * under such conditions of use as are customary or usual.'' Sections 201(p) and 505(d) of the act authorize FDA to require evidence establishing the safety and effectiveness of uses ''suggested'' by the manufacturer's labeling as well as those expressly recommended in the labeling. Thus, the agency has authority to require a manufacturer to establish the safety and effectiveness of, and adequately label its product for, use of the product in a subpopulation for which the product is not labeled if that use is common or suggested in the labeling.

As described in the proposal, there is extensive evidence that drugs and biologics indicated for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in pediatric patients. FDA may therefore consider pediatric use to be ''customary or usual'' or ''commonly used'' where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. FDA may also consider pediatric use to be ''suggested'' in a drug's labeling even where such use is not expressly recommended or is even disclaimed. The medical community generally expects that drugs and biological products will behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, e.g., differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease suffered equally by men, women, and children, and is not contraindicated in women or pediatric patients, the product will be widely prescribed for all three subgroups even if it were studied only in, or labeled only for, men.

FDA disagrees that it can know nothing, in advance of marketing, about whether a drug or biological product will be used in pediatric patients. The evidence cited in the proposal and confirmed by comments from the pediatric community is overwhelming that products indicated for diseases that affect both adults and children are and will be commonly used in pediatric patients. Indeed, pediatricians often have no choice but to use these products in pediatric patients. A drug product that provides a meaningful therapeutic benefit either because it represents a significant improvement in therapy or because it is a necessary therapeutic option can be expected to be routinely used in the treatment of pediatric patients. Under the rule, the decision that a product will provide a meaningful therapeutic benefit or will be used in a substantial number of pediatric patients is made on a case-by-case basis, depending upon such factors as the number of pediatric patients affected by the disease for which the product is indicated, the availability and adequacy of other therapeutic options to treat pediatric patients for the disease, and whether similar products, e.g., products in the same drug class, have been widely used in pediatric patients.

Finally, FDA emphasizes that this rule applies only where a product is expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer. The record before the agency documents widespread evidence of actual use of products in the pediatric population for indications labeled for adults. This record supports FDA's conclusion that it has authority to require pediatric studies of drugs and biologics that have or are expected to have clinically significant use among pediatric patients for the claimed indications. The agency has not examined evidence concerning the use of approved products for diseases or conditions not in the label, and the rule does not apply in those situations.

59. Two comments addressed the agency's reliance on section 701(a) of the act. One comment argued that 701(a) of the act, in combination with the substantive statutory provisions cited by FDA, authorizes this rule because the agency has demonstrated that the rule is reasonably related to the purposes of the act. Another comment argued that 701(a) of the act does not authorize the agency to enforce requirements beyond those imposed by the act.

Section 701(a) of the act gives the Secretary authority to issue regulations for the efficient enforcement of the act. Consonant with the Supreme Court's determination that the language of the act should not be read restrictively, but in a manner consistent with the act's purpose of protecting the public health, a regulation issued under section 701(a) of the act will be sustained so long as it is reasonably related to the purposes of the act. *United States* v. *Nova Scotia Food Products Corp.*, 568 F.2d 240, 246 (2nd Cir. 1977). FDA believes that it has demonstrated that this regulation is reasonably related to the purposes of the act.

V. Implementation Plan

FDA proposed that the rule would become effective 90 days after the date of its publication in the **Federal Register**. For new drug and biologic product applications submitted before the effective date of the final rule, the agency proposed a compliance date of 21 months after the effective date of the final rule (for a total of 2 years after issuance of the final rule). For new drug and biologic product applications submitted on or after the effective date of the final rule, the agency proposed a compliance date of 15 months after the effective date of the final rule (for a total of 18 months after issuance of the final rule). FDA has revised the final rule to become effective 120 days after publication in the **Federal Register**, to allow additional time for comment on the revised information collection requirements. FDA has also revised the compliance dates. All applications will have a compliance date of 20 months after the effective date of the rule (for a total of 2 years after publication of the final rule).

60. Two industry comments argued that the proposed effective dates were too short. One of these suggested that 15 and 21 months were too short to develop a pediatric program and formulation, conduct trials, analyze data, and submit an application. Two comments asked that FDA clarify what ''compliance'' means. According to one of these comments, 15 months would be adequate for initiation of discussions with a sponsor about plans, but inadequate for completion of studies. This comment also argued that it is not in children's interest to rush through pediatric studies to meet an arbitrary deadline. Another comment offered the example of Ritonavir, a drug to treat HIV infection, for which pediatric studies reportedly took 21 months even after development of a pediatric formulation. According to the comment, it took 15 months to agree on a protocol, 3 months to recruit patients, and 3 months to the first interim analysis of data. One disease-specific organization argued that the effective dates were too long. This comment proposed 12 months from the effective date of final rule, which could be extended by 6 months if genuine difficulties occurred. This comment also urged that compliance with the early discussion requirements be immediate. One comment argued that pending applications should be granted a full

waiver and treated as marketed products.

''Compliance,'' as referred to in the proposal, means the submission of an assessment of pediatric safety and effectiveness under § 314.55(a) (proposed § 314.50(g)(1) or 601.27(a)), unless a waiver or deferral for all relevant age groups has been granted. FDA has reconsidered the compliance dates and has concluded that applications submitted on or after the effective date of the final rule should be given 20 months from the effective date of the final rule to achieve compliance. Although FDA does not believe that development of, and agreement on, a protocol should take 15 months, protocol development, recruitment, enrollment, and data analysis may together take up to 2 years. There is no reasonable basis on which to distinguish between an application submitted 1 day before the effective date of the final rule, and one submitted a day later.

All other provisions of the rule will become effective on the effective date of the rule. One hundred twenty days from the date of publication in the **Federal Register** is sufficient time to meet these new requirements.

VI. Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection requirements are shown below with an estimate of the annual reporting burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

With respect to the following collection of information, FDA invited comment on: (1) Whether the proposed collection of information is necessary for proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

OMB filed a Notice of Action, not approving the proposed collection of information. OMB requested that, as part of the final rule, FDA address all comments received on the information collection requirements contained in the rule, particularly with respect to the reporting burden imposed by the rule. FDA received one comment concerning the proposed burden estimates of this rulemaking under the PRA. The comment contended that FDA underestimated the time required to comply with the annual reporting requirements of the proposed rulemaking.

The agency received several comments that questioned the accuracy of FDA's estimate of the burden of the proposed collection of information as being too low and requested changes. For example, one comment requested changes in the burden estimate for manufacturers requesting deferrals of submission of pediatric data as well as the estimate for manufacturers to submit pediatric information in their annual report. In addition, the estimate for manufacturers to submit in their annual reports the analysis of available safety and efficacy data conducted or obtained in the pediatric population as well as proposed labeling was questioned. Based on these comments the agency increased the proposed burden estimates. These issues are discussed in more detail in the preamble to the final rule.

Concerning § 314.50(d)(7), the comment stated that in order to comply with this requirement, ''one company'' estimated that, for one pediatric reporting project, medical staff had spent at least 118 hours, rather than the 8 hours that FDA had estimated, reviewing the medical literature and summarizing the findings. FDA does not believe that this comparison is fully appropriate because § 314.50(d)(7) does not require an applicant to review the medical literature, or other studies, *de novo*. It simply requires an applicant to provide a brief summary of data that have already been fully reported and analyzed elsewhere in the same application. However, because the data to be summarized may be more extensive than originally estimated, FDA has, in response to the comment, increased its estimate of the reporting burden for this requirement from 8 hours to 50 hours.

Concerning § 314.55(a), the comment contended that FDA's estimate of 10 companies submitting NDA's annually for NME's is too low. The comment implied that, based on data for 1996, 50 companies would be a more realistic estimate. The comment also contended that FDA's estimate of 16 hours for a manufacturer to prepare the report of the data supporting the safety and effectiveness of the drug for the indication for the pediatric population is too low. In response to this comment, FDA has revised its burden estimate from 16 to 48 hours. FDA has also made a corresponding change in the estimate for § 601.27(a). FDA has revised the estimate of the number of companies affected from 10 to 51 to reflect the broader scope of the rule.

Concerning § 314.55(b), the comment stated that FDA's estimate of 9 manufacturers requesting deferrals of the submission of pediatric study data and the estimate that this would take 8 hours to complete are too low. In response to this comment, FDA has revised its burden estimate from 8 hours to 24 hours. FDA has also made a corresponding change in the estimate for § 601.27(b). FDA has revised the estimate of the number of companies affected from 8 to 51 to respond to the comment and to reflect the broader scope of the rule.

Concerning § 314.81(b)(2)(i), the comment contended that FDA's estimate of 1.5 hours for manufacturers to submit pediatric information in their annual reports is too low. In response to this comment, FDA has revised its burden estimate from 1.5 hours to 8 hours and has made a corresponding change in its estimate for § 601.27(c).

Concerning § 314.81(b)(2)(vi)(*c*), the comment contended that FDA's estimate of 1.5 hours for manufacturers to submit in their annual reports the analysis of available safety and efficacy data conducted or obtained in the pediatric population as well as proposed labeling changes is too low. The comment stated that even an estimate of 15 hours would be too low. Although the comment did not provide an estimate of the hours required to satisfy § 314.81(b)(2)(i) and (b)(2)(vi)(*c*), FDA has increased its estimates to 8 and 24 hours, respectively.

Based upon these comments, FDA has decided to increase the agency's proposed burden estimates. These revisions are reflected in the Table 2 of this document. In addition, the burden estimates for §§ 314.55(a), (b), and (c), and 601.27(a), (b), and (c), have increased because of the new requirements in the final rule to include, in addition to applications for new chemical entities and never-before-approved biologics, applications for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration. These estimates are based upon FDA's analysis of all marketing applications and efficacy

supplements approved over the 5-year period of 1993 to 1997 and those that would likely have needed additional pediatric data had this rule been in effect by 1993 (see ''Analysis of Impacts,'' in section VIII of this document). In addition, burden estimates have been added in Table 2 of this document for the new requirements in the final rule concerning submissions for end-of-phase 1 and end-of-phase 2 meetings under § 312.47(b)(1)(iv) and submissions for pre-NDA meetings under § 312.47(b)(2). These estimates are based on FDA's records of the number of these meetings held during 1997. Finally, burden estimates have been added for new postmarket report requirements added for biological products under § 601.37 (a), (b), and (c), corresponding to § 314.81 (b)(2)(i), (b)(2)(vi)(*c*), and (b)(2)(vii). These estimates are based upon FDA's records of the number of licensed biological products.

Title: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients.

Description: This final rule includes the following reporting requirements: (1) Reports on planned pediatric studies in IND's (§ 312.23(a)(10)(iii)); (2) Reports for end-of-phase 1 and end-of-phase 2 meetings (§ 312.47(b)(1)(iv)) and reports for pre-NDA meetings (§ 312.47(b)(2)); (3) Summaries of data on pediatric safety and effectiveness in NDA's (§ 314.50(d)(7)); (4) Reports assessing the safety and effectiveness of certain drugs and biological products for pediatric use in NDA's and BLA's or in supplemental applications (§§ 314.55(a) and 601.27(a)); (5) Requests seeking deferral of required pediatric studies (§§ 314.55(b) and 601.27(b)); (6) Requests seeking waiver of required pediatric studies (§§ 314.55(c) and 601.27(c)); (7) Postmarketing reports of analyses of data on pediatric safety and effectiveness (§§ 314.81(b)(2)(vi)(*c*) and 601.37(a)(1)); (8) Postmarketing reports on patient exposure to certain marketed drug products (§§ 314.81(b)(2)(i) and 601.37(a)(2)); (9) Postmarketing reports on labeling changes initiated in response to new pediatric data (§§ 314.81(b)(2)(vi)(*c*) and 601.37(a)(3)); and (10) Postmarketing reports on the status of required postapproval studies in pediatric patients (§§ 314.81(b)(2)(vii) and 601.37). The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

Description of Respondents: Sponsors and manufacturers of drugs and biological products.

TABLE 2.—ESTIMATED ANNUAL REPORTING BURDEN [1]

21 CFR section	No. of respondents	Annual frequency per response	Total annual responses	Hours per response	Total hours
201.23	2	1	2	48	96
312.47(b)(1)(iv)	27	1.2	32	16	512
312.47(b)(2)	36	1.3	46	16	736
314.50(d)(7)	213	1	213	50	10,650
314.55(a)	51	1	51	48	2,448
314.55(b)	51	1	51	24	1,224
314.55(c)	176	1	176	8	1,408
314.81(b)(2)(i)	625	1	625	8	5,000
314.81(b)(2)(vi)(*c*)	625	1	625	24	15,000
314.81(b)(2)(vii)	625	1	625	1.5	937.5
601.27(a)	2	1	3	48	144
601.27(b)	2	1	3	24	72
601.27(c)	3	1	4	8	32
601.37(a)	69	1	69	8	552
601.37(b)	69	1	69	24	1,656
601.37(c)	69	1	69	1.5	103.5
Total					40,571

[1]There are no capital or operating and maintenance costs associated with this collection of information.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

A. Introduction and Summary

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. The Unfunded Mandates Reform Act (Pub. L. 104–4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments,

in the aggregate, or by the private sector, of $100 million or more in any one year (adjusted annually for inflation).

The agency has reviewed this final rule and has determined that the rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and in these two statutes. This rule is an economically significant regulatory action, because of its substantial benefits. It is also a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Since the rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an expenditure of $100 million or more in any one year, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

FDA is requiring that a limited class of important new drugs and biologicals that are likely to be used in pediatric patients contain sufficient data and information to support directions for this use. As the approved labeling for many of these new products lacks adequate pediatric information, their use in children greatly increases the risk of inappropriate dosing, unexpected adverse effects, and suboptimal therapeutic outcomes. This rule is designed to ensure that new drugs, including biological drugs, that are therapeutically important and/or likely to be used in a substantial number of children contain adequate pediatric labeling at the time of, or soon after, approval.

The agency estimated the costs to industry of the required new pediatric studies by first determining what the annual costs would have been in 1993 to 1997, had the rule become effective in 1993. The methodology included: (1) Constructing a data base of all 583 NDA's and efficacy supplements approved by the agency over that 5-year period for drugs and biologicals likely to produce health benefits in the pediatric population, (2) determining which of those applications would have been required to conduct additional pediatric studies, (3) calculating how many unapproved and already marketed drugs and biologicals would have needed additional pediatric studies, and (4) estimating the size and cost of the additional studies. The analysis indicated that, on average, this regulation would have required an estimated 378 additional pediatric studies on about 82 drugs and biologicals per year. These studies would have involved a total of 10,860 pediatric patients, 7,408 in efficacy studies, and 3,452 in PK studies. In addition, an estimated 33 of the 82 drugs and biologicals needing new pediatric data each year may have needed new pediatric dosage forms. FDA judges that the additional studies would have cost about $45 million and the new dosage formulations about $33 million annually, for a total annual cost of almost $80 million. The agency found, however, that roughly 42 percent of the costs of the studies would have been spent voluntarily had the extended pediatric exclusivity provisions of the recent FDAMA statute been in place. Adjusting for this effect lowers the agency's final cost estimate for this rule to about $46.7 million per year.

FDA could not develop a quantifiable estimate of the benefits of this regulation, although numerous anecdotal examples illustrate the current health problem. To consider some of the potential benefits, the agency examined hospitalization rates for five serious illness (asthma, HIV/AIDS, cancer, pneumonia, and kidney infections) and found significantly higher rates for children than for middle-aged adults. Although FDA can not estimate the extent to which these differentials reflect the relative lack of pharmaceutical safety and efficacy information for pediatric compared to adult use, the agency calculated that a 25 percent reduction in these differentials would lead to direct medical cost savings of $228 million per year. FDA also estimates that about two-thirds of the approved applications needing pediatric studies will be addressed by the incentives established by FDAMA. If the estimated medical cost savings were adjusted by a similar ratio, the analysis suggests that a 25 percent reduction in the pediatric/adult hospitalization rate differentials would yield annual savings of $76 million for these five illnesses.

B. Number of Affected Products and Required Studies

In the preamble to its proposal, FDA explained that neither the precise number of drugs that would require additional pediatric studies nor the cost of these studies could be predicted with certainty. To develop plausible estimates of the number of new drugs and biologicals that would be affected, the agency had examined the pediatric labeling status at time of approval for each NME and important biological approved from 1991 to 1995, and used these estimates to project the number of drugs that would have required additional pediatric data had the proposal been in place over that period.

Several industry comments declared that FDA's analysis of the proposal substantially underestimated the economic impact by understating both the number and size of the studies that would be required. Only two of the comments, however, included alternative estimates. One suggested that each new drug could require the testing of 300 or more pediatric patients for safety data alone. The other comment estimated that, ''each new drug studied would probably require a minimum of six clinical trials (two each in Phases I, II, and III), for one indication and one formulation.'' This comment explained that Phase I trials would include 20 patients, Phase II trials 50 patients, and Phase III trials 100 patients. Assuming two trials for each phase, the comment projected that 34,000 pediatric patients would need to be studied each year (170 patients x 2 trials x 100 drugs).

FDA agrees that some applications will require data from a substantial number of pediatric patients. The agency believes, however, that most studies will not include large numbers of pediatric patients. For example, FDA does not necessarily require two pediatric studies for each trial phase. Moreover, FDA's 1994 final rule (59 FR 64240) explains that extrapolations from adult effectiveness data based on PK studies and other safety data can be sufficient to provide the necessary pediatric dosing information for those drugs and biologicals that work by similar mechanisms in adults and children. The agency expects that the majority of the studies will rely, to some extent, on such extrapolations.

On the other hand, the proposal primarily addressed drugs and biologicals that contained no previously approved active moiety. The final rule requires pediatric data for new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration that represent a meaningful clinical benefit over existing treatments for children, or that are likely to be widely used in children. The rule also requires pediatric studies for marketed drugs and biologicals that are already widely used among children for the claimed indications, if the absence of adequate labeling could pose significant risks; or if the drug would provide a meaningful clinical benefit over existing treatments for pediatric patients, but additional dosing or safety information is needed to permit their safe and effective use in children.

To develop a revised estimate of the number of drugs and biologicals that

would require additional pediatric data, FDA constructed a data base of all 583 applications and efficacy supplements approved over the 5-year period from 1993 to 1997 for drugs and biologicals for which pediatric labeling would be likely to provide a significant health benefit. The selected drugs and biologicals included all those for which the active moiety was listed in the priority section in the **Federal Register** of May 20, 1998 (63 FR 27733), document entitled ''List of Drugs For Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population'' (''List''). Mandated by FDAMA, this publication includes the agency's priority list of drugs and biologicals that would likely provide a significant benefit to the pediatric population. The selection criteria used to prepare this priority list were almost identical to those set forth in this final rule, i.e.,

- The drug product, if approved for use in the pediatric population, would be a significant improvement compared to marketed products labeled for use in the treatment, diagnosis, or prevention of a disease in the relevant pediatric population (i.e., a pediatric priority drug); or,
- The drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year; or,
- The drug is in a class or for an indication for which additional therapeutic options for the pediatric population are needed.

FDA then identified each of the 583 applications that would likely have needed additional pediatric studies had this rule been in effect. The number and type of studies needed were projected based on specific decision rules derived from agency experience in reviewing drug applications and developed strictly for the purpose of estimating the regulatory costs of this rule. Although in practice, these rules would have been subject to numerous exceptions, in the aggregate, FDA believes that they provide plausible estimates of the total number and type of pediatric studies that would have been required. The decision rules were as follows:

1. All New Chemical Entities (NCE's) and biologicals were assumed to need both an efficacy study and a PK study for each age group identified in the priority section of the ''List'' as needing pediatric information, although FDA believes that this assumption overstates the true number of efficacy studies that will be needed.

2. For the following categories of applications, both an efficacy and a PK study were assumed for each designated age group. Again, FDA believes that this assumption may overstate the true number of efficacy studies that will be needed:

Neurological drugs;
Oncology drugs;
Nausea agents;
Pulmonary agents;
NSAIDs—arthritis/pain;
AIDS/HIV agents;
Asthma drugs;
Anesthesia drugs;
Hormones;
Dermatological agents;
Acne agents

3. A PK study alone was assumed sufficient for each relevant age group for the following types of non-NCE applications:

Allergies;
Infectious diseases;
Cardiovascular diseases;
Imaging agents;
Hematology agents;
GI disorders;
Urologic drugs

4. If pediatric labeling was already adequate as the result of an approved application, additional applications for new dosage forms were assumed to be exempt.

5. If a second applicant sought approval for the same indication of the same drug as a previous applicant that had already satisfied the pediatric labeling requirements, the second applicant was considered exempt from the pediatric labeling requirement.

6. Because the regulation imposes requirements only on new NDA's or efficacy supplements that specifically address an indication needing pediatric data, no pediatric requirements were assumed for an NDA supplement submitted for a new indication not identified as needing pediatric data.

7. Orphan drugs were excluded from additional research requirements.

The results of this analysis (see Table 3 of this document) show that about 44 percent, or an estimated 255, of the total 583 drug and biological applications for the products on the priority section of the ''List'' drugs approved over the 5-year period would have required additional pediatric studies, had the rule been in effect starting in 1993. Assuming separate studies for each pediatric age group specified in the ''List,'' indicates that an estimated 459 efficacy studies and 713 PK studies would have been required for these applications.

These estimates understate the required research effort, however, because they omit pediatric studies for drugs that fail to gain approval. It is difficult to judge how much additional pediatric research would be directed towards nonapprovable products. The agency notes, however, that because only about 63.5 percent of all NME's that enter phase III trials are eventually approved (Ref. 18), the number of drugs entering phase III trials is about 58 percent greater than the number of actual approvals (100/63.5 = 1.58). Moreover, there are two additional complications. First, under the rule, FDA expects to defer for several years the conduct of pediatric studies of ''me-too'' drugs that do not offer a meaningful therapeutic benefit and that are members of a drug class that already contains an adequate number of approved products with pediatric labeling. No additional pediatric studies would be expected for this group of never approved drugs. On the other hand, applications for ''lifesaving'' drugs may need to begin pediatric trials by the start of Phase II. On the assumption that these two factors would roughly offset, FDA has retained the 58 percent figure as a reasonable adjustment factor to account for the number of studies conducted for drugs that fail to gain approval. Finally, each year, the agency expects to identify about two ''already marketed'' drugs that require additional pediatric efficacy data.

As shown in Table 4 of this document, adjusting for the ''never approved'' and the ''already marketed'' applications implies that, had this rule become effective in 1993, about 1,892 new pediatric studies would have been required over the 1993 to 1997 period. About 740 of the studies would have been efficacy studies and 1,151 PK studies. Thus, on average, each year, the rule would have required about 378 new pediatric studies for about 82 NDA's and or NDA supplements—148 efficacy studies and 230 PK studies.

TABLE 3.—APPROVED NEW DRUG APPLICATIONS AND THEIR SUPPLEMENTS FROM 1993 TO 1997

Approval year	Applications for "List" Drugs	Applications needing pediatric studies	Efficacy studies required	PK studies required	Total studies required	New dosage forms
1993	77	43	63	122	185	12
1994	76	42	74	118	192	17
1995	107	38	69	107	176	13
1996	177	74	147	213	360	29
1997	146	58	106	153	259	19
Total	583	255	459	713	1,172	90
Average	117	51	92	143	234	18

TABLE 4.—ALL NEW DRUG APPLICATIONS AND THEIR SUPPLEMENTS FROM 1993 TO 1997 [1]

Approval year	Applications for "List" Drugs [2]	Applications needing pediatric studies	Efficacy studies required	PK studies required	Total studies required	New dosage forms
1993	124	69	102	197	299	22
1994	123	68	119	190	310	32
1995	173	61	111	173	284	24
1996	286	119	237	344	581	54
1997	236	94	171	247	418	35
Total	942	411	740	1,151	1,892	167
Average	188	82	148	230	378	33

[1] Includes estimates for "unapproved" and "already marketed" drugs.
[2] Adjusted for "unapproved" and "already marketed" drugs.

C. Number of Pediatric Patients

The number of pediatric patients needed varies with the particular type of drug studied. However, based on agency experience, FDA estimates that, for each pediatric age group studied, typical pediatric PK studies may involve about 15 patients and typical efficacy studies about 50 patients. For example, if 2 of the 4 age groups lack PK studies, FDA assumed that a total of 30 subjects would be needed for the studies. If 3 of the 4 age groups lack efficacy studies, a total of 150 subjects were assumed to be needed in all 3 age groups. These assumptions indicate that, had this rule become effective in 1993, each year, about 82 NDA's would have required additional pediatric studies; 7,408 pediatric patients in efficacy studies and 3,452 pediatric patients in PK studies, for an annual total of about 10,860 pediatric patients.

D. Costs of Compliance

1. Cost of Pediatric Studies

FDA's analysis of the proposal assumed that new studies would cost pharmaceutical firms from $5,000 to $9,000 per pediatric patient. Only one comment, that of a large U.S. pharmaceutical company, submitted actual estimates of the cost of conducting pediatric trials. This comment stated that a PK or bioavailability/bioeqivalency study of 20 patients would cost at least $100,000, a Phase II trial of 50 patients would cost a minimum of $150,000, and a Phase III trial of 100 patients would cost $200,000. For its revised analysis, therefore, FDA assumes that a PK study of 15 patients will cost $100,000 per affected age group and that an efficacy study of 50 patients will cost $150,000 per affected age group. Although a few trials may need to be larger and, thus more expensive; others will require substantially fewer pediatric patients. Thus, FDA believes these figures reasonably project the average added costs.

As FDA estimates that the regulation would have required pharmaceutical companies to annually conduct an estimated 378 additional pediatric studies for 82 NDA's, 148 efficacy studies, and 230 PK studies; the above unit cost estimates imply total industry costs of $45 million annually. Although the industry comment that included the cost data projected clinical trial costs totaling over $100 million per year, this estimate assumed the need for 34,000 additional pediatric patients. FDA found that had this rule been in place over the 1993 to 1997 period, it would have required additional data from about 10,860 patients per year.

2. Cost of New Formulations

In its earlier analysis of the proposal, FDA calculated that about 30 percent of all NME's were available only in tablets or hard capsules at the time of approval. Acknowledging the potential difficulties of developing new formulations for certain drugs, FDA estimated that the overall costs could average $1 million for each new formulation developed. Several comments questioned the agency's estimates. Based on an informal survey of its members, a major industry trade association reported that the development of a pediatric formulation could take from 5 months to 4 years and cost from $500,000 to $3.5 million. It also objected to the agency's estimate of the number of drugs that would require reformulation. The association, however, apparently misunderstood FDA's methodology. The agency had found that 10 of 14 drugs per year would not need reformulation because a potentially adequate dosage form (liquid, an injectable, a solution, a dermatological, etc.) was already available. The association believed that FDA has assumed that only tablets and/or capsules were available for the ten drugs. None of these comments,

however, offered an alternative methodology for projecting the aggregate value of these costs.

To develop reasonable estimates of the number of new dosage forms that would be needed, FDA again reviewed all of the 255 approved drug applications that would likely have required new pediatric studies during the 1993 to 1997 period, had this rule been in place. The agency generally assumed that those drugs identified as having a meaningful clinical pediatric benefit for the youngest three age groups, but available only in tablets or hard capsules at the time of approval, would have needed to develop an alternative dosage form. The agency also assumed that a new pediatric formulation would not be counted if a more appropriate pediatric dosage form was subsequently approved for the same drug. FDA is aware that these estimates can not be considered precise. For example, not all liquids are adequate for pediatric populations. On the other hand, new formulations may not be needed if a drug is used primarily for children between the ages of 8 and 12 years. Nevertheless, as shown in Table 3 of this document, the results of this methodology show that about 35 percent of the approved applications needing studies, or about 18 per year, would have needed new dosage forms. Table 4 of this document raises this estimate by 83 percent, or to 33 per year, to account for the number of new dosage forms developed for drugs not subsequently approved. While FDA cannot confidently predict a typical initiation time for this effort, the 83 percent adjustment calculation assumes that work on about 25 percent of all new formulations would be initiated at the start of Phase 2 trials and 75 percent by the start of Phase 3 trials. (The probability of approval was assumed to be .635 for a drug entering phase 3 trials and .31 for a drug entering phase 2 trials (Ref. 18).)

The development of some pediatric formulations will be difficult, the development of others relatively straightforward and achieved without substantial problem. The rule requires only that sponsors take all reasonable steps to develop needed new formulations. Thus, while acknowledging that the cost for particularly difficult formulations may be higher, FDA has retained its average cost estimate of $1 million to develop each new dosage form and projects this total industry cost at nearly $33 million per year.

3. Cost of Added Paperwork Requirements

The rule also requires additional industry effort for new or expanded paperwork reporting. Section VI of this document describes these reporting tasks, discusses the industry comment that questioned the agency's estimate of the paperwork burden for the proposal, and presents the agencies revised estimate for this final rule. As shown in that section, FDA projects an annual burden of about 40,000 hours per year. On the assumption that 25 percent of these hours will be for upper management staff, 50 percent for middle management staff, and 25 percent for administrative and clerical support, at respective labor costs of $52, $34, and $17 per hour, FDA estimates these total paperwork costs at about $1.4 million per year.

4. Total Costs

Table 5 of this document summarizes the agency's estimates of costs for efficacy studies, PK studies, new dosage forms, and paperwork. Because the expense of pediatric trials and dosage form development will be spread over 2 or 3 years for any given drug, the total costs to industry in any given year are unlikely to vary as much as shown in Table 5. Most importantly, however, the average $80.1 million annual cost figure reflects only what the rule would have cost had the rule been in effect from 1993 to 1997. The incentives generated by the additional 6-month marketing exclusivity offered by FDAMA will reduce the future costs of the regulation.

TABLE 5.—ESTIMATED INDUSTRY COSTS—COMPLIANCE WITH PEDIATRIC LABELING

[in millions]

Year	Efficacy studies	PK studies	New dosage form developed	Paperwork	Total
1993	$15.3	19.7	22.3	1.4	58.6
1994	17.9	19.0	31.6	1.4	69.9
1995	16.7	17.3	24.1	1.4	59.5
1996	35.6	34.4	53.9	1.4	125.2
1997	25.7	24.7	35.3	1.4	87.0
Average Per Year	$22.2	$23.0	$33.4	$1.4	$80.0

FDA cannot develop precise adjustments for the forthcoming effects of FDAMA, due to the complexity of the economic forecasting that would be needed. Nevertheless, the agency developed rough projections of the potential impact of this statute by comparing the estimated present value of the 6-month exclusivity gain with the estimated cost of the new pediatric studies, for each of the 85 drugs with applications approved in 1993 and 1994 that would have needed new pediatric labeling. (More recent years were not used, because the revenues of newer drugs are far below their peak values.) Where the estimated exclusivity gain exceeded the cost of all required studies, including the development of new dosage forms, FDA concluded that the studies for that drug would have been initiated voluntarily and their cost attributable to FDAMA rather than to this regulation.

The methodology assumed that a 6-month gain of marketing exclusivity would be worth about 25 percent of a drug's annual sales revenue during the year the exclusivity is needed, less 60 percent for production, administrative, and marketing costs (Ref. 19). Costs of conducting the required studies for each of the 85 drugs were based on the cost estimates described previously ($150,000 for each efficacy study, $100,000 for each PK study, and $1 million for each new dosage form. The present value of the additional revenues (at a 7 percent discount rate) were calculated from 1997 sales data published by IMS America (Ref. 20). Because 1997 sales revenues probably underestimate the sales revenues that will be realized at the time that the added exclusivity is used, this methodology likely underestimates the effects of FDAMA, hence overestimating the costs of the rule. In general,

however, this analysis was insensitive to the precise assumptions used. For example, using an 11 percent rather than 7 percent discount rate raises the cost totals by only $1.2 million per year.

The analysis found that the necessary studies would have been conducted voluntarily for 56 out of the 85 affected applications (66 percent). Adjusting estimates of only the approved applications by this percentage (FDAMA was not assumed to affect studies for applications not obtaining approval), FDA projects that the annual costs attributable to this rule will be approximately $46.7 million, or about 42 percent below the non-FDAMA adjusted figure of $80 million.

Further, although the agency has not yet evaluated the full economic impact of the FDAMA legislation, it believes that the present value of the net revenues expected from the 6 months of added exclusivity granted under the new FDAMA legislation will greatly exceed the additional costs imposed by this regulation. One industry publication (MedAdNews, June 1998, p. 10) for example, reports that products currently valued at $41 billion in annual sales will come off patent between 1998 and 2008, or an average of $11 billion per year. Alternatively, FDA estimates that the annual revenues for NCE's coming off patent may average between $200 and $300 million each. If 25 NCE's lose exclusivity each year, these annual revenues would range from $5 billion to $7.5 billion. If only 60 percent of these NCE's become eligible for extended exclusivity, the methodology described above implies that industry net incomes will increase from $300 to $450 million per year. Thus, FDAMA and this rule, taken together, will provide critical pediatric information without diverting current resources from pharmaceutical innovation.

COM041COM041*E. Benefits*

The rule addresses two major problems associated with the lack of adequate information on the effects of drugs on pediatric patients: (1) Adverse drug reactions in children due to inadvertent drug overdoses or other drug administration problems that could be avoided with better information on appropriate pediatric use; and (2) under use of safe and effective drugs for children due to the prescribing of an inadequate dosage or regimen, a less effective drug, or no drug at all because of uncertainty over the drug's effect on children or the unavailability of a pediatric formulation. By developing improved information on whether, and in what dosage, a drug is safe and effective for use in children, FDA believes that the regulation will result in fewer adverse drug reactions and fewer instances of less-than-optimal treatment of pediatric patients.

Despite numerous reports of children endangered by the absence of adequate drug labeling, FDA has found no systematic studies in the literature that evaluate the overall magnitude of the harm that results from the incomplete labeling of drugs for use in children. In the preamble to the proposal, the agency specifically requested, ''information on any available studies or data related to the incidence and costs of either undertreatment or avoidable ADE's in pediatric age groups due to the lack of information on the effects of pharmaceuticals.'' The comments received cited case after case of children who have died or suffered because of the inadequate testing of drugs in children, but the information was largely anecdotal and related to particular instances of drug misuse or underuse.

For example, physicians who care for HIV-infected patients expressed frustration at their inability to treat children with drugs known to be effective in adults. Pulmonary specialists described the dearth of information on risks versus benefits of new antimicrobials for pediatric patients, citing the example of ciprofloxacin, a quinolone that may be valuable in treating cystic fibrosis, although the safety and effectiveness of the drug in children has not been established. Comments received from asthma specialists reaffirmed the difficulties of administering medications, treating drug side effects, or withholding treatment for children with asthma, due to the lack of research on drug safety and effectiveness.

In both written comments and in commentary at the public hearing in October 1997, concerns were raised about the costs of not implementing a requirement for pediatric labeling. Avoidable adverse outcomes, cited in relation to pediatric dosage problems, included opportunistic infections from too much immunosuppression, and loss of grafts in pediatric renal transplant patients with too little immunosuppression. Comments also cited added health care, including increased hospitalizations, required as a result of less effective treatment for pediatric patients. One comment estimated the cost of delayed access in terms of infant deaths, attributing an additional 2,000 unnecessary infant deaths over a 2-year period to the delay in access to AZT for HIV-exposed infants. Another suggested using the Vaccine Injury Compensation program figure of $250,000 per child as the value of an avoided death resulting from an ADR. Other comments confirmed that many adverse outcomes develop quickly and would be detected in early clinical studies (e.g., ''gray syndrome'' in babies treated with chloramphenicol).

While clearly demonstrating the critical need for improved pediatric information, these comments do not suggest a practical methodology for quantifying the aggregate benefits of this rule. FDA, also, has been unable to develop a precise assessment of the probable regulatory benefits. The agency's approach to estimating regulatory benefits therefore is framed in terms of the following two questions: (1) Are data available to assess current differences in the *safety* of drug therapy for adults versus children with the same condition? and (2) Are data available to assess current differences in the *effectiveness* of drug therapy for adults versus children with the same condition?

FDA first attempted to assess the *safety* of drug therapy by looking for differences in the frequency and severity of ADR's for adults versus children treated for the same condition. The available clinical and health survey data, however, did not provide a reliable estimate of the contribution of ADR's to pediatric as compared to adult rates of mortality and morbidity. ADR-related data are limited by the lack of a general requirement and a ready mechanism for the comprehensive reporting of incidents directly attributable to ADR's (Ref. 21). Moreover, most available studies have not addressed ADR rates and associated death rates by age group within a treated condition (Refs. 22, 23, and 24). For example, one study of pediatric patients shows an ADR-related admission rate in the range of only 2.0 to 3.2 percent, well below the average for adult and pediatric studies combined. Pediatric cancer patients, however, experienced a 22 percent ADR-admission rate (Ref. 25), suggesting that pediatric risks may be significantly greater within condition-defined subpopulations. In addition, potential concerns about negative public attention (Ref. 26) or liability inhibit reporting of ADR's. Finally, for many seriously ill patients, it is very difficult to attribute a specific medical outcome to a particular medication, as opposed to some other complication in the patient's condition, or misadventure in the patient's care. The agency found therefore that it could not rely on available ADR studies to derive an assessment of the potential benefits of this rule.

Data to assess the *effectiveness* of drug therapy would indicate differences in clinical outcomes, or in other health care utilization concomitant with drug therapy. If drug therapies for children were less effective than that for adults with the same condition, one might see longer recovery times, or lower recovery rates, together with increased health services use, assuming a similar prognosis and course of illness. A limitation to this approach is that the prognosis and course of illness may not be the same in children and adults with the same serious health condition, even if the same drugs were included in best-practice treatment. Moreover, differential patterns of health care utilization may reflect variations in physician practice patterns, insurance benefits, or patient and family behavior and preferences, rather than measures of drug effectiveness. Notwithstanding such limitations, comparisons of health care resource use for one therapeutic approach compared to another are commonly used in evaluations of therapy effectiveness in the field of pharmacoeconomics. In this instance, FDA finds that health care utilization data may provide at least an indirect indication of potential benefits. Hospitalization rates, in particular, are the most extensively studied measure of morbidity related to adverse drug reactions and of quality of care for a number of chronic (e.g., asthma) and acute conditions (e.g., pneumonia) (Refs. 27 and 28). While hospitalizations due to adverse drug reactions or drug therapy undertreatment are not always recognized, these admissions are routinely classified with a primary diagnosis of the underlying disease. FDA therefore has relied on diagnosis-related hospitalization rates to develop an order-of-magnitude assessment of the potential benefits of this rule.

For this assessment, the agency compared rates of hospitalization of pediatric patients to rates of hospitalization of adult patients for several important disease conditions. Next, the agency examined the potential direct and indirect cost savings that would be realized by diminishing any age-related disparities. The pediatric population was defined to be all persons under the age of 15 and the comparison group to be those adults between the ages of 15 and 44. (The exclusion of older adult patients minimizes the confounding effect of the age-related increased morbidity and mortality.) Comparisons were limited to asthma, HIV/AIDS, cancer, pneumonia, and kidney infection, as these conditions are life threatening, occur in both adults and children, and comparable data are available for adult and pediatric patients. Moreover, reports received in the FDA Spontaneous Reporting System (SRS) in 1993 indicated that the therapeutic areas for which the highest number of ADR's were reported for patients under age 15, relative to the number reported for patients 15 to 44, included those for anti-infectives, pulmonary drugs and oncology drugs.

Direct costs were based on the estimated number of cases, hospitalization rates, and length of stay for each of the selected conditions. The number of cases reported were based on national health survey (Ref. 29) and public surveillance data (Refs. 30, 31, and 32). In 1994, the total number of cases for these 5 conditions, in patients under age 15, was approximately 6.65 million. The total number of cases for patients ages 15 to 44 was approximately 8.3 million. The number of hospitalizations per year for which the selected condition was the primary diagnosis was obtained from the National Hospital Discharge Survey (Ref. 33). As shown in Table 6 of this document, the pediatric hospitalization rate exceeded the adult rate for all five conditions.

TABLE 6.—HOSPITALIZATION RATES PER PATIENT PER YEAR

Primary diagnosis	Rate under age 15	Rate for ages 15–44
Asthma	.045	.024
HIV/AIDS	.533	.233
Cancer	4.247	3.903
Pneumonia	.147	.129
Kidney Infection	.191	.073

The average length of hospital stay (ALOS) for patients with the selected condition as the primary diagnosis (based on ICD–9 code) was obtained from recent hospital survey data (Ref. 34), the average cost per day of inpatient hospital care for each of the selected conditions was based on hospital charge data reported in the survey (Ref. 35), and the cost of physician services associated with each episode of hospitalization was based on physician charge data (Ref. 36). Each episode of care was assumed to include physician charges for emergency room service, daily inpatient visits, and a postdischarge office visit. For cancer hospitalizations, daily inpatient visits and a followup office visit were included. The calculation of indirect costs assumed 8 hours of parental time away from work for each episode of hospitalization and income and productivity losses based on average employee compensation, as reported in the 1997 U.S. Statistical Abstract. A detailed description of all assumptions, calculations, and data sources is included in the full agency report (Ref. 37).

The assumed hypothesis is that a substantial fraction of the difference between pediatric and adult hospitalization rates for like disease conditions are attributable to the greater range of drug therapies and better information on drug dosages for adults. FDA cannot estimate the precise magnitude of the relevant fraction. Nevertheless, if the differentials between pediatric and adult hospitalization rates were reduced by 25 percent, the resulting direct cost savings would be $228 million, with indirect cost savings of $5.3 million per year. If the differentials were reduced by as much as 50 percent, the direct cost savings would be $456 million per year, with indirect savings of $10.6 million. Even if the differentials were as low as 10 percent, the resulting reductions in hospitalization would lead to direct cost savings of $91.2 million, with indirect savings of $2.1 million per year.

The timing of the benefit after the rule's implementation is uncertain. The previous values represent the potential benefit over time as the safety and effectiveness of drugs are more extensively tested, new and already marketed drugs become labeled for use in children, and new formulations and dosage forms are developed to facilitate therapy for children. The figures may overestimate the impact for the selected conditions over the next few years, but may underestimate the potential benefits for these patients in the longer term if there is an increasing prevalence of asthma, cancer, and respiratory and other infectious diseases in the pediatric population. Thus, the lower reduction estimate may be more realistic in the near-term, with the higher reduction estimates offering a better indication of longer-term benefit.

As discussed previously, FDA believes that the new FDAMA statute will cause some of these pediatric studies to be conducted voluntarily. In its assessment of costs, the agency found that about two-thirds of the applications for approved drugs needing pediatric studies may be undertaken voluntarily due to the incentives established by FDAMA. Adjusting the previous medical cost savings by a similar ratio suggests that if all of the new pediatric studies achieved a 25 percent reduction in the pediatric/adult hospitalization differentials, the additional studies prompted by this rule would yield

annual savings of $76 million for just those five diseases. This estimate may represent a lower bound on the benefits to pediatric patients, however, because a number of other disease conditions are also common to children and adults, including such life-threatening conditions as hypertensive disease and renal disease. These pediatric populations also would experience significant benefits from increased safety and access to drug treatments currently available only to adult patients. Moreover, the analysis omits any quantification of benefits for reduced pain and suffering and reduced pediatric mortality. Thus, the full benefits of the rule could easily exceed $100 million per year. Therefore, in accordance with the SBREFA, the Administrator of the Office of Information and Regulatory Affairs of the Office of Management and Budget (the Administrator) has determined that this rule is likely to result in an annual effect on the economy of $100 million or more and thus is a major rule for the purpose of congressional review.

F. Small Entities

The rule will impose a burden on relatively few small entities, because new drug development is typically an activity completed by large multinational firms. Only one industry comment questioned the agency's determination that the rule would not have a significant effect on a substantial number of small entities. That comment indicated that about 1,500 small entities are conducting diagnostic and therapeutic R&D in the United States and that ''[c]ontributions to new drug approvals by the 'biotech' and 'small pharma' sector are increasing year by year, and the pace of change will—almost certainly—continue.''

FDA agrees that small firms contribute substantially to the early development of many new drugs and biologicals. Nevertheless, because of the considerable resources needed for clinical testing and marketing, the agency finds that very few of these small firms retain ownership and control through the large-scale clinical testing and approval stages. Moreover, many of the products that are sponsored by small companies are eligible for orphan designation and therefore exempted from this rule. To approximate the number of small firms that might be significantly affected, FDA determined the sponsor company size for all of the approved applications that may have required additional pediatric studies had this rule been in place over the years from 1993 to 1997. The agency found that, on average, based on the Small Business Administration's definition of a small firm, only three approved applications per year were submitted by small companies. Multiplying by the previously described 1.58 factor to account for unapproved applications increases this estimate of the number of small entities that may have been significantly affected by this rule to just five small firms per year. Because the agency has certified that the rule will not impose a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act does not require the agency to prepare a Regulatory Flexibility Analysis. Moreover, the agency further points out that the required new studies will comprise a very small part of the total cost of developing new drugs or biologics, which is generally estimated in the hundreds of millions of dollars for each new drug.

G. Regulatory Alternatives

The agency carefully examined two major alternatives to the final rule. The first alternative considered was the initial proposal, which covered only NCE's. The estimated cost of this alternative, excluding the FDAMA adjustment, would be about $40 million, or roughly 50 percent of the cost of the final rule. The agency rejected this alternative because of the predominant view of the medical community that additional pediatric data were needed for all of the drugs and biologicals that may be therapeutically significantly in pediatric populations, not just for the new chemical entities.

The other major alternative considered was to delay implementation of the rule until the effects of the new FDAMA statute were reviewed. FDA fully expects the FDAMA exclusivity provisions to provide a substantial incentive to conduct large numbers of pediatric studies. Nevertheless, the agency finds that relying on these incentives, alone, would leave numerous gaps in many important areas of pediatric labeling. For example, as described earlier in this preamble, voluntary research may overlook studies for many important drugs, especially where such studies require the development of new pediatric dosage forms. Thus, notwithstanding FDAMA incentives, FDA has determined that this regulation is necessary to protect the pediatric population and that further delay is not warranted.

IX. References

The following references have been placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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15. Tejeda, H. et al., ''Representation of African-Americans, Hispanics, and Whites in National Cancer Institute Cancer Treatment Trials,'' *Journal of the National Cancer Institute,* 88(12):812–816, 1996.
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List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 201, 312, 314, and 601 are amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.23 is added to subpart A to read as follows:

§ 201.23 Required pediatric studies.

(a) A manufacturer of a marketed drug product, including a biological drug product, that is used in a substantial number of pediatric patients, or that provides a meaningful therapeutic benefit over existing treatments for pediatric patients, as defined in §§ 314.55(c)(5) and 601.27(c)(5) of this chapter, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the approved indications may be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may also be required to develop a pediatric formulation for a drug product that represents a meaningful therapeutic benefit over existing therapies for pediatric populations for whom a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may by order, in the form of a letter, after notifying the manufacturer of its intent to require an assessment of pediatric safety and effectiveness of a pediatric formulation, and after offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within a time specified in the order, if FDA finds that:

(1) The drug product is used in a substantial number of pediatric patients for the labeled indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) There is reason to believe that the drug product would represent a meaningful therapeutic benefit over

existing treatments for pediatric patients for one or more of the claimed indications, and the absence of adequate labeling could pose significant risks to pediatric patients.

(c)(1) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed, or

(ii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(2) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, *and*

(B) Is not likely to be used in a substantial number of patients in that age group, *and*

(C) The absence of adequate labeling could not pose significant risks to pediatric patients; *or*

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed, or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group, or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(3) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the information or request for approval of a pediatric formulation described in paragraph (a) of this section within the time specified by FDA, the drug product may be considered misbranded or an unapproved new drug or unlicensed biologic.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371; 42 U.S.C. 262.

4. Section 312.23 is amended by redesignating paragraph (a)(10)(iii) as paragraph (a)(10)(iv) and adding new paragraph (a)(10)(iii) to read as follows:

§ 312.23 IND content and format.

(a) * * *

(10) * * *

(iii) *Pediatric studies.* Plans for assessing pediatric safety and effectiveness.

* * * * *

5. Section 312.47 is amended by revising paragraph (b)(1)(i) and the first sentence of paragraph (b)(1)(iv), by removing the fifth sentence of paragraph (b)(1)(v) and adding two sentences in its place, by revising the heading of paragraph (b)(2) and the second and last sentences of the introductory text of paragraph (b)(2), and by redesignating paragraph (b)(2)(iii) as paragraph (b)(2)(iv) and by adding new paragraph (b)(2)(iii) to read as follows:

§ 312.47 Meetings.

* * * * *

(b) * * *

(1) *End-of-Phase 2 meetings*—(i) *Purpose.* The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(iv) *Advance information.* At least 1 month in advance of an end-of-Phase 2 meeting, the sponsor should submit background information on the sponsor's plan for Phase 3, including summaries of the Phase 1 and 2 investigations, the specific protocols for Phase 3 clinical studies, plans for any additional nonclinical studies, plans for pediatric studies, including a time line for protocol finalization, enrollment, completion, and data analysis, or information to support any planned request for waiver or deferral of pediatric studies, and, if available, tentative labeling for the drug. * * *

(v) *Conduct of meeting.* * * * The adequacy of the technical information to support Phase 3 studies and/or a marketing application may also be discussed. FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and whether their submission will be deferred until after approval. * * *

(2) *''Pre-NDA'' and ''pre-BLA'' meetings.* * * * The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. * * * To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:

* * * * *

(iii) Information on the status of needed or ongoing pediatric studies.

* * * * *

6. Section 312.82 is amended by revising the last sentence of paragraph (a) and by removing the second sentence of paragraph (b) and adding two sentences in its place to read as follows:

§ 312.82 Early consultation.

* * * * *

(a) *Pre-investigational new drug (IND) meetings.* * * * The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* * * * The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 357, 371, 374, 379e.

8. Section 314.50 is amended by adding paragraph (d)(7) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(7) *Pediatric use section.* A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under § 314.55.

* * * * *

9. Section 314.55 is added to subpart B to read as follows:

§ 314.55 Pediatric use information.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. Studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(b) *Deferred submission.* (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after approval of the drug product for use in adults. Deferral may be granted if, among other reasons, the drug is ready for approval in adults before studies in pediatric patients are complete, or pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers*—(1) *General.* FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) *Full waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(3) *Partial waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) *FDA action on waiver.* FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) *Definition of ''meaningful therapeutic benefit''.* For purposes of this section and § 201.23 of this chapter, a drug will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the drug would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, for example, evidence of increased effectiveness in treatment, prevention, or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of compliance, or evidence of safety and effectiveness in a new subpopulation; or

(ii) The drug is in a class of drugs or for an indication for which there is a need for additional therapeutic options.

(d) *Exemption for orphan drugs.* This section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

10. Section 314.81 is amended by revising paragraph (b)(2)(i) and (b)(2)(vii), and by adding paragraph (b)(2)(vi)(*c*) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) *Summary.* A brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product. The report is also required to contain a brief description of actions the applicant has taken or intends to take as a result of this new information, for example, submit a labeling supplement, add a warning to the labeling, or initiate a new study. The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

* * * * *

(vi) * * *

(*c*) Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(vii) *Status reports.* A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

* * * * *

PART 601—LICENSING

11. The authority citation for 21 CFR part 601 is revised to read as follows:

Authority: 15 U.S.C. 1451–1461; 21 U.S.C. 321, 351, 352, 353, 355, 360, 360c-360f, 360h-360j, 371, 374, 379e, 381; 42 U.S.C. 216, 241, 262, 263.

12. Section 601.27 is added to subpart C to read as follows:

§ 601.27 Pediatric studies.

(a) *Required assessment.* Except as provided in paragraphs (b), (c), and (d) of this section, each application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, usually supplemented with other information in pediatric patients, such as pharmacokinetic studies. In addition, studies may not be needed in each pediatric age group, if data from one age group can be extrapolated to another. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) *Deferred submission.* (1) FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. Deferral may be granted if, among other reasons, the product is ready for approval in adults before studies in pediatric patients are complete, pediatric studies should be delayed until additional safety or effectiveness data have been collected. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time.

(2) If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers*—(1) *General.* FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant. A request for a waiver must provide an adequate justification.

(2) *Full waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) *Partial waiver.* An applicant may request a waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group;

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed;

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) *FDA action on waiver.* FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraphs (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(5) *Definition of ''meaningful therapeutic benefit''.* For purposes of this section, a product will be considered to offer a meaningful therapeutic benefit over existing therapies if FDA estimates that:

(i) If approved, the product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labeled for that use in the relevant pediatric population. Examples of how improvement might be demonstrated include, e.g., evidence of increased effectiveness in treatment, prevention, or diagnosis of disease;

elimination or substantial reduction of a treatment-limiting drug reaction; documented enhancement of compliance; or evidence of safety and effectiveness in a new subpopulation; or

(ii) The product is in a class of products or for an indication for which there is a need for additional therapeutic options.

(d) *Exemption for orphan drugs.* This section does not apply to any product for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.

13. Section 601.37 is added to subpart D to read as follows:

§ 601.37 Annual reports of postmarketing pediatric studies.

Sponsors of licensed biological products shall submit the following information each year within 60 days of the anniversary date of approval of the license, to the Director, Center for Biologics Evaluation and Research:

(a) *Summary.* A brief summary stating whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) shall be provided, including dosage form.

(b) *Clinical data.* Analysis of available safety and efficacy data in the pediatric population and changes proposed in the labeling based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population shall be included.

(c) *Status reports.* A statement on the current status of any postmarketing studies in the pediatric population performed by, or on behalf of, the applicant. The statement shall include whether postmarketing clinical studies in pediatric populations were required or agreed to, and if so, the status of these studies, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the BLA (including date).

Dated: November 24, 1998.

Michael A. Friedman,

Acting Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 98–31902 Filed 11–27–98; 8:45 am]

BILLING CODE 4160–01–P

Exhibit 22

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942 (Dec. 11, 1992)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 314 and 601

[Docket No. 91N–0278]

RIN 0905–AD66

New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing final regulations under which the agency will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provisions for any necessary continued study of the drugs' clinical benefits after approval or with restrictions on use, if necessary. These new procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic benefit compared to existing treatment. Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence from adequate and well-controlled studies of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under these procedures will have met the requisite standards for safety and effectiveness under the Federal Food, Drug, and Cosmetic Act (the act) or the Public Health Service Act (the PHS Act) and, thus, will have full approval for marketing.

EFFECTIVE DATE: January 11, 1993.

FOR FURTHER INFORMATION CONTACT: Marilyn L. Watson, Center for Drug Evaluation and Research (HFD–360), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–295–8038.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of April 15, 1992 (57 FR 13234), FDA published proposed procedures under which the agency would accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. FDA provided 60 days for public comment, and, upon request, in the **Federal Register** of June 18, 1992 (57 FR 27202), extended the comment period for an additional 30 days until July 15, 1992. The final rule incorporates all of the provisions of the proposed rule and provides additional clarification regarding both timing and content of the submissions of promotional materials and regarding the nature of required postmarketing studies. The agency has added a new provision clarifying when certain postmarketing requirements of the rule will be terminated.

Highlights of the final rule are summarized below, followed by a summary and discussion of the comments.

II. Highlights of the Final Rule

This final rule establishes procedures under parts 314 and 601 (21 CFR parts 314 and 601) under which FDA will accelerate approval of certain new drugs and biological products for serious or life-threatening illnesses, with provision for required continued study of the drugs' clinical benefits after approval or for restrictions on distribution or use, where those are necessary for safe use of the drugs. These procedures are intended to provide expedited marketing of drugs for patients suffering from such illnesses when the drugs provide meaningful therapeutic advantage over existing treatment. The preamble of the proposed rule (57 FR 13234) provides a description of other mechanisms available to facilitate access, speed development, and expedite review of therapeutic products (e.g., treatment investigational new drug applications (IND's), subpart E, parallel track). Where appropriate, these mechanisms can be utilized in concert with accelerated approval. The major provisions of the final rule are as follows:

A. Scope

The new procedures apply to certain new drug, antibiotic, and biological products used in the treatment of serious or life-threatening diseases, where the products provide meaningful therapeutic advantage over existing treatment (21 CFR 314.500 and 601.40).

B. Criteria for Approval

Accelerated approval will be considered in two situations: (1) When approval can be reliably based on evidence of the drug's effect on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity, pending completion of studies to establish and define the degree of clinical benefits to patients; and (2) when FDA determines that a drug, effective for the treatment of a disease, can be used safely only if distribution or use is modified or restricted. Drugs or biological products approved under this final rule will have met the requisite standards for safety and effectiveness under the act or the PHS Act and, thus, will have full approval for marketing (21 CFR 314.510, 314.520, 601.41, and 601.42). Ordinarily, products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies, will be considered for approval under the traditional process rather than under accelerated approval.

C. Postmarketing Studies

Where a drug's approval under these provisions is based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity, the applicant will be required to conduct clinical studies necessary to verify and describe the drug's clinical benefit and to resolve remaining uncertainty as to the relation of the surrogate endpoint upon which approval was based to clinical benefit, or the observed clinical benefit to ultimate outcome. The requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval; it is expected that the studies will usually be underway at the time of approval. The proposed regulations have been revised to clarify that required postmarketing studies must also be adequate and well-controlled (21 CFR 314.510 and 601.41).

D. Restrictions on Use After Marketing

FDA may grant marketing approval of a drug or biological product shown to be effective where safe use can only be assured if distribution or use is restricted. Under this final rule, FDA may: (1) Restrict distribution to certain facilities or to physicians with special training or experience, or (2) condition distribution on the performance of

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specified medical procedures. The restrictions on use will be tailored to the specific safety issue raised by the particular drug or biological product and agreed to by the applicant at the time of approval (21 CFR 314.520 and 601.42). FDA expects that the imposition of these restrictions on distribution will be rare.

E. Promotional Materials

The final rule requires submission of planned promotional materials, including promotional labeling and advertisements, both prior to approval (reflecting the initial campaign), and following approval, unless informed by the agency that such submission is no longer necessary, at least 30 days before the intended time of initial dissemination of the promotional labeling or initial publication of the advertisement (21 CFR 314.550 and 601.45).

F. Withdrawal of Approval

The final rule establishes an expedited procedure for the withdrawal of approval if: (1) Postmarketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the required postmarketing study with due diligence; (3) use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug or biological product; (4) the applicant fails to adhere to the postmarketing restrictions agreed upon; (5) the promotional materials are false or misleading; or (6) other evidence demonstrates that the drug or biological product is not shown to be safe or effective under its conditions of use (21 CFR 314.530 and 601.43).

G. Termination of Requirements

In response to comments, the final rule provides that the requirements set forth in §§ 314.520, 314.530, and 314.550 for new drugs and antibiotics and §§ 601.42, 601.43, and 601.45 for biological products ordinarily will terminate when FDA determines that the results of required postmarketing studies have demonstrated that the drug or biological product has clinical benefit, or, where restrictions on distribution or use have been imposed, when FDA determines that safe use of the drug or biological product can be ensured without such restrictions, e.g., through appropriate labeling. FDA will notify the applicant when these requirements no longer apply (21 CFR 314.560 and 601.46).

III. Effective Date

This regulation will become effective on January 11, 1993.

IV. Comments on the Proposed Rule

FDA received 54 comments on the proposed rule. The comments came from individuals, specific disease organizations, universities, pharmaceutical manufacturers, trade associations, health professionals, and professional societies. The comments reflect broad support and acceptance of the goal of expediting the approval of drugs intended for the treatment of serious and life-threatening illnesses. A number of comments asked that the proposal be finalized expeditiously without change. Many comments posed specific questions and raised important concerns.

A. General Comments

1. One comment suggested that the term "conditional approval" was less confusing and ambiguous than the term "accelerated approval." The comment also referred to the statement in the proposal that "Drugs * * * approved under this proposal will have met the requisite standards * * * under the (act)" and argued that because postmarketing conditions may be imposed, this statement can only be read to say that the requisite standards under the act can only be met by a lower standard of evidence in hand, combined with assurance that further evidence will be obtained.

Another comment expressed concern that the proposal appears to establish a standard for the evaluation of drug product effectiveness that is inconsistent with the substantial evidence requirement of section 505(d) of the act (21 U.S.C. 355(d)), which means "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling * * *." The comment argued that, with few exceptions, the agency has consistently interpreted the "substantial evidence" requirement as an instruction that determinations of effectiveness be based on data unambiguously reflecting the clinical status of subjects evaluated under controlled conditions in bona fide clinical experiments. In the absence of compelling empirical evidence documenting that a drug-induced change in a surrogate measure reliably and consistently predicts improved clinical outcome, a surrogate indicator is no more than a hypothetical construct. The comment asserted that the proposed rule's endorsement of the use of unvalidated surrogate endpoints, therefore, appears to represent a significant departure from traditional agency interpretations of "substantial evidence" within the meaning of the act because it allows belief rather than evidence to serve as the basis for a conclusion about the effectiveness of a new drug.

Three comments asserted that the new regulations are not needed to approve drugs intended to treat serious or life-threatening illnesses. Two comments cited FDA's approval, without new regulations, of didanosine (formerly called ddi) and zalcitabine (formerly called ddc) in combination with zidovudine (formerly called AZT) based on a surrogate marker, i.e., an increase in CD4 cell counts and the "subpart E" procedures at 21 CFR part 312, which address the need for expediting the development, evaluation, and marketing of new therapies intended to treat life-threatening or severely debilitating illnesses as examples of existing mechanisms for the expedited approval of important new drugs. One comment argued that the act requires that drugs be shown to be "safe" and "effective," and proof of effectiveness is not limited by the act to demonstration of an effect on "survival or irreversible morbidity," as the proposed rule seems to assume. The comment further argued that FDA has considerable statutory discretion to define what type of data constitutes proof of effectiveness, and demonstration of an effect on a surrogate marker is one type of such proof.

The agency believes that what the procedures are called is much less important than what the procedures are. The shorthand term selected by the agency reflects the intent of the rule, especially that part related to use of surrogate markers, which is to make drugs that provide meaningful improvement over existing therapies for serious illnesses widely available (through marketing) at the earliest time consistent with the law. The essence of the proposal is thus acceleration, not the imposition of conditions. Approval under these procedures is dependent on compliance with certain additional requirements, such as timely completion of studies to document the expected clinical benefit. The evidence available at the time of approval under this rule will meet the statutory standard, in that there must be evidence from adequate and well-controlled studies showing that the drug will have

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the effect it is represented to have in its labeling. That effect will, in this case, be an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit and labeling will refer to the effect on the surrogate, not to effect on clinical outcome.

While the act does not refer to particular endpoints or state a preference for clinical, as opposed to surrogate, endpoints, it is well established that the effect shown in well-controlled studies, must, in the judgment of the agency, be clinically meaningful. Moreover, the safety standard in the act, that a drug must be shown to be safe for its intended use, implies a risk/benefit judgment. The effect shown must be such as to outweigh the risks of the treatment under the conditions of use. Approval under this rule requires, therefore, that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a "lower standard" or one inconsistent with section 505(d) of the act, but rather an assessment about whether different types of data show that the same statutory standard has been met.

Approval based on surrogate endpoints is not new, although the issue has not previously been considered in regulations. The agency has, in a number of instances, approved drugs based on surrogate endpoints. For example, drugs for hypertension have been approved based on their effects on blood pressure rather than on survival or stroke rate. Similarly, drugs for hypercholesterolemia have been approved based on effects on serum cholesterol rather than on coronary artery disease (angina, heart attacks). But, in those cases there was very good evidence from clinical trials (in the case of hypertension) and from epidemiologic and animal studies (in the case of hypercholesterolemia) that improving the surrogate would lead to or is associated with the desired effects on morbidity and mortality. Even so, there is still today considerable debate about who will benefit from cholesterol lowering. Controlled trials assessing effects on clinical endpoints of morbidity and mortality from use of cholesterol-lowering drugs have been, and are being, conducted.

Reliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known. The expected risk/benefit relationship may fail to emerge because: (1) The identified surrogate may not in fact be causally related to clinical outcome (even though it was thought to be) or (2) the drug may have a smaller than expected benefit and a larger than expected adverse effect that could not be recognized without large-scale clinical trials of long duration. Reliance on surrogate markers therefore requires an additional measure of judgment, not only weighing benefit versus risk, as always, but also deciding what the therapeutic benefit is based upon the drug effect on the surrogate.

The sections of the final rule that address approval based upon a drug effect on a surrogate endpoint specifically clarify the regulatory approval criteria when the agency relies on a surrogate endpoint that, while "reasonably likely" to predict clinical benefit, is not so well established as the surrogates ordinarily used as bases of approval in the past. Postmarketing studies required to verify and describe actual clinical benefits would also be required to be adequate and well-controlled studies. Sections 314.510 and 601.41 have been revised to clarify this point. If, on completion of required postmarketing studies, the effect on the surrogate is not shown to correspond to a favorable effect on clinical benefit, the rule provides an expedited means of removing the drug from the market.

Approval of didanosine and zalcitabine under current procedures does not show that the rule is of no value. Although approval did rely on a surrogate endpoint that is of the kind specifically addressed by the rule, the fact that studies to define clinical benefit were nearly complete and were being conducted under the auspices of the National Institute of Allergy and Infectious Diseases made it less crucial to have additional guarantees that such studies would be conducted promptly. Moreover, the sponsors of didanosine and zalcitabine agreed prior to approval to expedited withdrawal of the drug from the market if benefit were not shown. The provisions of the final rule will ensure that appropriate safeguards exist for timely generation of data on actual clinical benefit, for appropriate promotional information about labeled indications, and for prompt withdrawal of the drug from the market if clinical benefit is not confirmed.

2. Pointing to a statement in the preamble to the proposed rule that it is in the public interest to make promising new treatments available at the earliest possible point in time for use in life-threatening and serious illnesses, one comment expressed concern that the proposed rule may lead to the marketing of large numbers of clinically ineffective, but pharmacologically active, drugs and this may not be in the interest of the public health. The comment argued that early access to so-called "promising" drugs is not the same as early access to safe and effective drugs, and the number of potential markers that may be advanced as surrogates of clinical outcome is exceedingly large. The comment suggested that it may be more appropriate to seek adoption of the proposed requirements through an amendment to the act.

FDA agrees with the contention that providing people who have serious or life-threatening illnesses with numerous clinically ineffective drugs would not be helpful. However, the agency does not agree that the rule can be expected to have this result. Although studies using surrogate endpoints may provide less assurance of clinical benefit than studies using clinical endpoints, FDA believes compliance with all of the elements of the accelerated approval program will not result in the marketing of large numbers of clinically ineffective drugs. The new procedures apply to a limited group of circumstances, namely, to drugs intended for serious or life-threatening illnesses when the drugs provide a meaningful therapeutic benefit over existing therapy. Reliance on a surrogate endpoint is not equivalent to reliance on any evidence of pharmacologic activity. The endpoint must be reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit.

Whether a given endpoint is, in fact, reasonably likely to predict clinical benefit is inevitably a matter of judgment. FDA, using available internal and external expertise, will have to make informed judgments in each case presented, just as it does now. The agency acknowledges that there are well-recognized reasons for caution when surrogate endpoints are relied on. Certain putative surrogates have ultimately been shown not to correspond to clinical benefit. Perhaps the most noteworthy example is the failure of antiarrhythmic agents in the Cardiac Arrhythmia Suppression Trial (CAST) to improve survival by depressing ventricular ectopic beats; effective suppression of ectopic beats was associated with increased mortality.

A sponsor must persuasively support the reasonableness of the proposed surrogate as a predictor and show how the benefits of treatment will outweigh the risks. Such presentations are likely to be persuasive only when the disease to be treated is particularly severe (so

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that considerable risk is acceptable) and/or when the surrogate endpoint is well supported. In addition, it will be the sponsor's clear obligation to resolve any doubts as to clinical value by carrying out definitive studies.

FDA does not agree that it would be more appropriate to seek an amendment to the act than to adopt the proposed requirements. As discussed in the preamble to the proposed rule as well as elsewhere in this preamble to the final rule, existing provisions of the act and the PHS Act authorize promulgation of the requirements in the final regulations.

3. One comment expressed concern that because the proposed rule would establish conditions on a drug's approval, third-party payors may decline reimbursement because the so-called approval would have attributes of investigational status.

The agency expects that, because drugs approved under the accelerated approval process meet the statutory standards for safety and effectiveness, they would be eligible for reimbursement under State Medicaid programs or other third-party plans. Drug products granted accelerated approval will not be, under the law, investigational, as suggested by the comment.

4. One comment asked if all drugs considered for accelerated approval must be reviewed by an advisory committee. The comment stated that because advisory committees meet infrequently, waiting for the next meeting may slow down the approval process.

FDA is not required to consult with an advisory committee before approving an application under these accelerated approval regulations, or any other regulation. However, FDA intends to consult the appropriate committee in most instances. Advisory committee meetings can usually be scheduled to avoid significant delays in the review process. The agency will consider any request by an applicant for referral of the application to an advisory committee.

B. Scope

5. Four comments asked for further clarification of what diseases are covered by the rule. One comment stated that the terms "serious," and "life-threatening," are defined in the proposal by reference to 21 CFR 312.34, followed by a brief statement explaining the role of judgment and examples of diseases that are currently judged to be serious. The comment asked that FDA also describe: (1) Diseases that are not currently included in the category of "serious," (2) examples of diseases that are currently judged "life-threatening," and (3) examples of diseases that are not currently included in the category "life-threatening."

One comment contended that the statement in the preamble that "seriousness of a disease is a matter of judgment, but generally is based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one" too narrowly limits diseases covered by the proposed rule (57 FR 13234 at 13235). The comment argued that some "less severe" diseases, even if treated, may progress to a more serious state, and that these diseases should also be covered by the rule. On the other hand, two comments argued that the language in the preamble that classifies diseases as "serious" was overly broad and subjective and far too large a number of illnesses could be eligible as being "serious."

FDA discussed the meaning of the terms "serious" and "life-threatening" in its final rules on "treatment IND's" (52 FR 19466 at 19467, May 22, 1987) and "subpart E" procedures (54 FR 41516 at 41518–41519, October 21, 1988). The use of these terms in this rule is the same as FDA defined and used the terms in those rulemakings. It would be virtually impossible to name every "serious" and "life-threatening" disease that would be within the scope of this rule. In FDA's experience with "treatment IND's" and drugs covered by the "subpart E" procedures there have not been problems in determining which diseases fall within the meaning of the terms "serious" and "life-threatening," and FDA would expect no problems under this accelerated approval program. The likelihood of progression to a serious condition with available treatments would also be considered in assessing whether the disease is within the scope of the final rule. The preamble to the proposed rule (57 FR 13234 at 13235) referred to chronic illnesses that are generally well managed by available therapy, but can have serious outcomes for certain populations or in some or all of their phases. Applicants are encouraged to consult with FDA's reviewing divisions early in the drug development process if they have questions about whether their specific product is within the scope of this rule.

The concerns expressed in these and other comments about considering too many illnesses eligible for consideration under the accelerated approval procedures may arise from the underlying fear that reliance on surrogate endpoints will become routine, the "normal" way drugs are brought to the market. This fear is groundless. The vast majority of drugs are directed at symptomatic or short-term conditions (pain, heart failure, acute infections, gastrointestinal complaints) whose response to drugs, if it occurs, is readily measured and where there is no need to consider or accept surrogate endpoints. Surrogates, with few exceptions, are of interest in the following situations: (1) Where the clinical benefit, if there is one, is likely to be well in the future; and (2) where the implications of the effect on the surrogate are great because the disease has no treatment at all or the drug seems to treat people with no alternative (e.g., because they cannot tolerate the usual effective treatment). In the first case, great care is needed, and would be given, as there would generally be no experience linking an effect on the surrogate to clinical success, and there have been conspicuous examples of lack of linkage (CAST, referred to above; drugs that increase cardiac output in patients with heart failure but that decrease survival; imperfect agreement of effects on coronary artery patency and effects on survival in patients with myocardial infarction; lack of beneficial effect on bone fracture rate despite favorable effects on bone density in patients with osteoporosis). FDA and outside experts will be aware of these examples as proposed surrogates are considered. The implications are especially great when considering prophylactic therapy, i.e., treatments to prevent chronic illness (coronary artery disease, cancer), in an essentially well population. In the second case, there will generally have been experience (with the standard therapy) to evaluate in considering linkage of the surrogate to benefit; this was, for example, the case with didanosine, where evidence from zidovudine studies of the relationship of an effect on CD4 lymphocytes and clinical outcome could be assessed. Similarly, there is considerable experience to show that durable complete responses in many cancers correspond to improved survival, so that an agent inducing them in refractory illness or in primary

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disease that had previously been poorly responsive would generally be seen as reasonably likely to provide a clinical benefit.

6. One comment stated that epilepsy is a serious and life-threatening condition and asked that it be included within the scope of the proposal. The preamble cited, among other illnesses, depression and psychoses as examples of chronic illnesses that can have serious outcomes even if they are generally well managed. One comment asserted that neither depression nor psychosis is a disease, nor is either one serious or life-threatening. The comment stated that depression and psychosis are diagnoses. The comment urged the agency to remove them from the definition of life-threatening "illnesses" or "diseases."

With respect to epilepsy, FDA notes that in the "treatment IND" final rule (52 FR 19466 at 19467, May 22, 1987), the agency listed "certain forms of epilepsy" as an example of a disease or stage of disease that would normally be considered "serious." Certain forms of epilepsy may also be considered "serious" under the accelerated approval program. It is unlikely, however, that a surrogate endpoint would be utilized in such a case, as seizure frequency, a clinical endpoint, is readily measured.

FDA's reference to depression and psychoses was intended to give examples of conditions or diseases that can be serious for certain populations or in some or all of their phases. While drugs for the treatment of depression and psychosis would be examples of those that could be covered by the accelerated approval program, it is not the use of surrogate endpoints that would be expected; the symptoms and signs of these diseases are readily studied. On the other hand, some of these drugs have been quite toxic (e.g., clozapine for refractory psychoses) and might be considered for approval with restrictions to ensure safe use.

7. Two comments asked how FDA will decide that a drug is eligible for accelerated approval. One comment asserted that the decision should be an option for the applicant to consider, not a decision for FDA to make unilaterally. Pointing to a statement in the preamble (57 FR 13234 at 13235) that FDA reserves the right not to apply accelerated approval procedures when it believes in good faith that the drug's foreseeable use is reasonably likely to be outside the scope of "life-threatening diseases without meaningful therapeutic benefit over existing therapy," the comments argued that, if there are patients with life-threatening conditions that can benefit from expedited approval, the needs of the patients should determine the procedures used to approve the drug. One comment contended that applicants of products considered candidates for accelerated approval may have their drug or biological product "forced" into the accelerated approval process and be forced to conduct a program of studies to substantiate that surrogate endpoints actually predict significant clinical benefits.

The medical reviewing divisions within FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) will determine the type of regulatory review that FDA may apply to an application. FDA encourages sponsors to meet with FDA early in the drug development process to discuss the applicability of the accelerated approval program to their product; however, FDA reserves the discretion to determine whether these procedures are applicable to a specific product.

With respect to the preamble statement cited by one comment, the comment misreads the preamble statement, which does not say that FDA will, in all cases, apply FDA's traditional approval mechanisms rather than this accelerated process for drugs where a majority of the drug's foreseeable uses are outside the scope of "life-threatening" diseases without meaningful therapeutic benefit over existing therapy. The statement merely informs applicants that FDA will consider the possible impact of widespread use of a drug for uses other than the one supporting accelerated approval; drugs approved under this program would often have only small safety data bases so that widespread off-label use might have serious implications. The agency does not believe that such a situation would regularly lead to exclusion from these provisions.

FDA does not agree that applicants seeking approval to market drug and biological products that would be candidates for accelerated approval will be forced to use the accelerated approval mechanism. It is true, however, that some proposed surrogate endpoints would not be considered acceptable bases for approval without assurance that the clinical studies to show clinical benefit will be conducted. A sponsor that wishes the application to be considered under the traditional approval process may request and receive such consideration.

The agency wishes to clarify the circumstances in which the accelerated approval regulations will apply. Sections 314.500 and 601.40 describe aspects of the scope of these regulations. Moreover, these regulations are intended to apply to applications based on surrogate endpoints whose validity is not fully established, to applications based on clinical endpoints that leave unanswered major questions about the product's effect on ultimate outcome, and to applications for products whose safe and effective use requires limitations on distribution or use. In all other situations, accelerated approval requirements will not apply.

Where approval is based on a surrogate endpoint that is accepted as validated to predict or correlate with clinical benefit, the product will be considered under the traditional process, and the postmarketing requirements under accelerated approval will not apply. Approvals of products for serious or life-threatening illnesses based on clinical endpoints other than survival or irreversible morbidity will usually also be considered under traditional procedures. Approvals based on such clinical endpoints will be considered under the accelerated approval regulations only when it is essential to determine effects on survival or irreversible morbidity in order to confirm the favorable risk/benefit judgment that led to approval. Applications for products for serious or life-threatening illnesses that provide a meaningful therapeutic benefit over existing therapy will receive a priority rating and expedited review, even when not considered under the accelerated approval procedures.

The agency also wishes to clarify that whenever an application is approved under § 314.510 or § 601.41, postmarketing studies confirming the product's clinical benefit will thus be required. Therefore, in order to eliminate potential confusion, the agency has amended §§ 314.510 and 601.41 to clarify these points.

FDA also recognizes that over time a particular surrogate, once acceptable as a basis for approval only under the accelerated approval regulations, could become recognized as validated by definitive studies (just as high blood pressure, for example, over time became validated as a surrogate with clinical significance). In such cases, a future application relying on such a surrogate would not require postmarketing studies confirming the surrogate's clinical benefit and the application would be considered under traditional procedures.

8. Two comments asked for clarification of the phrase "meaningful

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therapeutic benefit over existing therapy" as used in the description of what drugs the accelerated approval program should apply to. Specifically, pointing to an example described in the preamble that a new therapy would be eligible for accelerated approval if there was "a clear improvement" over existing therapy in being more effective or better tolerated, one comment urged FDA to clarify the meaning of "clear improvement" to discourage applicants of "me-too" products from wasting the agency's time and resources by applying for accelerated approval of such products. The comment also asked that FDA specify that if a new drug is approved under the accelerated approval provisions because the drug exhibits a "clear improvement" over an existing drug that was also granted accelerated approval, then specific restrictions will be placed on the prior approved drug to limit its use only to patients who cannot tolerate the new drug, or whose physicians assess that a change to the new drug might involve significant risks to the patient that outweigh the benefits. One comment asked that the term "meaningful therapeutic benefit over existing therapy" be interpreted and consistently applied to both drugs and biological products.

FDA believes that the examples given to help clarify the phrase "meaningful therapeutic benefit over existing therapy" (ability to treat unresponsive or intolerant patients or improved response compared to available therapy) are readily understood illustrations of the intent of the requirement. A drug that is essentially the same as available treatment (what the comment refers to as a "me too" drug) will not have a credible claim to a meaningful therapeutic benefit over that existing treatment and this should be easily detected.

With respect to restricting use of a drug previously approved under accelerated approval procedures when a new drug granted accelerated approval is a clear improvement over the prior approved drug, this would rarely be appropriate. Although, in some instances, certain therapies are identified as "second-line," this requires essentially unequivocal evidence of an advantage of alternative therapy, not likely on the basis of a surrogate endpoint. Labeling for both drugs will be accurate, however, allowing physicians to prescribe both the newly approved drug and the prior drug properly.

9. One comment asked if a change in the route of administration would be considered as a meaningful benefit and within the scope of the proposal.

A change in the route of administration may be a candidate for accelerated approval depending upon the particular evidence presented.

10. One comment asked if subpart E drugs currently under investigation will be considered for accelerated approval. The comment assumed that new drug applications (NDA's) and supplemental NDA's considered for accelerated approval will have the highest priority for review.

Subpart E drugs will be considered for accelerated approval if they satisfy both eligibility criteria for accelerated approval, i.e., if they are being developed for the treatment of serious or life-threatening illnesses and the products will provide meaningful therapeutic benefits to patients over existing treatment. As discussed above, applicants should consult with FDA early in the development process to determine the nature of the regulatory review. Early consultations are a critical part of subpart E procedures. Drugs being reviewed under accelerated approval procedures will receive high priority review. However, applications for drugs for acquired immunodeficiency syndrome (AIDS) and human immunodeficiency virus (HIV)-related conditions will receive the highest priority review.

C. Criteria for Approval

11. Two comments expressed concern that the proposal did not provide enough detail on what constitutes an appropriate surrogate endpoint. One comment recommended that FDA adopt specific criteria for what constitutes an appropriate surrogate endpoint. The comment suggested that such criteria should include: (1) The surrogate endpoint must be biologically plausible in that it must be consistent with what is known about the pathophysiology and pathogenesis of the disease; (2) the surrogate endpoint must be present or abnormal in a large percentage of people who have the disease; (3) the surrogate endpoint must be a good predictor of the disease progression and should correlate closely with the significant clinical endpoint; (4) there should be a correlation between the quantitative aspect of the surrogate endpoint and the progression of the disease (e.g., the more severe the disease, the more deviant the surrogate endpoint from normal); (5) the regression of the surrogate endpoint should be significantly associated with clinical improvement (e.g., those with the greatest improvement in the surrogate endpoint should also show the greatest clinical effects); conversely, the lack of regression of the surrogate endpoint should be commonly associated with a lack of clinical improvement; and (6) the incidence of regression or improvement in the surrogate endpoint should be significantly greater in treated than untreated patients.

One comment asked if the use of microalbuminuria data is a surrogate for diabetic nephropathy and if all drugs relying on surrogate endpoints would be eligible for accelerated approval, e.g., an angiotensin receptor antagonist with potential utility for treatment of congestive heart failure. The comment also asked what would happen if postmarketing studies demonstrate beneficial changes of surrogate endpoints but not beneficial clinical endpoints. The comment also asked if FDA will consider publishing guidelines on which surrogate endpoints would be appropriate for the diseases that may be affected by the proposed rule. Another comment expressed the belief that there is no evidence that surrogate endpoints are necessarily good indicators of therapeutic benefit. The comment stated that a drug may have an effect on a surrogate endpoint, but will not make any clinical difference because the advanced stage of the patient's disease precludes any effective therapy or the surrogate marker is not synchronous with the patient's clinical condition.

Another comment asserted that the requirement to base an approval on a surrogate endpoint that is "reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit other than survival or irreversible morbidity" is not restrictive enough to assure adequate consumer protection. Terms like "reasonably likely" and "or other evidence" allow drug manufacturers too much latitude for claiming that there is a correlation between surrogate endpoints affected by their drugs and clinical endpoints. The comment argued that until a correlation between a surrogate endpoint and a clinical endpoint has been established, a particular surrogate endpoint should only be used to approve subsequent drugs, without adequate clinical evidence, if there is a very strong effect of the drug on the surrogate marker or, if the effect is not sufficiently strong, there is an additional surrogate marker which corroborates the results of the first.

FDA intends to publish informal guidance concerning surrogate endpoints, but does not believe specific requirements for an appropriate surrogate should be specified by

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regulation. Any given specifications may not be applicable to a particular case. For example, the thoughtful suggested criteria supplied by the comment would rarely, if ever, be applicable to the first effective drug for a disease, because criterion 5 requires that regression of the surrogate endpoint be associated quantitatively with clinical improvement. If there had never been effective treatment, this would never be known. Yet the surrogate could be persuasive on other grounds, such as a well-documented etiologic relation. In general, it is likely that one or another strongly supportive piece of evidence might outweigh gaps in other areas.

In developing informal guidance on surrogate endpoints, FDA will consider the suggestions in this comment. Interested persons will have an opportunity to comment on any guidance documents in this area developed by the agency. In some cases, new or revised drug class, or disease-specific, clinical guidelines may refer to surrogate endpoints. FDA is not prepared, at this time, to comment on the acceptability of an endpoint that it has not specifically considered, e.g., microalbuminuria.

The final regulations make it clear that not all drugs submitted for approval based on surrogate endpoint data are eligible for accelerated approval (§§ 314.500 and 601.40). The drug in question must be for a serious or life-threatening condition and must provide meaningful therapeutic benefit over existing therapy. In the case of an angiotensin receptor antagonist posed by the comment, there is existing documented life-prolonging treatment for congestive heart failure. An application for a new agent, to be eligible for accelerated approval, would have to show potential benefit over available therapy as well as identify a reasonable surrogate endpoint. This is problematic since no accepted surrogate endpoint for studies to treat congestive heart failure has been identified to date. For example, some drugs with favorable effects on hemodynamic measures in heart failure patients have been clinically ineffective.

The regulations are clear in requiring that, for drugs approved under these provisions based on surrogate endpoints, the postmarketing studies must show clinical benefit, not just the previously shown effect on the surrogate (§§ 314.510, 314.530, 601.41, and 601.43).

Surrogates, or proposed surrogates, are not always good, nor necessarily bad, indicators of therapeutic benefit and must be judged on a case-by-case basis. Even very good surrogates may not be perfect: Blood pressure lowering has been a better predictor of effect on stroke than on coronary artery disease, cholesterol lowering has had a clearer effect on coronary artery disease than on survival. Moreover, a surrogate may be persuasive for a phase of disease with short expected survival but much less so in an earlier phase of the disease. Caution is always appropriate in evaluating surrogate endpoints and the particular therapeutic setting should always be considered. The agency believes that the evaluation of surrogate endpoint data and the safeguards built into these accelerated approval procedures will provide adequate consumer protection.

12. One comment expressed concern that if there is no accepted surrogate endpoint, an applicant's only option is to conduct a study using some clinical event as an endpoint, which may result in long, large studies that delay approval to the detriment of patients and sponsors. One comment suggested as an alternative that FDA permit approval of a drug based on a study using a clinical endpoint, but accept a less rigorous standard of statistical significance, e.g., 0.20 or 0.15 instead of 0.05. The comment further suggested that the sponsor could then complete postmarketing studies to establish statistical significance at conventional levels. The comment argued that this alternative is totally consistent with FDA's willingness to accept greater uncertainty in approving drugs for serious and life-threatening illnesses.

The intent of the rule is to allow FDA to utilize a particular kind of evidence, an effect on a surrogate endpoint, as a basis for approval, and, where appropriate, to ensure that remaining doubts about the relationship of the effect on the surrogate to clinical benefit are resolved by additional adequate and well-controlled studies with clinical endpoints. The rule is not intended to place into the market drugs with little evidence of usefulness. Although there is no statutory requirement for significance testing of any particular value, there are well-established conventions for assessing statistical significance to support the statutorily required conclusion that the well-controlled studies have demonstrated that a drug will have the effect it is represented to have. There is nothing about serious or life-threatening diseases that make them uniquely difficult to study. A meaningful effect on survival or morbidity where there is no effective therapy should be readily discerned. Such studies need be long and large only when the effect is small or difficult to detect. In that event, proper assessment of benefit, and valid weighing of its relation to risk, is especially critical.

13. One comment asked that FDA clarify that one study could be the basis of approval and that one postmarketing study should be all that is needed to establish the link between the endpoint used for approval and some relevant clinical benefit.

FDA interprets the statute, and good science, as requiring at least two adequate and well-controlled studies to establish effectiveness. In some instances, drugs have been approved on the basis of a single well-controlled study; this has been done where the study was of excellent design, showed a high degree of statistical significance, involved multiple study centers, and showed some evidence of internal replicability, e.g., similar effects in major study subsets. FDA encourages applicants to discuss with FDA early in a drug's development the basis for the applicant's choice of a specific endpoint and, where applicable, the basis for its belief that a single study would be a sufficient basis for approval. With respect to postmarketing studies, FDA anticipates that the requirement will usually be met by studies already underway at the time of approval. As stated in the proposed rule, the requirement for any additional study to demonstrate actual clinical benefit will not be more stringent than those that would normally be required for marketing approval of the same drug for the same claim.

14. One comment expressed concern that the preamble to the proposed rule implied that a sponsor of an AIDS drug might have to do a postmarketing study to establish an effect on survival after showing an effect on such endpoints as weight or incidence of opportunistic infection (57 FR 13234 at 13235–13236). The comment stated that FDA's own advisory committee indicated that it was pleased to see an effect from a nucleoside analogue on the incidence of opportunistic infections with AIDS patients but did not suggest that further work should be done to show an effect on mortality. The comment argued that in some cases direct correlation with clinical endpoints such as mortality is difficult to prove and urged FDA to be flexible on this issue to encourage sponsors to go through the accelerated approval process.

Ordinarily, an effect on a meaningful clinical endpoint, e.g., on rate of opportunistic infections in AIDS, is a sufficient basis for approval without need for followup studies. Other endpoints, however, might leave major questions unanswered. For example, a

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modest effect on weight gain in AIDS without other demonstrated benefit, if considered an adequate basis for approval, while a clinical endpoint, might leave sufficient doubt as to the ultimate value of the effect so that further studies would be necessary. FDA intends to interpret this provision of the regulations with flexibility. This provision should also serve as a reminder, however, that for life-threatening diseases, the ultimate aim of therapy is improved survival as well as improved symptoms.

15. One comment asked FDA to clarify what a sponsor's obligation is to continue supplying medication on a compassionate basis if clinical efficacy is not demonstrated to FDA's satisfaction in postmarketing studies but individual patients appear to be benefiting from use of the drug.

Sponsors are not obligated to supply drugs on a "compassionate basis." Whether, if clinical studies did not show effectiveness, further availability of the drug would be appropriate under any mechanism would be determined case-by-case.

D. Promotional Materials

16. Three comments asserted that requiring advance submissions of promotional materials is both beyond FDA's statutory authority and is unnecessary. Although FDA stated in the proposal that it does not intend specifically to approve promotional materials, two comments contended that is the likely effect of advance submission. The comment cited section 502(n) of the act (21 U.S.C. 352(n)), which provides that no regulation promulgated under that provision shall require prior FDA approval of the content of any advertisement "except in extraordinary circumstances," and asserted that the "extraordinary circumstances" language would not apply to drugs approved under the accelerated approval program. One comment argued that submission of promotional material prior and subsequent to approval is unwarranted when dealing with treatments for serious or life-threatening illnesses where dissemination of the most current and timely information is important to the treating physician. One comment questioned why there would be any greater likelihood of misleading promotional claims for products approved under the proposed accelerated approval process than for drugs intended to treat serious or life-threatening diseases that are approved under the normal NDA procedures. The comment also expressed the hope that the proposed requirement for advance submission of promotional materials was not based upon an assumption that promotional materials for drugs intended to treat serious diseases are more likely to be misleading than promotional materials for other types of drugs because any such assumption would be unfounded. One comment argued that if an advertisement or labeling is inaccurate, the product is misbranded and FDA could then obtain injunctive relief, seize the product, and/or initiate criminal proceedings. Another comment considered requiring advance submission of promotional materials unreasonable because companies are not required to do so now. One comment questioned the legal authority for requiring presubmission of promotional material following approval of a drug product, and the reason for the requirement.

The agency believes that the requirements for submission of promotional materials in the context of accelerated approval are authorized by statute. Subsections 505(d)(4) and (d)(5) of the act provide that, in determining whether to approve a drug as safe and effective, the agency may consider not only information such as data from clinical studies but also "any other information" relevant to safety and effectiveness under the proposed conditions of use. Such information would include information about how the drug would be promoted. In determining whether the drug's proposed labeling would be "false or misleading" under section 505(d)(7) of the act, the agency is similarly authorized to evaluate "all material facts" during the approval process, including the facts about promotion.

FDA is also authorized by section 505(k) of the act to require reporting of information subsequent to approval necessary to enable the agency to determine whether there may be grounds for withdrawing the approval. Among the grounds for withdrawal specified in section 505(e) of the act are that the evidence reveals the drug is not shown to be safe and effective under its conditions of use. In addition, drug approval may be withdrawn if information shows the labeling to be false or misleading. Information on how the drug will be promoted is again relevant to whether the drug's marketing approval should be withdrawn. Section 701(a) of the act (21 U.S.C. 371(a)) generally authorizes FDA to promulgate regulations for the efficient enforcement of the act.

For biological products, additional authority in section 351 of the PHS Act (42 U.S.C. 262) authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products. The content of promotional materials is important to the continued safe and effective use of biologicals.

Therefore, the provisions of the final rule requiring submission of promotional materials prior to approval under the accelerated approval procedures and subsequent to such approval are authorized by statutory provisions. FDA might also invoke the authority of section 502(n) of the act (21 U.S.C. 352(n)) to require prior approval of the content of any prescription drug advertisement in "extraordinary circumstances." Whether FDA could appropriately rely on section 502(n) of the act in promulgating §§ 314.550 and 601.45 need not be determined, however, because FDA is not relying upon section 502(n) of the act as legal authority for these (or any other) sections of the accelerated approval regulations.

The agency believes that advance submissions of promotional materials for accelerated approval products are warranted under the accelerated approval circumstances. The special circumstances under which drugs will be approved under these provisions and the possibility that promotional materials could adversely affect the sensitive risk/benefit balance justify review of promotional materials before and after approval. For example, if the promotional materials exaggerate the known benefits of the drug, wider and inappropriate use of the drug could be encouraged, with harmful results.

Similarly, high risk drugs that are approved based on postmarketing restrictions would not have been approved for use without those restrictions because the risk/benefit balance would not justify such approval. If promotional materials were to undermine the postmarketing restrictions, the health and safety of patients could be greatly jeopardized.

Although there is potential harm from any misleading promotion, and there is no reason to believe improper promotion is more likely in this setting than in others, the risk/benefit balance is especially sensitive in this setting. The relatively small data base available and the minimal published information available also can contribute to making the physician and patient populations particularly vulnerable under accelerated approval circumstances.

Reliance on court actions (such as seizures, injunctions, and criminal prosecutions) can be effective in ending false promotions, but can only be initiated after the fact, when harm has already occurred. Corrective efforts can

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be helpful but are always somewhat delayed. Under the circumstances of accelerated approval, FDA believes that it is far preferable to avoid problems by reviewing the promotional materials in advance of drug approval and of dissemination of the materials.

17. Two comments supported the provision about submission of promotional materials. One comment urged the agency to require that specific patient information be included in promotional materials to indicate the fact that the drug's clinical benefit has not yet been established. For drugs approved under the restricted use provision, the comment recommended that the labeling specify in detail the exact restrictions placed on the drug. In both cases, the comment recommended that this patient information appear as boxed warnings.

Section 502(n) of the act and regulations at § 202.1(e)(1) (21 CFR 202.1(e)(1)) require prescription drug advertisements (promotional material) to contain, among other things, a true statement of information in brief summary relating to side effects, contraindications, and effectiveness, which would include warnings, precautions, and limitations on use. The information in brief summary relating to side effects, contraindications, and effectiveness is required to be based solely on the approved labeling. Therefore, to the extent that a drug's labeling reflects the extent of clinical exposure and includes appropriate warnings, a drug's promotional material would also include this information.

FDA regulations governing prescription drug labeling (21 CFR 201.56 and 201.57) require that serious adverse reactions and potential safety hazards, as well as limitations in use imposed by them, be included in the "Warning" section of the labeling. In the case of approval based upon effect on a surrogate endpoint, the "Indications and Usage" section of the labeling would reflect the nature of the demonstrated effect. If the approval is based on use restrictions, the label would also specify the restrictions.

FDA may require boxed warnings if there are special problems associated with a drug, particularly those that may lead to death or serious injury (21 CFR 201.57(e)). The agency does not agree that information related to clinical benefit or use restrictions for accelerated approval drugs would necessarily always require a boxed warning.

As indicated by §§ 314.550 and 601.45 of the final rule, applicants will be required to submit promotional materials prior to approval and in advance of dissemination subsequent to approval whether the product is a new drug, an antibiotic, or a biological product.

18. One comment contended that FDA review and approval of all promotional pieces before their use will indefinitely delay product marketing campaigns and other patient and physician educational activities, which are essential to market a product, thereby significantly diminishing the advantage of securing an early approval for the applicant. The comment further contended that the requirement to submit "all promotional materials * * * intended for dissemination or publication upon marketing approval" will be overly burdensome for FDA and will unnecessarily slow down the process for review of all materials, not just those for products subject to this proposed rule. The comment recommended that FDA only request for review the primary advertising pieces, such as the introductory letter to physicians, the main detail piece, and the main journal advertisement, but not the secondary materials, e.g., a letter to pharmacists, of the initial promotional campaign.

As previously discussed in this preamble, FDA will be reviewing an applicant's planned promotional materials both prior to approval of an application (reflecting the initial campaign) and subsequent to approval to ascertain whether the materials might adversely affect the drug's sensitive risk/benefit balance. Because all promotional materials, including those referred to by the comment as "secondary" materials, can have significant adverse effects if they are misleading, the agency does not agree that such materials should, as a matter of course, not be requested for review. Insofar as such materials may be directly derived from the introductory letter to physicians, or other materials characterized by the comment as "primary" materials, the additional time to review the derivative materials should not be extensive.

The agency does not agree with the comment's contention that the requirement to submit all promotional materials prior to and subsequent to approval will indefinitely delay marketing campaigns and educational activities or be overly burdensome to FDA reviewers. FDA is committed to rapid review and evaluation of all drugs considered for approval under this rule and will promptly review the promotional materials.

19. One comment suggested a passive, time-limited clearance system for review of advertising after the initial promotional campaign such as that used for review of IND's, which would allow the sponsor to proceed to use promotional materials after an allotted timeframe, such as 30 days, unless otherwise notified by FDA.

As indicated by this comment and others, additional clarification regarding both timing and content of the submissions of promotional materials seems useful. Therefore, the agency is revising proposed §§ 314.550 and 601.45 to make it clear that, unless otherwise informed by the agency, applicants must submit during the preapproval review period copies of all promotional materials intended for dissemination or publication within the first 120 days following marketing approval. The initial promotional campaign, sometimes referred to as the "launch campaign," often has a significant effect on the climate of use for a new product. As discussed elsewhere in this preamble, the risk/benefit balance of accelerated approval products is especially sensitive, and inappropriate promotion may adversely affect the balance with resulting harm.

There may be some instances in which promotional materials that had not been completed and submitted by the applicant prior to approval would be beneficial in fostering safe and effective use of the product during the first 120 days. Under revised §§ 314.550 and 601.45, FDA would have the discretion to consider such materials at a later time. An applicant who requested permission to include additional materials among those disseminated within the first 120 days following product approval would be notified of FDA's determination. If FDA agreed that dissemination of such materials was acceptable, the materials could then be disseminated or published upon notification.

For promotional materials intended for dissemination subsequent to the initial 120 days under §§ 314.550 and 601.45 FDA would review the submitted materials within 30 days of receipt. This 30-day period is meant to be time-limited, so that the applicant will be assured of no unnecessary delay. It will be important for the applicant to identify the materials being submitted appropriately, so that it is clear that the materials are subject to the 30-day review period. The agency intends to review all such materials promptly, and to notify the applicant of any identified problems as soon as possible. The agency expects that, if the agency notifies the applicant of significant objections to the proposed materials, no materials will be disseminated or published until the agency's objections are resolved. The applicant should plan to allow sufficient time after receiving

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FDA's comments for resolving differences and incorporating requested changes in the submitted materials prior to dissemination or publication.

When FDA removes the requirement for advance submission of promotional material, the agency will continue to offer a prompt review of all voluntarily submitted promotional material.

E. Postmarketing Restrictions

FDA received many comments on the proposed requirement to limit distribution to certain facilities or physicians with special training or experience, or condition distribution on the performance of specified medical procedures if such restrictions are needed to counterbalance the drug's known safety concerns.

20. Several comments questioned FDA's authority to impose restrictions on distribution or use after an approved drug is marketed. Two comments disagreed with the statutory provisions cited by FDA in the proposed rule as its authority to impose restrictions on distribution or use stating that they refer only to FDA's general authority to ensure that drugs are not misbranded, which is an entirely separate issue. Another comment argued that section 503(b) of the act (21 U.S.C. 353(b)) contemplates that the issues warranting a restriction as to distribution are not factors in whether a drug product is "safe" for purposes of approval, but rather only whether the product must be limited to prescription status. Two comments said that, in the absence of specific statutory authority, the courts clearly have refused to permit FDA to impose restrictions on distribution and cited *American Pharmaceutical Association (APhA)* v. *Weinberger*, 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff'd sub nom. APhA* v. *Mathews*, 530 F.2d 1054 (D.C. Cir 1976), a case concerning conditions placed on the approval of the drug methadone.

Some comments asserted that placing restrictions on the distribution of an approved drug to only certain facilities or physicians, or restricting use to certain medical procedures interferes with the practices of medicine and pharmacy, which the comments contended FDA does not have the authority to regulate.

The agency believes that the restrictions to ensure safe use contemplated for approvals under §§ 314.520 and 601.42 are authorized by statute. As discussed in the preamble to the proposed rule (57 FR 13234 at 13237), sections 501, 502, 503, 505, and 701 of the act provide broad authority for FDA to issue regulations to help assure the safety and effectiveness of new drugs.

The agency does not agree with the comments' contention that the misbranding provisions of the act are irrelevant. Section 502(a) of the act prohibits false or misleading labeling of drugs, including (under section 201(n) of the act) failure to reveal material facts relating to potential consequences under customary conditions of use. Section 502(f) of the act requires drugs to have adequate directions for use and adequate warnings against unsafe use, such as methods of administration, that may be necessary to protect users. In addition, section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Each of these misbranding provisions is intended, at least in significant part, to protect consumers against the marketing of drugs that would not be safe under certain conditions of use. Section 701(a) of the act authorizes FDA to issue regulations for the efficient enforcement of the act. The restrictions on use contemplated by §§ 314.520 and 601.42 help to ensure that products that would be misbranded under section 502 of the act are not marketed.

The restrictions on use imposed under section 503 of the act, which relate to prescription use limitations, primarily concern whether a drug is safe for use except under the supervision of a licensed practitioner. While the agency agrees that the restrictions imposed under §§ 314.520 and 601.42 concerning distribution to certain facilities or physicians with special training or experience would be in addition to ordinary prescription limitation, FDA believes these restrictions are consistent with the spirit of section 503 of the act, as well as the other provisions of the act referred to, in ensuring safe use.

New drugs may be approved under section 505(d) of the act only if they are safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. In addition, for approval, a drug's labeling must not be false or misleading based on a fair evaluation of all material facts, which would include details about the conditions of use. For biological products, section 351(d) of the PHS Act also authorizes the imposition of restrictions through regulations "designed to insure the continued safety, purity, and potency" of the products.

The agency disagrees with the comments' implication that the courts' rulings in *American Pharmaceutical Association (APhA)* v. *Weinberger* mean there is no statutory authority to impose restrictions on distribution for accelerated approval drugs. The situation considered in that case is readily distinguishable from the situation addressed in §§ 314.520 and 601.42 of the accelerated approval regulations. The *APhA* case concerned a regulation that withdrew approval of NDA's for methadone, but permitted distribution to certain maintenance treatment programs and certain hospital and community pharmacies. Because methadone is a controlled substance within the provisions of the Controlled Substances Act, which is implemented by the Drug Enforcement Administration with the Justice Department, the district court concluded that the question of permissible distribution of the drug was within the jurisdiction of the Justice Department, not FDA. The Court of Appeals determined that the type of misuse associated with methadone, i.e., misuse by persons who have no intent to try to use drugs for medical purposes, differed from safety issues contemplated for control under section 505 of the act. In contrast, the restrictions contemplated under §§ 314.520 and 601.42 are precisely those deemed necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use. It is clearly FDA's responsibility to implement the statutory provisions regarding new drug approval.

Nor does FDA agree that the provisions placing restrictions on distribution to certain facilities or physicians, or conditioned on the performance of certain medical procedures, impermissibly interfere with the practice of medicine and pharmacy. There is no legal support for the theory that FDA may only approve sponsors' drugs without restriction because physicians or pharmacists may wish to prescribe or dispense drugs in a certain way. The restrictions under these provisions would be imposed on the sponsor only as necessary for safe use under the extraordinary circumstances of the particular drug and use. Without such restrictions, the drugs would not meet the statutory criteria, could not be approved for distribution, and would not be available for prescribing or dispensing. The agency, as a matter of longstanding policy, does not wish to interfere with the appropriate practice of medicine or pharmacy. In this instance, the agency believes that rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases,

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approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing.

21. One comment asserted that postmarketing restrictions on distribution to certain facilities or physicians with certain training or experience should be limited to rare occasions in cases of extreme hazard to patient safety in which toxicity of a particular drug may require it, but should not be applied because of insufficient efficacy data. Some comments argued that safety issues in the context of drug use should be addressed through patient management and effective product labeling, not through restricted distribution. In support of this argument, the comments cited the labeling of oncologic drugs, which provides physicians with adequate warnings and recommendations for their use without limiting distribution.

FDA agrees with these comments in part and intends to impose restrictions on distribution or use under this rule only in those rare instances in which the agency believes carefully worded labeling for a product granted accelerated approval will not assure the product's safe use. As stated in the preamble to the proposed rule (57 FR 13234 at 13237), FDA believes that the safe use of most prescription drugs will continue to be assured through traditional patient management by health professionals and through necessary safety warnings in the drug's labeling.

22. Two comments asked who will determine if restricted distribution should occur and what facilities or physicians with special training or experience will participate. Several comments expressed concern that restricted distribution and/or conditional use may not include all health care professionals who should participate in safe and effective patient care. Two organizations representing pharmacists asked that FDA develop functional and objective criteria that clearly establish the activities of pharmacists, physicians, and others in the care of patients receiving a drug under restricted distribution. The comments asserted that any health care professional that met these criteria should be allowed to participate in distribution of the drug and care of the patient. One comment recommended that any postmarketing restrictions on distribution or use of a drug approved under the accelerated approval process be developed by appropriate FDA advisory committees or panels expanded to include physicians and pharmacists with expertise in the therapeutic area being considered and in relevant drug distribution systems. Where appointment of pharmacists to these committees or panels is not feasible, the comment recommended that FDA use pharmacists in a consultant capacity. Another comment argued that current systems for drug distribution incorporate "checks and balances" such that prescribers and pharmacists work together to assure safe use of a drug by a patient. Two comments would oppose any restricted distribution system that allows manufacturers exclusively to deliver prescription drugs directly to patients. One comment asked whether FDA or the applicant would monitor the criteria for restricted distribution sites or physicians.

The medical reviewing divisions within FDA's CDER and CBER will determine if restricted distribution or use should be imposed. FDA will usually seek the advice of outside expert consultants or advisory committees before making this determination, and will, of course, consult with the applicant.

The agency does not agree that FDA should develop criteria that clearly establish the activities of health care professionals in the care of patients receiving a drug approved under this rule and for which restricted distribution has been imposed. Any postmarketing restrictions required under this rule will impose an obligation on the applicant to ensure that the drug or biological product is distributed only to the specified facilities or physicians. FDA will seek the advice of outside consultants with expertise in distribution systems or advisory committees when necessary in determining the need for or type of restricted distribution. The limitations on distribution or use imposed under this rule, including specific distribution systems to be used and the applicant's plan for monitoring compliance with the limitations, will have been agreed to by the applicant at the time of approval. The burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. As appropriate, FDA may monitor the sponsor's compliance with the specified terms of the approval and with the sponsor's obligations.

23. One comment recommended that proposed § 314.520 be modified to include therapeutic outcomes monitoring as a third example of a permissible postmarketing restriction. The comment defined therapeutic outcomes monitoring as the systematic and continual monitoring of the clinical and psychosocial effects of drug therapy on a patient which achieves the objective of preventing problems with drug therapy. Some comments argued that through therapeutic outcomes monitoring, a physician, a pharmacist, and a patient can work together to prevent problems with drug therapy by being constantly alert to signs of trouble. One comment said that indicator data can be routinely reported to a central collection point for utilization review by health care professionals, followed by educational programs to further improve the efficacy of drug therapy.

The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction. Therapeutic outcomes monitoring does not contribute to that enhancement, and would not be required under this rule.

24. Some comments asked that FDA clarify how products will move from restrictive status to a regular prescription drug status. The comments asserted that all conditions associated with accelerated approval should automatically terminate following completion of confirmatory clinical trials; one comment urged FDA to explicitly state this in the final rule. One comment asserted that restrictions should automatically be removed 180 days after a supplemental application containing the data from the postmarketing study has been filed if FDA has not yet acted upon the supplemental application and the product should be deemed approved as if by "traditional" procedures and all other provisions of the act should apply, e.g., the applicant must have a formal hearing before removal of the product from the market.

FDA will notify the applicant when a particular restriction is no longer necessary for safe use of the product. In the case of drugs approved with a requirement for postapproval studies, FDA would expect that all of the postapproval requirements set forth in this rule, i.e., submission of promotional material and use of expedited withdrawal procedures, would no longer apply after postmarketing studies have verified and described the drug's clinical benefit. Concurrent with the review of the postmarketing studies, if requested, FDA will also review the need to continue any restrictions on distribution that have been imposed. In the case where restrictions on distribution or use have been imposed, such restrictions would be eliminated only if FDA determines that safe use of the product can be assured without them, through appropriate labeling. In

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some cases, however, that assurance could not be expected and the nature of the specific safety issue raised by the product might require continued restrictions. FDA has added new §§ 314.560 and 601.46 to state when postapproval requirements will no longer apply and state that the applicant may petition the agency, in accordance with 21 CFR 10.30, at any time to remove specific postapproval requirements.

With respect to the suggested time period for removing restrictions on distribution or use following submission of a supplemental application containing the data from a postmarketing study, FDA does not believe it should prescribe any specific time period. These applications will receive a priority rating and FDA is firmly committed to expedited review of an application considered for accelerated approval and all data submitted from a postmarketing study to verify clinical benefit and believes most reviews will be completed and action taken within 180 days.

25. One comment argued that, as proposed, it is not clear how accelerated approval would apply to drugs which fall under the conditions described in §§ 314.520 and 601.42, which state the postmarketing restrictions on distribution or use that FDA may apply, because the language of these sections explicitly states that the sections apply to products "shown to be effective," which are already adequately covered by the act. To the comment, the language "shown to be effective" implies that full Phase 3 efficacy trials have been conducted, assessed, and deemed to demonstrate that the drug is effective for its proposed use. If the clinical data demonstrate that the product has an acceptable safety profile, the safe use of the drug should be addressed in the product labeling. Thus, the comment argued that §§ 314.520 and 601.42 should not be included in new subpart H of part 314 and subpart E of part 601, respectively, which deal with accelerated approval because these sections explicitly apply to products shown to be effective under a full drug development program.

Sections 314.520 and 601.42 apply not only to drugs and biological products approved on the basis of an effect on a surrogate endpoint but also to drugs and biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses using clinical endpoints and that have serious toxicity. In either case, if the products are so potentially harmful that their safe use cannot be assured through carefully worded labeling, FDA will approve the products for early marketing only if postmarketing restrictions on distribution or use are imposed. The phrase "shown to be effective" was not intended to distinguish drugs approved under new subpart H from drugs approved under any other subpart of the regulations. All drugs approved will have had effectiveness demonstrated on the basis of adequate and well-controlled studies, whether the endpoint of the studies is a surrogate endpoint or a clinical endpoint.

26. One comment expressed concern that the proposed restricted distribution or use provisions would restrict or eliminate the wholesale distribution of drugs approved through the accelerated approval process.

The limitations on distribution or use required under this rule are imposed on the applicant. Therefore, the burden is on the applicant to ensure that the conditions of use under which the applicant's product was approved are being followed. This rule does not specify how a manufacturer will distribute its product to those receiving the product under the approval terms. FDA will only determine which facilities or physicians may receive the drug, and the applicant will have agreed to this limitation on distribution or use.

27. One comment expressed concern that the proposed postmarketing restriction provision does not preclude a physician to whom restricted distribution applies from prescribing drugs approved under the accelerated approval process for unapproved (off-label) uses.

The comment is correct that this rule does not itself prevent a physician from prescribing a drug granted accelerated approval for an unapproved use. Under the act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug's safety and effectiveness have been established and that FDA has approved. Physicians may choose to prescribe the drug for a condition not recommended in labeling. Such off-label use would, of course, be carried out under the restrictions imposed under this section. FDA also believes that physicians will be cognizant of the product's special risks and will use such drugs with particular care. The labeling of products approved under this rule will include all necessary warnings and full disclosure labeling would generally reflect the extent of clinical exposure to the drug.

F. Postmarketing Studies

28. Three comments argued that FDA does not have the authority to require postmarketing studies to be performed as a condition of approval based on a "surrogate" endpoint. One comment stated that it is widely accepted that the act empowered the agency to define the type and extent of efficacy data necessary to approve a product application. If a surrogate marker can be shown to be sufficiently related to actual patient benefit, then, the comment asserted, data regarding the effect of a drug on a surrogate marker constitute acceptable proof of efficacy under the act. Two comments urged FDA to continue to ask applicants to agree voluntarily to perform postmarketing studies when medically warranted as is the current policy under the traditional approval process. One comment expressed concern that requiring postmarketing studies may become the norm rather than the exception.

The agency's response to comment 1. explained the circumstances in which FDA might conclude that a drug should be marketed on the basis of an effect on a surrogate endpoint reasonably likely to predict clinical benefit only if studies were carried out to confirm the presence of the likely benefit. As discussed in the preamble to the proposed rule (57 FR 13234 at 13236), FDA believes that it is authorized by law to require postmarketing studies for new drugs and biological products. Section 505(d) of the act provides for the approval of new drugs for marketing if they meet the safety and effectiveness criteria set forth in section 505(d) of the act and the implementing regulations (21 CFR part 314). As discussed in the proposed rule, to demonstrate effectiveness, the law requires evidence from adequate and well-controlled clinical studies on the basis of which qualified experts could fairly and responsibly conclude that the drug has the effect it is purported to have. Under section 505(e) of the act, approval of a new drug application is to be withdrawn if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if new information shows that the drug's labeling is false or misleading.

Section 505(k) of the act authorizes the agency to promulgate regulations requiring applicants to make records and reports of data or other information that are necessary to enable the agency to determine whether there is reason to withdraw approval of an NDA. The agency believes that the referenced reports can include additional studies to evaluate the clinical effect of a drug approved on the basis of an effect on a surrogate endpoint. Section 701(a) of the act generally authorizes FDA to issue

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regulations for the "efficient enforcement" of the act.

With respect to biological products, section 351 of the PHS Act provides legal authority for the agency to require postmarketing studies for these products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

The agency notes that it has in the past required postmarketing studies as a prerequisite for approval for some drugs (see 37 FR 201, January 7, 1972; and 37 FR 26790, December 15, 1972).

29. One comment recommended that FDA require that specific timelines for completion of the required postmarketing studies be included in the marketing application. The comment further suggested that, if the sponsor fails to meet its timelines, approval of its application be withdrawn, or in the event it is difficult to withdraw approval of drugs for serious or life-threatening diseases, FDA should establish substantial fines and penalties for sponsors that deliberately withhold information from FDA regarding the preliminary results and the progress of their postmarketing studies, or delay the completion of such studies. The comment also urged FDA to publish in the **Federal Register** identification of manufacturers who are not meeting their obligation to complete the required postmarketing studies on time. These recommendations were prompted by the comment's concern that once a manufacturer is granted approval for its product, the manufacturer will have little incentive to complete postmarketing studies in a timely manner, especially if the preliminary results of such studies indicate that the drug may not be safe and/or effective. Another comment urged FDA to include in the final rule language that requires the participation of pharmacists in postmarketing studies because pharmacists can serve as an additional source of information on therapeutic outcomes of patients taking drugs approved under this rule and monitoring for such drugs.

The agency expects that the requirement for postmarketing studies will usually be met by studies already underway at the time of approval and that there will be reasonable enthusiasm for resolving the questions posed by those studies. The plan for timely completion of the required postmarketing studies will be included in the applicant's marketing application. In addition, in accord with the annual reporting requirements at § 314.81(b)(2)(vii) (21 CFR 314.81(b)(2)(vii), an NDA applicant is required to provide FDA with a statement of the current status of any postmarketing studies. FDA declines to impose the sanctions suggested by the comment for failure of an applicant to meet its plans for completion of a postmarketing study. FDA believes this rule applies appropriate regulatory sanctions. Under the proposed rule and this final rule, FDA may withdraw approval of an application if the applicant fails to perform the required postmarketing study with due diligence.

FDA believes that it is not within the scope of this rule to establish the role of pharmacists in postmarketing studies. That role should more properly be defined by the clinical investigator and each institution or facility at which a postmarketing study is conducted.

30. One comment asserted that the proposal sets forth an inherent contradiction between the way FDA evaluates the benefit and risk for drugs today and the way the proposal contemplates. The comment argued that now, if postmarketing data raise questions about the risk associated with a drug product, FDA considers that data along with the other data known about the product, and determines whether, based on the overall knowledge about the drug, there is a need to seek withdrawal of approval. Under this proposal, if the postmarketing study data raised questions about the risk of the product, FDA would seek withdrawal of approval, whether or not the new data really made a fundamental difference to what is known about the benefit and risk of the product.

FDA does not agree that the contradiction described by the comment exists. Under the circumstances of accelerated approval, approval would be based on a weighing of the benefit suggested by the effect on the surrogate endpoint against known and potential risks of the drug. Should well-designed postapproval studies fail to demonstrate the expected clinical benefit, the benefit expected at the time of approval (reasonably likely to exist) would no longer be expected and the totality of the data, showing no clinical benefit, would no longer support approval. This evaluation of the data is not different from considerations that would apply in evaluating data in the case of a drug approved under other provisions of the regulations.

31. Two comments expressed the view that the proposed requirement for postmarketing studies may raise important ethical questions because once a drug product is approved, it may be unethical, depending on the circumstances, for a physician to conduct a study using a placebo control. One comment also contended that a postmarketing study requirement could compromise the NDA holder's ability to enroll sufficient numbers of patients in the study when the new approved drug and possible alternative therapies are widely available to patients.

Usually, and preferably, because of problems suggested in the comment, the requirement for postmarketing studies will be met by studies already underway at the time of approval, e.g., by completion of studies that showed an effect on the surrogate. FDA recognizes that ethical considerations will play a central role in the type of study carried out, a choice that will depend upon the type and seriousness of the disease being treated, availability of alternative therapies, and the nature of the drug and the patient population. There often are alternatives to use of a placebo control, including active control designs and dose-response studies that can satisfy both the demands of ethics and adequacy of design.

32. One comment contended that the term "postmarketing study" is used inconsistently in the proposed rule. The comment argued that "postmarketing study" is an accepted regulatory term of art which, to this point, has referred to studies conducted to confirm safety (not efficacy), after an approval has been granted, whereas in this proposal, a "postmarketing study" refers to a study required to establish clinical efficacy (i.e., a Phase 3 study), but not necessarily safety, although safety data will be collected. To prevent confusion and to differentiate between these required postmarketing confirmatory efficacy studies and safety studies traditionally conducted after approval and to clarify that products granted accelerated approval have been approved on the basis of Phase 2 (surrogate endpoint) data, the comment suggested changing the term "postmarketing study" to "Phase 3 study" in this rule except where traditional postmarketing studies are intended. The comment also suggested that the term "Phase 3 study" be defined as a study required to confirm findings of efficacy based upon surrogate data collected in Phase 2, which will be conducted after an accelerated approval has been granted and will be required before restrictions set forth in § 314.520 are removed.

The agency does not believe that the comment has accurately described accepted meanings of various terms.

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The term postmarketing study does not refer to any particular kind of study, but to studies carried out after a drug is marketed, often as part of an agreement by a sponsor to do so. These have included pharmacokinetic, drug-drug interaction, and pediatric studies, studies of dose-response or of higher doses, and studies of new uses. The term is not limited to safety studies. Moreover, Phase 2 and 3 studies are not distinguished by the endpoints chosen. Phase 3 hypertension studies, for example, still measure blood pressure, not stroke rate. The agency believes that the use of the "postmarketing study" in the final rule is appropriate and consistent.

G. Withdrawal of Approval

33. One comment supported the proposed withdrawal of approval procedure. Other comments asserted that the proposed procedure does not provide the applicant with the procedural safeguard of a formal evidentiary hearing guaranteed by section 505 of the act and the Administrative Procedure Act (APA). As an example, the comments said that based on a finding of a single study failing to show clinical benefit or misuse of any promotional material, an approved new drug would be subject to withdrawal from the market with only a minimal opportunity for the NDA holder to be heard. The comments argued that section 505(e) of the act guarantees applicants "due notice and opportunity for a hearing" on withdrawal of an NDA in compliance with APA hearing standards, thus FDA must conduct hearings on withdrawals of NDA's using the formal adjudicatory procedures of the APA. One comment asserted that, under the proposed procedure, there is the absence of a discernible legal standard, an inability to cross-examine, the prosecuting attorney and judge are one and the same person, and there is a lack of even minimal formal evidentiary procedures. The comment expressed doubt that the proposed procedure would be sufficient to create a record suitable for review by a Court of Appeals, which must be able, on the basis of such a record, to determine whether the approval is supported by "substantial evidence."

FDA believes the withdrawal procedures set forth in proposed §§ 314.530 and 601.43 and in this final rule are consistent with relevant statutes and provide applicants adequate due process. As stated in the proposed rule, in issuing its general procedural regulations, FDA decided to afford NDA holders an opportunity for a formal evidentiary hearing even though the courts had not decided that such a hearing was necessarily legally required (see 40 FR 40682 at 40691, September 3, 1975). In promulgating its procedural regulations, FDA also determined that a formal evidentiary hearing is not required before withdrawing approval of biological products, but that it would be appropriate to apply the same procedures to biological products as to drug removal (see 40 FR 40682 at 40691).

Through the hearing process in this final rule, as in the proposed rule, applicants will be afforded the opportunity to present any data and information they believe to be relevant to the continued marketing of their product. The proposed process also would have permitted the presiding officer, the advisory committee members, a representative of the applicant, and a representative of the Center that initiates the withdrawal proceedings to question any person during or at the conclusion of the person's presentation. As discussed below in response to a comment, FDA has decided to allow up to three representatives of the applicant and of the Center to question presenters. Participants could comment on or rebut information and views presented by others. As with ordinary 21 CFR part 15 hearings, the hearing will be transcribed. Subsequent to the hearing, the Commissioner of Food and Drugs would render a final decision on the matter. The agency believes that the administrative record created through this process would be sufficient for judicial review.

The agency emphasizes that, as part of the approval process under this rule, applicants will have agreed that these withdrawal procedures apply to the drug for which they seek approval; applicants objecting to these procedures may forego approval under these regulations and seek approval under the traditional approval process. Under such circumstances, applicants would not have the benefit of accelerated approval; if the drug were subsequently approved, however, before withdrawal of the approval, the applicant would have an opportunity for a 21 CFR part 12 hearing.

34. One comment noted that the "imminent hazard" provision of section 505(e) of the act allows FDA to suspend approval of a product, immediately, if it is found to pose an imminent hazard to the public health. As an alternative to the proposed withdrawal procedure or in addition to the "imminent hazard" statutory provision, the comment suggested that, when confronted with a dangerous product on the market, FDA could request that the applicant voluntarily withdraw its product, and most applicants would comply if a legitimate hazard exists.

As noted in the proposed rule, FDA and applicants have often reached mutual agreement on the need to remove a drug from the market rapidly when significant safety problems have been discovered. However, applicants usually have been unwilling to enter into such agreements when doubts about effectiveness have arisen, such as following the review of effectiveness of pre-1962 approvals carried out under the Drug Efficacy Study Implementation (DESI) program. For drugs approved under the accelerated procedure regulations, the risk/benefit assessment is dependent upon the likelihood that the surrogate endpoint will correlate with clinical benefit or that postmarketing restrictions will enable safe use. If the effect on the surrogate does not translate into a clinical benefit, or if restrictions do not lead to safe use, the risk/benefit assessment for these drugs changes significantly. FDA believes that if that occurs, rapid withdrawal of approval as set forth in this rule is important to the public health.

35. Under the proposed withdrawal procedures, in addition to other persons, one representative of the Center that initiates the withdrawal proceedings may question participants at a withdrawal of approval hearing. One comment objected to limiting the Center to one representative because detailed knowledge about a drug product is likely to be available from several scientists.

The proposed limitation of questioning to single representatives of the initiating Center and the applicant was intended to make the proceedings manageable. On further consideration, the agency has determined that it would be appropriate and manageable to allow up to three persons to be designated as questioners for the applicant and for FDA. Sections 314.530(e)(2) and 601.43(e)(2) have been revised accordingly.

36. Some comments questioned FDA's ability to withdraw approval under the proposed procedures efficiently or effectively because of: (1) The lack of assurance that the results of postmarketing studies will be promptly provided to FDA; (2) limited agency resources to review study results and act upon them promptly; (3) the difficulties associated with establishing that an approved drug is "ineffective;" and (4) political pressure not to rescind the approval of NDA's for drug products that may lack evidence of effectiveness,

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especially if no clearly effective alternative treatments are available. One comment offered the opinion that where a drug shows only modest evidence of benefit, perhaps on a surrogate endpoint, and only shows equivocal evidence of clinical efficacy in postmarketing studies it would be difficult and socially disruptive to withdraw approval and remove the drug from the market if the drug has become well established and accepted, and there is no issue of toxicity. Another comment believed it would be difficult to withdraw approval of a drug that may be beneficial in a subpopulation but which, in fact, has not been shown to be efficacious in broader patient population studies. The comments suggested the need for a lesser sanction.

Another comment suggested that expediting removal of a product from the market could be accomplished by using a procedure like the "imminent hazard" provision of the act, i.e., immediate removal of the drug from the market if any of the conditions listed in proposed § 314.530 were met followed by a hearing.

Although the potential difficulties cited by the comments are real, they are not fundamentally different from determinations FDA regularly must make in carrying out its responsibilities. The new regulations provide for an expedited procedure to withdraw approval; they do not guarantee that results of studies will be wholly unambiguous or that FDA will always be able to prevail in its view as to the need for withdrawal, any more than current withdrawal procedures do. The studies being carried out under these provisions will be conspicuous and important and their completion will be widely known. There is no reason to believe their results would or could be long hidden. A study that fails to show clinical effectiveness does not prove a drug has no clinical effect but it is a study that, under § 314.530, will lead to a withdrawal procedure because it has failed to show that the surrogate endpoint on which approval was based can be correlated with a favorable clinical effect. This may have occurred because the study was poorly designed or conducted; while FDA will make every effort to avoid this, the commercial sponsor has the responsibility for providing the needed evidence confirming clinical benefit. As previously discussed, §§ 314.510 and 601.41 have been revised to clarify that required postmarketing studies must also be adequate and well-controlled. The possibility that an ineffective drug has become "accepted" is not a basis for continued marketing. FDA intends to implement the provisions of § 314.530 as appropriate; data that are ambiguous will inevitably lead to difficult judgments.

A drug with clear clinical effectiveness in a subset of the population, but not in the population described in labeling, would have its labeling revised to reflect the data. Withdrawal would be inappropriate under such circumstances.

If an imminent hazard to the public health exists, the Secretary of Health and Human Services may suspend approval of an application and then afford the applicant an opportunity for an expedited hearing. In the absence of a significant hazard requiring immediate withdrawal, FDA believes the expedited procedure described in the rule satisfies the need for prompt action while, at the same time, allowing opportunity for discussion and debate before withdrawal.

37. One comment noted that the proposed rule would allow FDA to withdraw approval for failure to perform the required postmarketing studies with due diligence. The comment asserted that the act does not permit FDA to withdraw approval on this ground. Another comment, however, suggested that because proposed §§ 314.530 and 601.43 cite grounds for withdrawal of approval that are not grounds under the act, the language of these proposed sections should be revised to use language that closer aligns to that used in the act, e.g., describe a "postmarketing study" in statutory language.

FDA reaffirms the position expressed in the preamble to the proposal (57 FR 13234 at 13239) that there is adequate authority under the act to withdraw approval of an application for the reasons stated under proposed §§ 314.530 and 601.43, which include failure of an applicant to perform the required postmarketing study with due diligence. Section 505(e) of the act authorizes the agency to withdraw approval of an NDA if new information shows that the drug has not been demonstrated to be either safe or effective. Approval may also be withdrawn if the applicant has failed to maintain required records or make required reports. In addition, approval may be withdrawn if new information, along with the information considered when the application was approved, shows the labeling to be false or misleading.

For biological products, section 351(d) of the PHS Act authorizes approval of license applications under standards designed to ensure continued safety, purity, and potency. "Potency" for biological products includes effectiveness (21 CFR 600.3(s)). The PHS Act does not specify license revocation procedures, except to state that licenses may be suspended and revoked "as prescribed by regulations."

For drugs approved under § 314.510, FDA will have determined that reports of postmarketing studies are critical to the risk/benefit balance needed for approval; if those reports are not forthcoming, then, under authority of section 505(d) of the act, the drug cannot on an ongoing basis meet the standards of safety and efficacy required for marketing under the act. Therefore, it is important to ensure that the applicant make a good faith effort to complete any required postmarketing studies in a timely manner so that FDA can rapidly determine whether the surrogate endpoint upon which the drug was approved has been confirmed to correlate with clinical benefit. Failure to submit the study results in a timely fashion would also constitute failure to make a required report. Similarly, without submission of the information from required postmarketing studies on biological products approved under these procedures, the biological product is not assured of continued safety and effectiveness. The license application may, therefore, appropriately be revoked as described in § 601.43.

FDA does not find the statements of the grounds for withdrawal of approval under §§ 314.530 and 601.43 of this rule inconsistent with statutory language or ambiguous. The agency notes that, in the event none of the grounds for withdrawal specifically listed in § 314.530 or § 601.43 applies, but another ground for withdrawal under section 505 of the act or section 351 of the PHS Act and implementing regulations at 21 CFR 314.150 or 601.5 does apply, the agency will proceed to withdraw approval under traditional procedures.

38. Two comments expressed concern that it may be difficult for the agency to enforce the requirement that postmarketing studies be pursued with due diligence. The comments asked what would happen if a sponsor using due diligence is unable to recruit enough patients, or if the sponsor questions the validity of the data from the required postmarketing study, and would clumsy data management be seen as sufficient reason to rescind approval for a marketed drug? Another comment stated that once a product is approved and, by definition, provides a "meaningful therapeutic benefit over existing therapies," study accrual may drop off dramatically as patients may refuse to receive the "old" therapy or

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placebo, or physicians may consider it unethical not to treat all patients with the approved indication with the new drug or biological product. Under these circumstances, the comment expressed the opinion that neither the sponsor nor the product should be penalized, nor should there be a threat to withdraw approval. Based on FDA's past history in postmarketing studies, which one comment characterized as resulting in poorly done studies, studies conducted much later than agreed upon, or not at all, the comment expressed the opinion that the "due diligence" with which applicants are expected to carry out postmarketing studies may be an overly great expectation. One comment asked FDA to give examples of when it may withdraw approval if "other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use" (proposed §§ 314.530(a)(6) and 601.43(a)(6)).

FDA does not agree that it will be difficult to enforce the "due diligence" provision of this rule. The "due diligence" provision was designed to ensure that the applicant makes a good faith effort to conduct a required postmarketing study in a timely manner to confirm the predictive value of the surrogate marker or other indicator. Any requirement for postmarketing studies will have been agreed to by the applicant at the time of approval, and if the study is not conducted in a timely manner as agreed to by the applicant, approval of the applicant's application will be withdrawn. FDA will expect any required postmarketing study to be conducted in consultation with the agency. Therefore, should the applicant encounter problems with subject enrollment in a study or ethical difficulties about the type of study to conduct, FDA expects the applicant to discuss these problems with the agency and reach agreement on their resolution.

Examples of other evidence demonstrating the drug product is not shown to be safe and effective could include further studies of the effect of the drug and the surrogate endpoint that fail to show the effect seen in previous studies, new evidence casting doubt on the validity of the surrogate endpoint as a predictor of clinical benefit, or new evidence of significant toxicity.

39. Some comments objected to withdrawal of approval of a drug product approved under the accelerated approval process because of perceived misconduct by the applicant, such as failure to perform a required postmarketing study with due diligence or use of promotional materials that are false or misleading. The comments argued that the primary purpose of the accelerated approval process is to provide improved treatments to desperately ill patients at the earliest possible time, and withdrawal of approval of the new treatments for reasons not directly related to safety or efficacy undermines the purpose of the proposed rule. Two comments suggested that correction of the promotional material without interruption of access to the drug would be a better approach. Another comment suggested that there may be circumstances where continued access to the drug, if accompanied by informed consent, would be appropriate even if substantial questions arise about a product's safety and effectiveness. One comment urged that anticipated withdrawal of approval be preceded by measures to ensure that patients and their physicians will have an uninterrupted supply until alternative treatment arrangements can be made.

The need for "due diligence" in conducting the agreed to postmarketing studies is discussed in paragraph 37. The reasons for concern about misleading promotional materials are discussed under paragraph 16. With respect to promotional materials, FDA expects that, in most cases, any disagreements between the applicant and FDA will be resolved through discussion and modification of the materials, so that the drug or biological product can continue to be marketed. If, however, FDA concludes that the promotional materials adversely affect the risk/benefit conclusion supporting the drug's marketing, the agency intends to minimize the risk to the public health by removing the product from the market through the withdrawal procedures in this rule.

40. One comment expressed concern that the proposed withdrawal procedure may give the appearance of bias or preconceived notions on the part of the agency because the final decision to withdraw approval of a drug would be made by the Commissioner of Food and Drugs and the intention to withdraw approval of the drug will already have been determined by the agency.

Under the withdrawal provisions of this rule, FDA's CDER or CBER, rather than the Commissioner, will initiate the withdrawal proceedings. The withdrawal process will begin with a letter from CDER or CBER notifying the applicant that the Center proposes to withdraw marketing approval and stating the reasons for the proposed action. Although separation of functions will not apply under the provisions of §§ 314.530 or 601.43, the Commissioner's decision regarding withdrawal would not occur until after the applicant had an opportunity for hearing as described in those sections. The Commissioner would then expect to review the issues with objectivity and fairness having had the benefit of the presentations and discussions at the hearing and of the advisory committee's recommendations.

H. Safeguards for Patient Safety

41. One comment asked if drugs approved under the accelerated approval process will be held to the same standards concerning postmarketing safety as drugs approved by the traditional process.

As discussed in the preamble to the proposed rule, applicants gaining approval for new drugs through the accelerated approval procedures will also be expected to adhere to the agency's longstanding requirements for postmarketing recordkeeping and safety reporting (see 21 CFR 314.80 and 314.81). Information that comes to FDA from the applicant or elsewhere that raises potential safety concerns will be evaluated in the same manner that such information is evaluated for drugs approved under the agency's traditional procedures. If the postmarketing information shows that the risk/benefit assessment is no longer favorable, the agency will act accordingly to remove the drug from the market.

42. One comment urged FDA, if the proposed rule were adopted, to require written informed consent so that patients would know that the drugs with which they were being treated had risks and that the benefits had not been adequately established.

The agency does not agree that patients using drug products approved under the accelerated approval regulations should be asked to provide written informed consent. Drugs approved under these provisions are not considered experimental drugs for their approved uses. Like all approved drugs, drugs approved under these provisions will have both risks and benefits. As previously discussed in this preamble, for drugs approved based on studies showing an effect on a surrogate endpoint, the approved labeling will describe that effect. In addition, the labeling will contain information on known and potential safety hazards and precautionary information. As with all prescription drugs, the physician has the responsibility for appropriately advising the patient regarding the drug being prescribed.

43. One comment asked that FDA require manufacturers to maintain an updated list of names, addresses, and phone numbers of physicians prescribing their products approved

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under this rule, and in the case of recall or withdrawal of approval, require manufacturers to contact these physicians and encourage them to notify their patients.

FDA does not believe such a procedure is necessary. Furthermore, maintaining such a registry for drugs prescribed through pharmacies would be very difficult. Agency experience with recalls and product withdrawals indicates that the methods of notification that have been developed for such circumstances are adequate.

44. One comment recommended that FDA require patient package inserts (PPI's) for all drugs granted accelerated approval that would state the specific restrictions placed on a drug product and/or the reason for requiring postmarketing studies. In addition, the comment recommended that FDA require the manufacturer to include an adverse drug reaction "hotline" phone number in the PPI along with an FDA phone number. The PPI should inform the patient to report immediately any adverse drug reaction experienced to his or her doctor, the manufacturer, and FDA, and the manufacturer should be required to contact FDA immediately after receiving a report of a serious adverse reaction.

FDA concludes that patient package inserts are not routinely needed for drugs granted accelerated approval, although if circumstances made one appropriate, one would be developed for a particular drug. As with any prescription drug, the approved labeling for a product granted accelerated approval will contain information about the safe and effective use of the product, including all necessary warnings and the extent of clinical exposure. In addition, the conditions of use will be carefully worded to reflect the nature of the data supporting the product's approval. Physicians have the responsibility to inform patients about the safe and effective use of an approved product. Labeling includes suggestions to the physician concerning information to be provided to patients.

The agency notes that in this final rule limited editorial changes have been made to the wording of the proposed rule. The agency has determined that these changes do not affect the intent of the proposed rule.

V. Economic Impact

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this final rule and has determined that it is not a major rule as defined by the Order. Indeed, because firms will not be forced to use the accelerated approval mechanism, applicants will most probably choose to take advantage of the program only where its use is expected to reduce net costs, Similarly, the final rule does not impose a significant economic impact on a substantial number of small entities so as to require a regulatory flexibility analysis under the requirements of the Regulatory Flexibility Act of 1980.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1980

This rule does not contain new collection of information requirements. Section 314.540 does refer to regulations that contain collection of information requirements that were previously submitted for review to the Director of the Office of Management and Budget (OMB) under section 3504 of the Paperwork Reduction Act of 1980 (Adverse Drug Experience Reporting, OMB No. 0190–0230).

List of Subjects

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Biologics, Confidential business information.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 314 and 601 are amended as follows:

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

1. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 376).

2. Subpart H consisting of §§ 314.500 through 314.560 is added to read as follows:

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

Sec.

314.500 Scope.
314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
314.520 Approval with restrictions to assure safe use.
314.530 Withdrawal procedures.
314.540 Postmarketing safety reporting.
314.550 Promotional materials.
314.560 Termination of requirements

Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses

§ 314.500 Scope.

This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 314.510 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 314.520 Approval with restrictions to assure safe use.

(a) If FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the drug product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the drug product.

§ 314.530 Withdrawal procedures.

(a) For new drugs and antibiotics approved under §§ 314.510 and 314.520, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to assure safe use of the drug product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Drug Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 314.510 or § 314.520. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the Federal Register in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 314.540 Postmarketing safety reporting.

Drug products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved drug products, as provided in §§ 314.80 and 314.81.

§ 314.550 Promotional materials.

For drug products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 314.560 Termination of requirements.

If FDA determines after approval that the requirements established in § 314.520, § 314.530, or § 314.550 are no longer necessary for the safe and effective use of a drug product, it will so notify the applicant. Ordinarily, for drug products approved under § 314.510, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the drug product's clinical benefit and the drug product would be appropriate for approval under traditional procedures. For drug products approved under § 314.520, the restrictions would no longer apply when FDA determines that safe use of the drug product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

PART 601—LICENSING

3. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 708, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 376, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

4. Subpart E consisting of §§ 601.40 through 601.46 is added to read as follows:

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

Sec.

601.40 Scope.
601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.
601.42 Approval with restrictions to assure safe use.
601.43 Withdrawal procedures.
601.44 Postmarketing safety reporting.
601.45 Promotional materials.
601.46 Termination of requirements.

Subpart E—Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses

§ 601.40 Scope.

This subpart applies to certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).

§ 601.41 Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity.

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic,

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pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

§ 601.42 Approval with restrictions to assure safe use.

(a) If FDA concludes that a biological product shown to be effective can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to assure safe use of the biological product, such as:

(1) Distribution restricted to certain facilities or physicians with special training or experience; or

(2) Distribution conditioned on the performance of specified medical procedures.

(b) The limitations imposed will be commensurate with the specific safety concerns presented by the biological product.

§ 601.43 Withdrawal procedures.

(a) For biological products approved under §§ 601.40 and 601.42, FDA may withdraw approval, following a hearing as provided in part 15 of this chapter, as modified by this section, if:

(1) A postmarketing clinical study fails to verify clinical benefit;

(2) The applicant fails to perform the required postmarketing study with due diligence;

(3) Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the biological product;

(4) The applicant fails to adhere to the postmarketing restrictions agreed upon;

(5) The promotional materials are false or misleading; or

(6) Other evidence demonstrates that the biological product is not shown to be safe or effective under its conditions of use.

(b) *Notice of opportunity for a hearing.* The Director of the Center for Biologics Evaluation and Research will give the applicant notice of an opportunity for a hearing on the Center's proposal to withdraw the approval of an application approved under § 601.40 or § 601.41. The notice, which will ordinarily be a letter, will state generally the reasons for the action and the proposed grounds for the order.

(c) *Submission of data and information.* (1) If the applicant fails to file a written request for a hearing within 15 days of receipt of the notice, the applicant waives the opportunity for a hearing.

(2) If the applicant files a timely request for a hearing, the agency will publish a notice of hearing in the **Federal Register** in accordance with §§ 12.32(e) and 15.20 of this chapter.

(3) An applicant who requests a hearing under this section must, within 30 days of receipt of the notice of opportunity for a hearing, submit the data and information upon which the applicant intends to rely at the hearing.

(d) *Separation of functions.* Separation of functions (as specified in § 10.55 of this chapter) will not apply at any point in withdrawal proceedings under this section.

(e) *Procedures for hearings.* Hearings held under this section will be conducted in accordance with the provisions of part 15 of this chapter, with the following modifications:

(1) An advisory committee duly constituted under part 14 of this chapter will be present at the hearing. The committee will be asked to review the issues involved and to provide advice and recommendations to the Commissioner of Food and Drugs.

(2) The presiding officer, the advisory committee members, up to three representatives of the applicant, and up to three representatives of the Center may question any person during or at the conclusion of the person's presentation. No other person attending the hearing may question a person making a presentation. The presiding officer may, as a matter of discretion, permit questions to be submitted to the presiding officer for response by a person making a presentation.

(f) *Judicial review.* The Commissioner's decision constitutes final agency action from which the applicant may petition for judicial review. Before requesting an order from a court for a stay of action pending review, an applicant must first submit a petition for a stay of action under § 10.35 of this chapter.

§ 601.44 Postmarketing safety reporting.

Biological products approved under this program are subject to the postmarketing recordkeeping and safety reporting applicable to all approved biological products.

§ 601.45 Promotional materials.

For biological products being considered for approval under this subpart, unless otherwise informed by the agency, applicants must submit to the agency for consideration during the preapproval review period copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. After 120 days following marketing approval, unless otherwise informed by the agency, the applicant must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

§ 601.46 Termination of requirements.

If FDA determines after approval that the requirements established in § 601.42, § 601.43, or § 601.45 are no longer necessary for the safe and effective use of a biological product, it will so notify the applicant. Ordinarily, for biological products approved under § 601.41, these requirements will no longer apply when FDA determines that the required postmarketing study verifies and describes the biological product's clinical benefit and the biological product would be appropriate for approval under traditional procedures. For biological products approved under § 601.42, the restrictions would no longer apply when FDA determines that safe use of the biological product can be assured through appropriate labeling. FDA also retains the discretion to remove specific postapproval requirements upon review of a petition submitted by the sponsor in accordance with § 10.30.

Dated: December 7, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

[FR Doc. 92-30129 Filed 12-9-92; 9:51 am]

BILLING CODE 4160-01-F

Exhibit 23

FDA Letter to Population Council re: NDA (Feb. 18, 2000)

/S/

NDA 20-687

FEB 18 2000

Population Council
Attention: Sandra P. Arnold
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for mifepristone 200 mg tablets.

We acknowledge receipt of your submissions dated September 18 and 26, 1996; January 30, March 6 and 31, July 28, August 5, September 3 and 24, November 26, 1997; January 30, February 19, April 27, June 25, October 26, December 7 and 8, 1998; February 8, 22, March 31, April 28, May 10, 20, June 3 (2), 15, 25, 30, July 14, 22, August 3, 13, 18, 30, September 3, 8, 13, 30, October 5, 26, 28, November 16, 29 (2), December 6, 7, 23, 1999; January 21, 28 (2), and February 16, 2000. Your submission of August 18, 1999 constituted a complete response to our September 18, 1996 action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry

Drug Substance

Drug Product

Redacted 1

pages of trade

secret and/or

confidential

commercial

information

Labeling

Address the recommendations in the enclosed draft labeling for the Physician Insert and Patient Package Insert.

It will be necessary for you to submit revised draft labeling for the drug. We recommend that the

labeling be identical in content to the enclosed draft labeling (text for the Physician Package Insert and Patient Package Insert).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Phase 4 Commitments

We remind you of your commitments dated September 16, 1996, to perform the following Phase 4 studies:

1. To monitor the adequacy of the distribution and credentialing system,

2. To follow-up on the outcome of a representative sample of mifepristone-treated women who have surgical abortion because of the method failure,

3. To assess the long-term effects of multiple use of the regimen,

4. To ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not,

5. To study the safety and efficacy of the regimen in women (1) under 18 years of age, (2) over age 35, and (3) who smoke,

6. To ascertain the effect of the regimen on children born after treatment failure.

Distribution Plan

We have completed our review of this application, including the restrictions on the distribution and use of this product proposed in your January 21, 2000 submission, entitled "Distribution Plan". We have concluded that adequate information has not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for use as recommended. The restrictions on distribution will need to be amended.

We have thus considered this application under the restricted distribution regulations contained in 21 CFR 314.500 (Subpart H) and have concluded that restrictions as per CFR 314.520 on the distribution and use of mifepristone are needed to assure safe use of this product.

Promotional Activities

Please note that promotional activities for this NDA are subject to 21 CFR 314.550. As such, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the [redacted] and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you have regarding your new drug. Please provide updated information as

listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call

Sincerely,

/S/

Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Exhibit 24

2000 FDA Approval Memorandum to Population Council re: NDA 20-687 Mifeprex (mifepristone) (Sept. 28, 2000)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM: /S/

SUBJECT:

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains [redacted] Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from [redacted] in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided [redacted] 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H. (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

Exhibit 25

2000 FDA Approval Letter for Mifeprex (mifepristone) Tablets (Sept. 28, 2000)

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/

[redacted]

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Exhibit 26

2003 Citizen Petitioners' Response to Opposition Comments filed by The Population Council, Inc. and Danco Laboratories, LLC (Oct. 10, 2003)

Kirkpatrick & Lockhart LLP

1800 Massachusetts Avenue, NW
Suite 200
Washington, DC 20036-1221
202.778.9000
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October 10, 2003

VIA HAND DELIVERY

Dockets Management Branch
U.S. Food and Drug Administration
Document Control Room
5630 Fishers Lane, First Floor
Room 1061 (HFA-305)
Rockville, Maryland 20852

Re: Docket No. 02P-0377
Response to Opposition Comments filed by The Population Council, Inc. and Danco Laboratories, LLC

We submit these comments on behalf of The American Association of Pro Life Obstetricians and Gynecologists ("AAPLOG"), the Christian Medical Association ("CMA"), and Concerned Women for America ("CWA") (collectively, "the Petitioners"), in response to Opposition Comments filed by the makers/distributors of Mifeprex™ (mifepristone) 200 mg tablets (NDA 20-687).[1] In particular, The Population Council, Inc. ("the Council") and Danco Laboratories, LLC ("Danco") (collectively, "the Sponsor") submitted comments on March 13, 2003 opposing the Citizen Petition and Request for Administrative Stay ("Petition") filed by the Petitioners on August 20, 2002.[2]

Not surprisingly, the Council and Danco ask the Food and Drug Administration ("FDA") to maintain the status quo, so that they can continue to sell Mifeprex, a "non-surgical" alternative to abortion. By contrast, the Petitioners seek to protect women from the unknowing use of a dangerously unsafe drug by pursuing an immediate stay and withdrawal of FDA's approval of the new drug application ("NDA") for mifepristone.

Although opposing comments were inevitable, the Petitioners are concerned that the Sponsor has refused to acknowledge any problems regarding the safety, effectiveness and overall

[1] Opposition of The Population Council, Inc. and Danco Laboratories, LLC to Citizen Petition and Request for Administrative Stay Regarding Mifeprex® (Mifepristone), Docket No. 02P-0377 (March 13, 2003) ("Opposition Comments") (available at: <http://www.fda.gov/ohrms/dockets/dailys/03/Mar03/031303/031303.htm>).

[2] Citizen Petition of the American Association of Pro Life Obstetricians and Gynecologists, the Christian Medical Association, and Concerned Women for America, Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Days' Gestation, Docket No. 02P-0377 (filed Aug. 20, 2002) (available at: <http://www.aaplog.org/newscitizenpetitionru486.htm>).

medical suitability of the Mifeprex Regimen.[3] The Petitioners are not surprised, however, that the Sponsor has failed to produce medical-scientific data and adequate explanations for the administrative irregularities described in the Petition. This failure is consistent with the Petitioners' contention that the clinical data in support of the Mifeprex Regimen are scarce, not the product of adequate and well-controlled trials, and cannot support a reasoned risk-benefit analysis by FDA. Instead, the available evidence points to the fact that Mifeprex should never have been approved by FDA.

We have set forth below our responses to the Sponsor's Opposition Comments, along with additional evidence that the safety and effectiveness of Mifeprex have not been established in accordance with FDA's regulations. In particular, the drug, which was not lawfully entitled to consideration under Subpart H, could not have been approved apart from that provision's special distribution restrictions; the clinical trials relied on to support the NDA were legally and clinically insufficient; the inclusion of misoprostol in the Mifeprex Regimen without a corresponding misoprostol approval was unlawful; and the Regimen's use is inherently unsafe, as proven by recent life-threatening adverse events and even deaths. With this evidence, FDA is both statutorily empowered and obligated to grant an Administrative Stay to suspend the Mifeprex NDA approval and expedite withdrawal proceedings.

I. The Safety and Effectiveness of Mifeprex Have Not Been Established in Accordance with FDA's Regulations.

FDA's approval of a drug product must rest on the Agency's conclusion that the drug is safe and effective for its labeled conditions for use. In the case of Mifeprex, the Petitioners previously provided evidence that the NDA should not have been approved, and the Sponsor's Opposition Comments did not rebut that evidence. In fact, as described below, although the Opposition Comments reiterate the Sponsor's confidence in the safety and efficacy of the Mifeprex Regimen, they also expose the dearth of pre- or post-approval evidence for that position. Consequently, given the body of evidence now before FDA, the Agency should withdraw its approval of the Mifeprex NDA at this time.

A. Subpart H Enables FDA to Place Special Restrictions on Especially Risky Drugs like Mifeprex.

Although Petitioners maintain their original position that FDA's reliance on Subpart H was unlawful for this drug, the Sponsor's response that Mifeprex could have been approved alternatively under Section 505 is incorrect. The Sponsor's Opposition Comments repeat an argument that the Sponsor made when it was trying to convince FDA not to use Subpart H – that "[t]he restrictions FDA imposed under Subpart H could as well have been imposed (and enforced) under Section 505 [of the FD&C Act][4] itself, without reference to Subpart H."[5] The

[3] When FDA approved the Population Council's NDA for mifepristone, it approved the drug for use in conjunction with misoprostol. In this Response, "Mifeprex Regimen" will refer to the combined use of Mifeprex and misoprostol to effect an abortion.

[4] Federal Food, Drug, & Cosmetic Act of 1938 ("FD&C Act"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et seq.*).

fact that FDA proceeded under Subpart H suggests that the Agency did not subscribe to this argument. Indeed, had FDA taken this position, it would not have promulgated the restricted distribution prong of Subpart H,[6] but would simply have relied on Section 505 to impose restrictions. When FDA adopted Subpart H, it noted that "the restrictions to ensure safe use contemplated for approvals under [Subpart H] are authorized by statute."[7] FDA went on to explain that Subpart H would enable the Agency to impose on drugs restrictions "necessary to ensure that section 505 criteria have been met, i.e., restrictions to ensure that the drug will be safe under its approved conditions of use."[8] Additional restrictions are necessary because Mifeprex and other Subpart H drugs carry greater risks than drugs approved through the typical new drug approval processes.[9] In short, when FDA adopted Subpart H, it added a new tool to its regulatory toolbox enabling it to approve drugs that otherwise could not have been approved because the safe usage mandates in Section 505 would not have been satisfied.[10] Therefore, the Sponsor errs in asserting that the approval of the Mifeprex NDA is independently grounded in Section 505(d).

The Sponsor also claimed that its cooperation with FDA to devise restrictions obviates the need to rely on Subpart H.[11] The Sponsor's unfailing confidence in the safety of mifepristone even in the face of scientific evidence to the contrary is part of the reason that restrictions under section 505 could not be effective. The Sponsor's bias in favor of Mifeprex clouds its analysis of the inherent hazards of the Regimen. In fact, the Sponsor refused to participate in devising restrictions that were designed to protect Mifeprex patients.

As "evidence" of its cooperation, the Sponsor pointed to the restricted distribution plan it proposed to an FDA advisory committee in 1996.[12] The FDA Advisory Committee's reaction to

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[5] *See* Opposition Comments at 3 (citing 21 U.S.C. § 355). *See also* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 3-5 [FDA FOIA Release: MIF 001333-49].

[6] 21 C.F.R. § 314.520.

[7] New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval*, Final Rule*, 57 Fed. Reg. 58942, 58951, § 20 (Dec. 11, 1992) ("*Subpart H Final Rule*").

[8] *Subpart H Final Rule*, 57 Fed. Reg. at 58951, § 20. *See also* New Drug, Antibiotic, and Biological Product Regulations; Accelerated Approval, *Proposed Rule*, 57 Fed. Reg. 13234, 13237, sec. III.B.3. (April 15, 1992) ("*Subpart H Proposed Rule*") (noting that without Subpart H restrictions, the drug "would be adulterated under section 501 of the act, misbranded under section 502 of the act, or not shown to be safe under section 505 of the act").

[9] *See Subpart H Final Rule*, 57 Fed. Reg. at 58952, § 23 ("The postmarketing restrictions set forth in the proposal and in this final rule are intended to enhance the safety of a drug whose risks would outweigh its benefits in the absence of the restriction.").

[10] FDA explained that "rather than interfering with physician or pharmacy practice, the regulations permit, in exceptional cases, approval of drugs with restrictions so that the drugs may be available for prescribing or dispensing." *Subpart H Final Rule*, 57 Fed. Reg. at 58951-52, § 20.

[11] *See* Opposition Comments at 5-6.

[12] *See* Opposition Comments at 4. The Sponsor was referring to a plan presented to FDA's Reproductive Health Drugs Advisory Committee ("FDA Advisory Committee"). *See* FDA Advisory Committee, *Hearings on New Drug Application for the Use of Mifepristone for Interruption of Early Pregnancy*, at 7 (July 19, 1996) (*FDA Hearings Transcript*)[FDA FOIA Release: MIF 005200-90, MIF 005209]. The Petitioners will, at times, cite to documents

the proposal, however, reveals its inadequacy; the Advisory Committee stated that "[w]e agree in concept with the proposal but have serious reservations on how it is currently described in terms of assuring safe and adequate credentialing of providers."[13] The Sponsor also cited to its "comprehensive distribution plan" submitted in January 2000 and to its revised distribution plan submitted to FDA in March 2000.[14] The Sponsor indicated in its January 2000 submission that it was providing the proposal only "in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns,"[15] and the March 2000 submission was prefaced with a denial that mifepristone was "a highly toxic and risky drug."[16] However, as the Petition explained, the plans that the Sponsor submitted on both occasions were not designed with the safety of the patient in mind and when FDA proposed a set of restrictions that focused on patient safety, the Sponsor balked.[17] Further, even if the Sponsor had participated willingly in drawing up restrictions that embodied key safeguards for patients, FDA could not necessarily expect similar cooperation from future generic producers of mifepristone.[18]

Conclusion

As explained above, the Mifeprex approval cannot rest independently on Section 505(d) of the FD&C Act. The Sponsor refused to acknowledge that there are serious risks associated with the Mifeprex Regimen, let alone to propose restrictions designed to counteract those risks. FDA approved Mifeprex under Subpart H in order to impose mandatory safety restrictions on the distribution and use of the drug. That being said, the proper course would have been for FDA to have rejected the NDA because Mifeprex is unsafe and ineffective under Section 505 and fails to satisfy the Subpart H prerequisites that it treat a serious or life-threatening illness and provide a meaningful therapeutic benefit above existing treatments.[19]

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contained in FDA's January 31, 2002 public release of documents (approximately 9,000 pages in 94 files) made pursuant to a Freedom of Information Act ("FOIA") request ("FDA FOIA Release") filed by the non-profit organization, Judicial Watch. These bracketed citations will reflect the page numbering FDA has stamped on the bottom of each page of the document cited, for example: [FDA FOIA Release: MIF 000001-05]. The FDA webpage posting the 94 files is: <http://www.fda.gov/cder/archives/mifepristone/default.htm>.

[13] FDA Advisory Committee, Minutes of July 19, 1996 Meeting (approved July 23, 1996): at 7 [FDA FOIA Release: MIF 000539-45, MIF 000545] (citing statement voted on unanimously by the FDA Advisory Committee).

[14] *See* Opposition Comments at 4-5.

[15] Amendment 039 to the NDA, Cover Letter, Danco to FDA (Jan. 21, 2000): at 1 [FDA FOIA Release: MIF 000525-26, MIF 000525]. The Sponsor's reference to the "unique situation surrounding abortion provision in the United States" reveals the Sponsor's primary concern in proposing restrictions, namely that the safety and confidentiality of *abortion providers* be maintained, not that patient safety be maximized.

[16] Responses by Population Council to "FDA Letter, [redacted] to Arnold, Sandra (February 18, 2000)" (Mar. 2000): at 1 [FDA FOIA Release: MIF 000523-24, MIF 000523].

[17] *See* Section I.D. herein; *see also* Petition at 50-54.

[18] *See* FDA, Memorandum, re: NDA 20-687 (Feb. 17, 2000): at 3 [FDA FOIA Release: MIF 000583-85, MIF 000585] ("Subpart H approval will also allow the FDA to impose similar distribution restrictions and system on any future generic mifepristone approved for this indication.").

[19] *See* Petition at 18-23 (explaining why Mifeprex was an inappropriate candidate for Subpart H).

B. The Mifeprex Clinical Trials Were Legally and Clinically Insufficient.

The Petition describes numerous problems that plagued the clinical trials underlying the approval of Mifeprex. The Sponsor's Opposition Comments, rather than demonstrating the sufficiency of the clinical trial data that formed the basis for the Mifeprex NDA, heightened the Petitioners' concerns about the legal and clinical sufficiency of the French and U.S. Clinical Trials (collectively, "Mifeprex Trials"). First, a close reading of the Sponsor's Opposition Comments reveals that the Mifeprex Trials were not historically controlled but, rather, were *uncontrolled*.[20] Second, even if the Mifeprex trials were historically controlled, as the Sponsor maintains, the use of historically controlled trials to support this NDA violated clearly established FDA rules and agency policies.[21] Finally, the Sponsor's additional arguments in support of the scientific adequacy of the Mifeprex trials do not answer the objections presented in the Petition. Untested by adequate clinical trials, the Mifeprex Regimen cannot be deemed to be safe and effective; accordingly, the marketing of Mifeprex must be halted.

1. The Mifeprex Trials Were Uncontrolled.

A review of the record regarding the scope and methodology of the trials, prompted by the Sponsor's defense of the Mifeprex Trials,[22] reveals that the trials used to support the Mifeprex NDA were not historically controlled, but were *uncontrolled*.[23] The Petition cited to the discussion between a member of FDA's Advisory Committee and an FDA official in which the Mifeprex Trials were characterized as "historically" controlled.[24] The Petitioners noted, however, that the Mifeprex Trials appeared to have been uncontrolled.[25]

The French Clinical Trials consisted of two studies in which all participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment.[26] The Sponsor did not describe any historical (or "external") control group,[27]

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[20] Because the Mifeprex Regimen was the first drug regimen that FDA approved to induce abortions, in order to scientifically demonstrate the safety and effectiveness of this drug regimen, the Sponsor should have compared this new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period.

[21] The Petitioners believe that a longitudinal analysis of all past occasions on which FDA accepted uncontrolled and historically controlled trials as an adequate basis for an NDA and all past occasions on which it has rejected the use of uncontrolled or historically controlled clinical trials would demonstrate the inadequacy of the clinical trials underlying this NDA. FDA is uniquely qualified to perform such an analysis.

[22] *See* Opposition Comments at 6-9.

[23] One consequence of the failure to conduct properly controlled trials is that a *statistical* evaluation of effectiveness could not be made. As FDA's statistical reviewer noted, with reference to the French trials: "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgment whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy." *See* FDA, Statistical Review and Evaluation (May 21, 1996): at 7-8.

[24] Petition at 36, n.168 (referring to statements by Dr. Cassandra Henderson, a member of the FDA Advisory Committee, and FDA's Dr. Ridgely C. Bennett at the Advisory Committee Hearings).

[25] Petition at 35.

[26] Letter, C. Wayne Bardin, Population Council, to FDA/CDER (June 5, 1995) (Submission Serial Number: 131) at 3-4 ("Bardin Letter")[FDA FOIA Release: MIF 004746-47]. The patients in the French Clinical Trials took 600 mg of mifepristone followed by 400 μg of misoprostol. In one of the French Clinical Trials, some patients received an

nor did the Sponsor indicate that any of the well-established scientific guidelines for selecting a proper control group before commencing a historically controlled study were used for the French Clinical Trials.[28] The Sponsor, nevertheless, informed FDA that "[a]ll studies conducted with mifepristone in the induction of abortion can be regarded as having historical controls which consist of the body of information available on abortion using surgical procedures."[29] This observation appears to be the only basis for the Sponsor's claim that the French Clinical Trials were historically controlled, and it is inadequate.

The U.S. Clinical Trial mimicked the design of the French Clinical Trials.[30] All participants were given a mifepristone-misoprostol regimen, and no concurrent control group underwent a different abortion treatment. Descriptions of the U.S. Clinical Trial do not mention a control group, historical or otherwise, or the procedures according to which a control group was selected.[31] The absence of any reference to a control group suggests that the U.S. Clinical Trial was not historically (externally) controlled.[32]

The Sponsor's failure to precisely identify a historical control group is fatal to its claim that the Mifeprex Trials were historically controlled. Postulating the existence of some generic,

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extra 200 µg of misoprostol if the first 400 µg was not sufficient to complete the abortion. The approved Mifeprex Regimen consists of 600 mg of mifepristone followed by 400 µg of misoprostol.

[27] Bardin Letter at 3-4.

[28] FDA guidance lists "some approaches to design and conduct of externally controlled trials could lead them to be more persuasive and potentially less biased:"

> A control group should be chosen for which there is detailed information, including, where pertinent, individual patient data regarding demographics, baseline status, concomitant therapy, and course on study. The control patients should be as similar as possible to the population expected to receive the test drug in the study and should have been treated in a similar setting and in a similar manner, except with respect to the study therapy. Study observations should use timing and methodology similar to those used in the control patients. To reduce selection bias, selection of the control group should be made before performing comparative analyses; this may not always be feasible, as outcomes from these control groups may have been published. Any matching on selection criteria or adjustments made to account for population differences should be specified prior to selection of the control and performance of the study."

FDA, "Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials," (Rockville, Md.: May 2001): at 27 (§ 2.5.2) (*ICH: E10*). *ICH: E10* is available at: <http://www.fda.gov/cder/guidance/4155fnl.pdf>.

[29] Bardin Letter at 4.

[30] For a description of the U.S. Clinical Trial, s*ee* Irving M. Spitz, M.D., C. Wayne Bardin, M.D., Lauri Benton, M.D., and Ann Robbins, "Early Pregnancy Termination with Mifepristone and Misoprostol in the United States," *New England Journal of Medicine* 338 (Apr. 30, 1998): 1241-47 ("Spitz Article") [FDA FOIA Release: MIF 006692-97].

[31] *See, e.g.*, Spitz Article.

[32] The Spitz Article does compare two groups, patients who are differentiated by the age of their pregnancies, but a comparison of that type does not generate data about whether mifepristone-misoprostol abortions are safe and effective. To the extent the Sponsor believed that a correlation existed between the age of the pregnancy and the safety and efficacy of mifepristone-misoprostol abortions, any historical control group that the Sponsor used should have been classified by, among other characteristics, gestational age.

undefined comparison group based on the literature about surgical abortion does not suffice.[33] In sum, the Mifeprex Trials were uncontrolled and cannot support the Mifeprex NDA.[34]

2. Mifeprex Is Not a Drug for Which Historically Controlled Trials Were Appropriate.

Assuming arguendo, as the Sponsor maintains, that the Mifeprex Trials were historically controlled, they were nevertheless not *adequately* controlled and did not provide an adequate basis for approving the Mifeprex NDA. In its Opposition Comments, the Sponsor erroneously suggested that "historically controlled" trials yield data of the same quality as data generated in concurrently controlled trials.[35] In fact, the scientific community (and FDA specifically) regard historically controlled studies to be little better than uncontrolled studies and, therefore, generally disfavor their use with a few well-defined exceptions.[36]

Mifepristone-misoprostol abortions do not fall within any of those exceptions. The Rochester Glossary states that historical controls are "mainly used in the study of rare diseases" in which sample size would not be sufficient to support a randomized clinical trial.[37] This exception is inapplicable because the number of pregnant women seeking to terminate their pregnancies is large enough to support randomized, concurrently controlled trials. Section 314.126(b)(2)(v) of FDA's rules cautions that the use of historical controls is "usually reserved

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[33] In addition, the Sponsor, in its Opposition Comments, invented a historical control group *ex post facto* by comparing the rate of spontaneous abortions in the general population of pregnant women with the rate of abortions in patients who underwent a mifepristone-misoprostol regimen during the Mifeprex Trials. *See* Opposition Comments at 6-7 ("In these major studies, 92-95% of the 2508 women evaluated for efficacy had complete abortions … . By comparison, the rate of spontaneous abortion in the first trimester is assumed to be about 10%."). Using the general population as a historical control group and retrospectively assuming a rate of spontaneous abortion in this group is not a scientifically acceptable approach to identifying a control group, particularly when, as here, an established surgical treatment group could have been used as the control group.

[34] Section 314.126(e) of FDA's rules states that "[u]ncontrolled studies or partially controlled studies *are not acceptable* as the *sole* basis for the approval of claims of effectiveness." 21 C.F.R. § 314.126. A publicly available FDA staff presentation about clinical trials illustrates this point. The presentation explained, under the heading "Phase 3 – Comparative trial to evaluate drug," "Comparator group important – Standard of care, placebo, never nothing in serious or life-threatening diseases (ICH E3, E9, E10)." *See* Peter A. Lachenbruch, "Some Things You Always Wanted to Know about Clinical Trials but Were Afraid to Ask," Slide Presentation for *CBER 101: An Introduction to the Center for Biologics Evaluation and Research (CBER)* (March 24-26, 2003): at 5 (emphasis in original) (available at: http://www.fda.gov/cber/summaries/cber101032403pl.pdf).

[35] *See* Opposition Comments at 6-8.

[36] For example, the Research Subjects Review Board of the University of Rochester Medical Center authored a guidance document, which states that "[h]istorical controls are considered to be the least reliable because they compare results obtained in another time, in another place and by another investigator." University of Rochester Medical Center, Research Subjects Review Board, "Glossary of Research Terms," at 2 ("Rochester Glossary") (available at: http://www.urmc.rochester.edu/rsrb/pdf/glossary.pdf). Similarly FDA has explained, "[t]he limitations of historical controls are well known (difficulty of assuring comparability of treated groups, inability to blind investigators to treatment, etc.) and deserve particular attention." FDA/CDER, *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988): at 54.

[37] Rochester Glossary at 2 ("Historical controls are mainly used in the study of rare diseases where the **n** is not sufficient for a randomized clinical trial.").

for special circumstances" and cites "studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism)."[38] Mifepristone-misoprostol abortions do not fit within either of these categories. First, the Regimen does not treat a condition with "high and predictable mortality." Second, the effects of the Regimen are not "self-evident" as in the case of general anesthetics. The Sponsor's discussion of the adequacy of its trial data reflects the Sponsor's fundamental misconception that there are only two possible outcomes of the Mifeprex Regimen, both of which are self-evident: regimen failure (failed abortion) and regimen success (death and complete expulsion of the fetus). The Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes. Such outcomes include tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects.

The Sponsor's reliance on FDA Guidance, *ICH: E10*, is also misplaced.[39] Although *ICH: E10* includes a discussion of situations in which externally controlled trials may be used, it also warns of their inherently problematic nature.[40] The Sponsor's reliance on the acknowledgement in *ICH: E10* that historical controls are appropriate in some circumstances is misplaced. *ICH: E10* explains:

> An externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable and the disease or condition to be treated has a well-documented, highly predictable course. It is often possible, even in these cases, to use alternative, randomized, concurrently controlled designs (see section 2.1.5).[41]

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[38] 21 C.F.R. § 314.126(b)(2)(v) provides:

> *Historical control*. The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

[39] Opposition Comments at 7.

[40] *See ICH: E10* at 29 (§ 2.5.7)("The externally controlled study cannot be blinded and is subject to patient, observer, and analyst bias; these are major disadvantages. It is possible to mitigate these problems to a degree, but even the steps suggested in section 2.5.2 cannot resolve such problems fully, as treatment assignment is not randomized and comparability of control and treatment groups at the start of treatment, and comparability of treatment of patients during the trial, cannot be ensured or well assessed. It is well documented that externally controlled trials tend to overestimate efficacy of test therapies. It should be recognized that tests of statistical significance carried out in such studies are less reliable than in randomized trials."). *See also* Henry Sacks, Ph.D., M.D., Thomas C. Chalmers, M.D., Harry Smith, Jr., Ph.D., "Randomized Versus Historical Controls for Clinical Trials," *The American Journal of Medicine* 72 (Feb. 1982): 233-240, 233 ("The data suggest that biases in patient selection may irretrievably weight the outcome of [historical controls] in favor of new therapies.").

[41] *ICH: E10* at 28 (§ 2.5.4).

Even proponents of mifepristone-misoprostol abortions would not argue that such abortions are superior to alternative methods of abortion.[42] In fact, the Mifeprex Regimen has been shown to be an inferior method of abortion.[43] Absent a clear belief in the Regimen's superiority, concurrently controlled trials should have been performed.[44] Furthermore, pregnancies often do not follow a "well-documented, highly predictable course."[45] Mifepristone-misoprostol abortions do not satisfy either prong of the *ICH: E10* prerequisite for the use of historically controlled studies.[46]

3. The Mifeprex Clinical Trials Did Not Establish a "Meaningful and Therapeutic Benefit" As Required By Subpart H.

Drugs, like Mifeprex, approved pursuant to Section 314.520 (Subpart H) of the Agency's rules,[47] must provide a "meaningful therapeutic benefit to patients over existing treatments."[48] Subpart H drugs "will have had effectiveness demonstrated on the basis of adequate and well-controlled studies."[49] The Sponsor argued that "meaningful therapeutic benefit" does not impose design features for the clinical trials required to support an NDA approved pursuant to Subpart H.[50] The Sponsor's position is inconsistent with the plain meaning of the rule. Subpart H is reserved for drugs that have a higher risk profile than drugs approved through standard FDA processes. A meaningful therapeutic benefit over available therapies justifies the heightened risks, and only well-controlled clinical trials can demonstrate that such a benefit exists.[51]

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[42] *See, e.g.*, Richard Hausknecht, M.D., "Mifepristone and Misoprostol for Early Medical Abortion: 18 Months Experience in the United States," *Contraception* 67 (2003): 463-65, 465 ("Hausknecht Article") ("Which approach to early abortion, medical or surgical, is safer remains unknown but it does appear that medical abortion is as safe as early surgical abortion. There are no recent data on failed surgical abortions but the failure rate of mifepristone/misoprostol medical abortions is higher than that reported decades ago for suction curettage.")

[43] Petition at 21-22 (discussing Jeffrey T. Jensen, Susan J. Astley, Elizabeth Morgan, and Mark D. Nicols, "Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study," *Contraception* 59 (1999): 153-159 [FDA FOIA Release: MIF 000438-44]).

[44] The Petitioners believe that trials comparing mifepristone-misoprostol abortion with the surgical alternative were not conducted for precisely this reason *(i.e.*, such trials would have demonstrated that mifepristone-misoprostol abortions were inferior). Because of its inferiority, the Mifeprex Regimen is contraindicated.

[45] Even though pregnancy occurs regularly, complications arise during pregnancy on a frequent basis (*e.g.*, approximately 2% of pregnancies are ectopic and others involve such complications as high blood pressure, ruptured placenta, infection, cysts, abnormal pain, anemia, and fetal malposition).

[46] Even if mifepristone-misoprostol abortion were deemed to be an acceptable candidate for historically-controlled testing, the Sponsor should have attempted to devise concurrently controlled trials anyway. *ICH: E10* states that even when historically controlled testing may be appropriate, "[i]t is often possible … to use alternative, randomized, concurrently controlled designs." *ICH: E10* at 28 (§ 2.5.4).

[47] 21 C.F.R. § 314.520.

[48] 21 C.F.R. § 314.500.

[49] *See Subpart H Final Rule*, 57 Fed. Reg. at 58953, § 25.

[50] Opposition Comments at 8.

[51] The Sponsor also argued that by the time FDA decided to approve Mifeprex using Subpart H, the Sponsor had completed the Mifeprex Trials and that FDA could not have required the Sponsor to modify the trial design and perform new trials for Subpart H purposes. *See* Opposition Comments at 9, n. 4. FDA is under no obligation to

The Sponsor argued that two of the examples of "meaningful therapeutic benefit" listed in Section 314.500 ("ability to treat patients unresponsive to, or intolerant of, available therapy") present situations in which comparative trials with the existing therapy are not feasible.[52] Yet, sponsors who intend their drugs to treat unresponsive or intolerant patients are not exempt from the requirement to conduct "well-controlled" trials. In fact, Subpart H trials are routinely designed to compare, in unresponsive or intolerant patients, the safety and effectiveness of the new therapy with either the standard of care or a placebo.[53]

The Sponsor further claimed that FDA "routinely approves Subpart H drugs on the basis of study designs that do not compare the Subpart H drug directly to existing therapy."[54] In support of this claim, the Sponsor offered one example, the Subpart H approval of the leprosy drug, Thalomid (thalidomide).[55] That example is inapposite because the Thalomid NDA was supported by three controlled trials despite the existence of factors that might have supported an exemption from the standard trial requirements.[56] In one of the three underlying trials, thalidomide plus the standard treatment was compared against the standard treatment alone plus a placebo.[57] This study design allowed for a meaningful statistical analysis of the effectiveness of this drug in comparison with the current available standard of care – in direct contrast to the faulty study designs and minimal statistical analysis associated with the Mifeprex NDA.

Conclusion

By statute and agency regulation, drug applications must be supported by adequate and well-controlled studies. The failure of the Sponsor to offer legally and scientifically sufficient trial data should have been fatal to its NDA and now requires withdrawal of that approval.[58]

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approve an NDA at all, let alone to approve an NDA based on insufficient trial data. It is not uncommon at any stage of the NDA review process for FDA to require a drug sponsor to correct or amend an NDA by conducting properly designed and executed studies. Had the sponsor followed standard scientific norms and performed randomized, concurrently controlled trials comparing mifepristone-misoprostol abortion with surgical abortion it would have been able to supply comparative data.

[52] *See* Opposition Comments at 8-9. Mifepristone-misoprostol abortions do not fall within either of these examples. Because surgical abortion, the standard of care, is the backup procedure if the Mifeprex Regimen fails, *ipso facto* the Regimen cannot be used to treat patients unresponsive to or intolerant of the standard of care.

[53] Furthermore, in this instance, the Sponsor did not attempt to test the drug in populations that it identified as intolerant or unresponsive and, indeed, the Mifeprex Regimen is not an option for patients unresponsive to or intolerant of surgical abortion because surgical abortion is the back-up procedure for Mifeprex patients.

[54] Opposition Comments at 9.

[55] NDA 20-785.

[56] The fact that leprosy is a rare disease in the U.S. makes it difficult to perform clinical trials. In addition, there are compassionate reasons for not awaiting the results of randomized, double-blinded comparator controlled clinical trials before treating patients suffering from leprosy. The fact that well-controlled trials were employed despite the existence of these mitigating factors is evidence of the value that the scientific community places on well-controlled trials.

[57] *See* Petition at 39 (discussing the thalidomide trials). In one study, all participants received either thalidomide or a placebo in addition to the standard dapsone treatment.

[58] *See* Petition at 30-35 (discussing statutory and regulatory requirements for clinical trials).

C. The Inclusion of Misoprostol in the Mifeprex Regimen Was Unlawful.

The Mifeprex Regimen combines the use of mifepristone and a second drug, misoprostol (Cytotec™). Although FDA never approved misoprostol as a stand-alone abortifacient, it approved misoprostol for use as an abortifacient in combination with mifepristone and mandated this use in the Mifeprex Package Insert. As explained in the Petition, FDA effectively sanctioned the use and promotion of misoprostol for an unapproved indication.[59] The promotion of an unapproved use contradicts the FD&C Act, which takes the position that "a drug manufacturer may not promote [its] product for any use other than the ones for which the company received FDA approval."[60]

In its Comment, the Sponsor defended the *de facto* approval of misoprostol for a new indication as an abortifacient and asserted that "FDA routinely approves drugs for use in combination with previously approved drugs without requiring any change in the labeling of the previously approved drug."[61] The Sponsor denied that this practice "puts either FDA or the sponsor of the later-approved drug in the position of 'promoting' off-label use of the previously approved drug."[62] The Sponsor offered four examples to support its position that this practice is not uncommon.[63]

In fact, the Sponsor's four examples support the position set forth in the Petition that subsequently approved drugs (Drug Bs – like Mifeprex) may reference previously approved drugs (Drug As – like misoprostol) on Drug B's labeling only for *FDA-approved* indications.[64]

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[59] *See* Petition at 41-48. The drug's manufacturer, G.D. Searle & Co. ("Searle"), did not file a supplemental NDA to obtain approval for misoprostol's use as an abortifacient. Searle has subsequently been purchased, most recently, by Pfizer. *See* Petition at 42, n.188.

[60] *See* Elizabeth A. Weeks, "Is It Worth the Trouble? The New Policy on Dissemination of Information on Off-Label Drug Use under the Food and Drug Modernization Act of 1997," *Food and Drug Law Journal* 54 (1999): 645-65, 645.

[61] Opposition Comments at 9.

[62] Opposition Comments at 10.

[63] Opposition Comments at 9-10.

[64] The first example offered by the Sponsor is the approval by FDA on September 10, 2001 of the combination of Xeloda (capecitabine) and Taxotere (docetaxel) for treating patients with metastatic breast cancer that has progressed after treatment with an anthracycline-containing cancer therapy. FDA initially approved Xeloda, an oral therapy, for the treatment of breast cancer on April 30, 1998, and FDA approved Taxotere, an intravenous product, for the treatment of advanced breast cancer on May 15, l998. *See* FDA Press Release, "FDA Approves Xeloda in Combination with Taxotere for Advanced Breast Cancer" (Sept. 10, 2001) (available at: <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01101.html>). Thus, when Xeloda and Taxotere are used together, each is being used for an FDA-approved use.

The Sponsor's second example is FDA's approval on July 15, 1999 of Actos to improve glycemic control in patients with Type 2 diabetes. Actos is indicated as a monotherapy and for use in combination with a sulfonylurea, metformin, or insulin "when diet and the single agent does not result in adequate glycemic control." Letter, FDA/CDER to Mikihiko Obayashi, President, Takeda America Research & Development Center, Inc. (July 15, 1999). When used alone or together to treat Type-2 diabetes, each drug is being used for one of its FDA-approved indications.

Each example describes drug products that are being used in combination to treat indications approved for the single drugs at issue.

Upon close examination, the Sponsor's four examples underscore the fact that FDA's approval of mifepristone for use in combination with misoprostol, a drug never approved as an abortifacient, constitutes a significant departure from FDA precedents. As Professor Richard Merrill explained, "[i]n FDA's view, to promote any use of [its] new drug, the manufacturer must have agency approval – allowing that use to be included in the official labeling."[65] The approval in this instance struck at the heart of FDA's long-held policy that in order for a new drug use to be promoted, the drug's sponsor must submit an application seeking to demonstrate the safety and effectiveness of that new use.[66] It defies logic to imagine that Danco could be allowed to do with misoprostol what Searle could not do with its own drug – that is, promote an unapproved use of misoprostol. Yet, that activity is exactly what FDA permitted in Mifeprex's case. FDA's regulatory framework would be rendered toothless if third parties were permitted to behave in this manner.

In fact, Searle, which held the patent for misoprostol,[67] apparently *objected* to adding an indication for abortion to the Cytotec label. Searle's objections were overridden because only the combined regimen was effective. As the Sponsor explained, "[t]he fact is that mifepristone used as contemplated in 1983 was a failed drug – it was not sufficiently efficacious to have ever been approved."[68] Perhaps to avoid having to obtain Searle's cooperation, in an unprecedented

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The Sponsor's third example is FDA's approval on October 26, 2001 of Viread (tenofovir disoproxil fumarate), a nucleotide reverse transcriptase inhibitor of HIV, for combined use with other antiretroviral agents for the treatment of HIV-1 infection in adults. The antiretroviral agents with which Viread is to be used have separately been approved for the treatment of HIV. Letter, FDA/CDER to Rebecca Coleman, Gilead Sciences, Inc. (Oct. 26, 2001) (NDA 21-356). The fact that Viread was not approved for use as a monotherapy in the treatment of HIV does not alter the analysis, but rather makes it a useful comparison for mifepristone, which has been approved as an abortifacient only in conjunction with misoprostol. Thus, when used together, each drug is being used for one of its FDA-approved indications.

The Sponsor offers as its fourth example FDA's approval of Nexium (esomeprazole magnesium) on February 20, 2001 for the treatment of erosive esophagitis and other symptoms associated with GERD (Gastroesophageal Reflux Disease). Letter, FDA/CDER to Kathryn D. Kross, AstraZeneca, LP (Feb. 20, 2001) (NDA 21-153; NDA 21-154). For one of its approved indications, *H. pylori* eradication, Nexium is used in combination with amoxicillin and clarithromycin, both of which have been approved for treating *H. pylori*. Thus, when they are used in combination with Nexium, each drug is simply being used for one of its approved indications.

[65] Richard A. Merrill, "The Architecture of Government Regulation of Medical Products," *Univ. of Virginia Law Review* 82 (1996): 1753-1866, at 1766, n.40. As noted in the Petition, former FDA general counsel, Peter Barton Hutt, observed that FDA's actions with respect to misoprostol "set[ ] an extraordinary precedent" because FDA was "seemingly encouraging a drug's unapproved use." *See* Petition at 42-43 (Hutt's quotation was reported in Rachel Zimmerman, "Clash Between Pharmacia and FDA May Hinder the Use of RU-486," *Wall Street Journal* (Oct. 18, 2000): at B1).

[66] A drug may be deemed "new" because of "[t]he newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body." 21 C.F.R. § 310.3(h)(4).

[67] The patent for misoprostol has since expired, but at the time the Mifeprex Regimen was approved, Searle held exclusive rights to that patent.

[68] Population Council Response to the Request for Revision of the Regulatory Review Period Determination for MIFEPREX® Submitted by Corcept Therapeutics Inc., Docket No. 01E-0363 (July 2, 2002): at 3 ("Sponsor's

"joint decision" in July 1994, FDA and the Sponsor "determined that the NDA need not cover misoprostol as well as mifepristone."[69] The Sponsor subsequently explained, however, that "there can be no doubt that the approved human drug product contemplates both mifepristone and misoprostol, as shown in the approved labeling,"[70] which "specifically states that administration of mifepristone must be followed by administration of misoprostol."[71] The Sponsor added that "FDA has made clear on numerous occasions, FDA review of an NDA is 'inextricably intertwined' with the proposed labeling for the product."[72] In so stating, the Sponsor speaks out of both sides of its mouth – acknowledging that combined use with misoprostol is necessary for Mifeprex's effectiveness and labeling, but "agreeing" with FDA that a corresponding misoprostol approval is not necessary.

Conclusion

In summary, the inclusion of misoprostol in the Mifeprex Regimen, outside of the NDA approval process for misoprostol, was unlawful. In order to reverse the extraregulatory approval of misoprostol as an abortifacient, FDA must withdraw its approval of the Mifeprex NDA.

D. Mifeprex-Misoprostol Abortions Are Not Safe.

The Sponsor continued in its Opposition Comments to defend the safety of Mifeprex, but has not allayed the concerns set forth in the Petition.[73] Rather than address the scientific and medical issues raised in the Petition, the Sponsor has mischaracterized them. As discussed above, the trials submitted by the Sponsor to support its NDA did not establish the safety of mifepristone-misoprostol abortions, and post-approval data on the Regimen have done no better -- serving only to raise the Petitioners' concerns about the safety of the Mifeprex Regimen.

1. FDA Determined that Mifeprex Would Be Unsafe without Restrictions.

FDA approved mifepristone under the restricted distribution prong of Subpart H, which FDA reserves for drugs that "can be used safely only if distribution or use is modified or restricted."[74] Accordingly, the Mifeprex Regimen includes a number of restrictions.[75] As the

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Response to Corcept"). In this document, the Sponsor responded to Corcept's June 10, 2002 request that FDA consider 1983 rather than August, 4, 1994 as the starting date for the regulatory review of the Mifeprex investigational new drug application ("IND"). The Sponsor sought to convince FDA that the appropriate period for determining patent length began on August 4, 1994, the date of the IND that allowed for the investigation of mifepristone plus misoprostol to induce abortions. The Sponsor did not obtain the patent extension that it sought. The initial ruling in the Population Council's favor was reversed by FDA. *See Note*, Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex; Amendment, 67 Fed. Reg. 65358 (Oct. 24, 2002).

[69] Sponsor's Response to Corcept at 2.

[70] Sponsor's Response to Corcept at 3.

[71] Sponsor's Response to Corcept at 2.

[72] Sponsor's Response to Corcept at 2-3 (citation omitted).

[73] *See* Opposition Comments at 10-14.

[74] *Subpart H Final Rule*, 57 Fed. Reg. at 58942 ("Summary").

Petition explained, however, these restrictions were inadequate to make the drug safe.[76] Moreover, the Sponsor never acknowledged the inherent dangers posed by the approved Mifeprex Regimen, balked at implementing distribution restrictions, and dismissed out of hand the challenges about the adequacy of the restrictions to reduce the dangers of the Mifeprex Regimen.[77] Now that it has FDA's imprimatur to market the drug, the Sponsor takes minimal, if any, actions to carry out the required restrictions.[78]

Additionally, FDA's final decision to omit key restrictions from the approved Regimen has subjected patients who use the Mifeprex Regimen to unnecessary risks. A pre-procedure ultrasound, for example, is necessary to evaluate the gestational age because the Mifeprex Regimen has been shown to be less effective and riskier to the patient as gestational age increases.[79] Ultrasound is also necessary to identify women whose pregnancies are ectopic and who should not undergo the Mifeprex Regimen.[80] Further, because complications and failures are common and predictable and can seriously endanger the health of the patient, FDA should

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[75] For a list of the restrictions, *see* Letter, FDA/CDER to Sandra P. Arnold, Population Council (Sept. 28, 2000): at 2 ("Mifeprex Approval Letter"). The Sponsor contends in its Opposition Comments that it cooperated with FDA by proposing restrictions. *See* Opposition Comments at 10-11. This contention reflects the Sponsor's failure to distinguish between restrictions on the distribution of a drug to prescribing physicians and restrictions designed to ensure patient safety. Furthermore, contrary to the Sponsor's suggestion that decisions about the restrictions in the Mifeprex Regimen were the product of "discussion, negotiation, give and take, debate, even on occasion disputes, between FDA and the Sponsors [that] is characteristic of the review process for many drugs" (Opposition Comments at 11), the Sponsor went to great lengths to avoid including safety restrictions in the Mifeprex Regimen. In fact, after the Sponsor failed to suggest appropriate restrictions to protect Mifeprex patients, FDA proposed its own set of restrictions. Then, the Sponsor complained publicly about the allegedly onerous restrictions. FDA relented and inappropriately eliminated a number of key restrictions. *See* Petition at 49-57 for a discussion of the development of and the Sponsor's opposition to safety restrictions.

[76] *See* Petition at 57-65.

[77] *See* Opposition Comments at 10. The Petition did not assert that the approved regimen must exactly follow the regimen employed during the trials. Nevertheless, if trials include important safeguards that are omitted from the approved regimen, then the relevance of the data generated by those trials is undermined. For this reason, a trial should be designed to reflect the anticipated conditions under which a drug will be used. *See* Petition at 75-76. For example, had the Sponsor designed the trial to reflect anticipated conditions of use, misoprostol probably would have been administered vaginally during the trials, which appears to be the standard method of administration now that the Mifeprex Regimen is approved. Had the trial protocol called for vaginal administration, it would have drawn attention to the unlawful inclusion of misoprostol in the Regimen because misoprostol is approved only for *oral* use. As FDA has explained, "[i]n order to change or add a new dosing regimen to the labeling, the sponsor must submit data to FDA from clinical trials that show the new regimen is safe and effective." *See* FDA, "Mifepristone Questions and Answers 4/17/2002" ("FDA Q & As") at Question 9 ("Why are physicians using misoprostol 'off-label,' in other words, using misoprostol virginally at different doses?") (available at: <http://www.fda.gov/cder/drug/infopage/mifepristone/mifepristone-qa_4_17_02.htm>).

[78] *See* Section I.D.3, herein.

[79] *See* Spitz Article at 1241 ("Results").

[80] The Sponsor's Opposition Comments addressed the use of ultrasound only for the purpose of dating pregnancies. As explained in the Petition, ectopic pregnancies cannot be treated by the Mifeprex Regimen and the symptoms of ectopic pregnancy are likely to be mistaken as the normal effects of undergoing a Mifeprex abortion. For a more complete discussion of the necessity of using ultrasound to identify ectopic pregnancies, *see* Petition at 60-61.

have required prescribing physicians to be trained in mifepristone-misoprostol administration and surgical abortions and to have *admitting* privileges at a nearby emergency facility.[81]

FDA determined that Subpart H restrictions were necessary because, without them, mifepristone-misoprostol abortions were not safe. Thus, the Petitioners' concerns with the Regimen's safety rest on the belief that the weakness of the Regimen's restrictions is inconsistent with FDA's decision to approve the drug under Subpart H.

2. Post-approval Evidence Confirms that the Approved Distribution Restrictions Were Insufficient to Adequately Protect Patients.

The Sponsor's analysis inaccurately characterized the post-approval experience with the Mifeprex Regimen.[82] A number of life-threatening adverse events experienced by Mifeprex patients caused FDA to work with the Sponsor to issue a letter to health care providers.[83] The

[81] In fact, FDA proposed to include such restrictions in the Mifeprex Regimen. The set of restrictions proposed by FDA on June 1, 2000, would have required physicians prescribing Mifeprex to be "trained and authorized by law" to perform surgical abortions, to be trained in administering the Mifeprex Regimen and handling resulting adverse events, and to have "continuing access (*e.g.*, admitting privileges) to a medical facility equipped for instrumental pregnancy termination, resuscitation procedures, and blood transfusion at the facility or [one hour's] drive from the treatment facility." *See* FDA, "FDA Proposed Restricted Distribution System for NDA 20-687 on 6/1/00" (June 1, 2000) [FDA FOIA Release: MIF 000522]. *See also* American College of Obstetricians and Gynecologists, "Analysis of the Possible FDA Mifepristone Restrictions" (July 27, 2000): at 1 (setting forth FDA's second proposed restriction, which is redacted in the publicly available copy of FDA's proposal; also providing the redacted portion of the fifth restriction)[FDA FOIA Release: MIF 001366-69].

[82] Opposition Comments at 10, 13-14. The Sponsor pointed to a recent article authored by the medical director of Danco, Dr. Richard Hausknecht, as evidence that Mifeprex is safe. *See* Opposition Comments at 10 (citing Hausknecht Article); regarding Dr. Hausknecht, *see also* Petition at 71, n.309. Unfortunately, the article, which reports on the drug's use in the United States since approval, relies on data that are incomplete and of questionable quality. First, reliable data as to the number of patients who have undergone the Mifeprex Regimen is not available. Dr. Hausknecht used a figure of 80,000, which was derived from "sales figures [for Mifeprex] and known patterns of mifepristone utilization." Hausknecht Article at 464. This number may be too high as it may not take into account drugs that were ordered but not used. Second, the number of adverse events reported is likely to be significantly underestimated. Abortion clinics, which (according to Dr. Hausknecht's estimates) carried out approximately 90% of Mifeprex abortions, may have a disincentive to report adverse events from a procedure that they promote and may be less likely than physicians in private practice to report adverse events. In addition, it is likely that many patients were lost to follow up. In the U.S. Clinical Trial, 106 of the 2,121 patients (or nearly 5%) did not return for their third required visit. A higher "lost to follow up" number is to be expected outside of the clinical setting. Finally, the article's descriptions of the adverse events that were reported generally appear to be incomplete and tend to downplay any possible connection with the Mifeprex Regimen. For example, the article explained that a twenty-one year old woman had suffered a coronary artery occlusion five days after she received misoprostol. *See* Hausknecht Article at 464, col. 2. The article provided few details about her Mifeprex abortion and pointed to her "strong family history of heart disease" without also mentioning that there are no data on the safety of the Mifeprex Regimen in women with cardiac problems and these women were excluded from the Clinical Trials. In sum, an objective assessment of the safety and efficacy of mifepristone-misoprostol abortions would require a concurrently-controlled, randomized comparison of a mifepristone-misoprostol regimen reflecting actual conditions of use with surgical abortion. The Sponsor did not conduct or provide data from such trials in support of its application and Dr. Hausknecht's article – a very general overview without the first-hand, patient-level detail necessary to scientifically assess the safety of the Mifeprex Regimen – does not fill this void.

[83] Danco Laboratories, Open Letter to Health Care Providers (Apr. 19, 2002) ("Dear Doctor Letter") (available at: <http://www.fda.gov/medwatch/SAFETY/2002/mifeprex_deardoc.pdf>).

Petition discussed these life-threatening adverse events which included ruptured ectopic pregnancies, serious systemic bacterial infections, and a coronary event.[84] The Sponsor, in its Opposition Comments, insisted that "FDA has not found any causal connection" between the Mifeprex Regimen and these adverse events.[85] However, the clear implication of the issuance of the Dear Doctor Letter and FDA's accompanying "Questions and Answers" is that such a causal link does exist.

The serious adverse events reported to date are consistent with concerns about the drug regimen that were expressed prior to the approval.[86] The recent death of Holly Patterson, an eighteen year old from Livermore, California, unfortunately epitomizes the concerns of the Petitioners.[87] According to Ms. Patterson's father, at the time of his daughter's death, she was terminating her pregnancy with a Mifeprex Regimen prescribed by the Planned Parenthood in Hayward, California. Apparently, Ms. Patterson started the abortion procedure on Wednesday, September 10, 2003, by taking mifepristone tablets. On Saturday, September 13, 2003, she apparently took the misoprostol that the clinic had given her. By Sunday she was having such severe cramping and bleeding that her boyfriend took her to the emergency room. Ms. Patterson received pain killers and was sent home, but she continued to bleed severely and experienced acute pain that prevented her from walking. Early Wednesday, September 17, 2003, Ms. Patterson's boyfriend took her back to the emergency room, where she died that afternoon.

According to Mr. Patterson, the doctor told him that his daughter "hadn't aborted all the fetus, and she had fragments left in her, and she had a massive systemic infection and went into septic shock."[88] The results of the coroner's investigation are not expected to be released for several months, but Ms. Patterson's apparent death of a serious systemic bacterial infection is not the first such death since FDA approved Mifeprex. As noted above, the Dear Doctor Letter

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[84] *See* Petition at 65-71. As the number of mifepristone-misoprostol abortions rises, the number of serious adverse events associated with these abortions is likely to increase as well. Because the normal progression of the Mifeprex Regimen is characterized by prolonged bleeding, the patient bears the responsibility for determining how much bleeding is excessive and whether she needs to seek medical assistance. Health care providers who are not experienced providers of abortion, generally, or mifepristone-misoprostol abortions, specifically, may be poorly equipped to assist the patient in determining whether medical intervention is necessary, let alone to provide the needed medical intervention.

[85] *See* Opposition Comments at 13.

[86] *See* Americans United for Life *et al.*, Citizen Petition (Feb. 28 1995) (requesting FDA's consideration of a number of potential hazards of mifepristone-misoprostol abortions) [FDA FOIA Release: MIF 006144-6248].

[87] Julian Guthrie, "Pregnant Teen's Death Under Investigation; East Bay Woman Had Taken RU-486, According to Father," *San Francisco Chronicle* (Sept. 19, 2003): at A21 (available at: http://www.sfgate.com). *See also* Gina Kolata, "Death at 18 Spurs Debate Over a Pill for Abortion," *New York Times* (Sept. 24, 2003): at A24 ("There were 264 adverse reactions, including infections, bleeding, allergic reactions and tubal pregnancies.").

[88] *Id*. *See also* Julian Guthrie, Sabin Russell, and Katherine Seligman, "After Daughter's Death, Father Wants Close Look at RU-486; Abortion Pill's Safety Defended by Doctors as Better than Surgery," *San Francisco Chronicle* (Sept. 20, 2003): at A17 (available at: http://www.sfgate.com/cgi-bin/article.cgi?file=/chronicle/archive/2003/09/20/BA310011.DTL) ("Patterson said the attending physician at Pleasanton's Valley Care Medical Center told him his daughter had died of septic shock – a severe bacterial infection. 'The doctor told me she had fragments of the fetus still left in her uterus and that caused the infection.'").

reported "[t]wo cases of serious systemic bacterial infection (one fatal)."[89] The presence of retained products of conception can lead to the development of intrauterine or systemic infection, and it is possible that mifepristone could potentiate this possibility via negative effects on immune system function or normal protective mechanisms.[90]

In addition to questions about Mifeprex causation in this case, questions also have been raised about the role that Ms. Patterson or her local hospital emergency room may have played in contributing to her death.[91] These questions cannot be answered without recognizing that patients and emergency room physicians may be unable to distinguish the normal progress of the Regimen from a life-threatening situation. Consequently, it is not at all clear that emergency rooms will be able to rescue dangerously ill Mifeprex patients from the peril in which they have been placed by the Regimen. Consider the plausible scenario described in the footnote below.[92] The severity of the reported adverse events requires FDA action to remove Mifeprex from the market.

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[89] Dear Doctor Letter at 1. The fatality apparently precipitated a halt in the Population Council's clinical trials of mifepristone in Canada.

[90] Given the nature of the Mifeprex Regimen, the embryo or other products of conception will not be expelled from the uterus in a number of cases. It is well known that the presence of retained necrotic products of conception can lead to intrauterine and systemic infection. Furthermore, it is possible that mifepristone itself may alter the local immune response at the level of the endometrium or the cervix. There are numerous alterations of the immune system during pregnancy, and progesterone can affect immune system function. Therefore, it is plausible that a progesterone receptor antagonist like mifepristone could negatively affect the normal immune system within the uterus, or compromise antibacterial mechanisms of the cervix, making a woman more susceptible to infection. *See*, *e.g.*, World Health Organization (WHO), "Pregnancy Termination with Mifepristone and Gemeprost: A Multicenter Comparison between Repeated Doses and a Single Dose of Mifepristone," 56 Fertility & Sterility 32-40 (1991) (29.4% of patients with incomplete abortion compared with 2.6% of those with complete abortion received antibiotics during a six week follow-up period for suspected genitourinary infection; both groups combined accounted for 3.9% of the total study population).

[91] *See, e.g.*, Gina Kolata, "Death at 18 Spurs Debate Over a Pill for Abortion," *New York Times* (Sept. 24, 2003): at A24 ("But it is unclear what happened to Holly Patterson. Did she have enough medical supervision while taking the pills? When did she seek medical attention? Did she wait until it was too late? Did she tell the doctors in the emergency room that she had taken mifepristone? Why, in fact, did she die?").

[92] A patient comes to the emergency room complaining of significant pelvic pain and cramps. She reports that she has taken Mifeprex and misoprostol for a medical abortion. At this time, she has no significant change in vital signs (*i.e.*, no fever or very low grade fever – which can be related to misoprostol – and no significant tachycardia, etc.). The emergency room physician, knowing that this drug combination normally causes cramping at this stage in the process, assumes she has a personal low pain tolerance threshold, and, therefore, gives her pain medications to try to alleviate her discomfort until the abortion completes. However, the patient may be in the early stage of an intrauterine infection even though she is not yet manifesting other signs of that condition aside from pain and bleeding which are both part of the Mifeprex abortion process. At this stage, the emergency room physician has no good way to detect that an infection has begun. Furthermore, even if the emergency room physician found evidence of retained tissue in the uterus, the physician would not be surprised or alarmed by that discovery given the nature of mifepristone-misoprostol abortions. Unless the patient had significant hemorrhaging or evidence of infection, no intervention would be necessary or even warranted since one would presume that the abortion was going according to plan at that juncture (recall that bleeding can last up to several weeks duration). So to continue this hypothetical scenario, the patient goes home, and the infection subsequently becomes systemic. The patient goes into septic shock and is not able to be saved by the time she re-presents to the emergency room. It would not be surprising if Ms. Patterson's death followed such a course given statements made to the press by her father. In this credible scenario the Mifeprex Regimen, after having placed her in great danger, effectively camouflaged the seriousness of her condition from the emergency room physician.

Furthermore, FDA cannot rely on the "spotty" reporting of adverse events for the Mifeprex Regimen. The usual flow of post-approval adverse event information will not be forthcoming for this drug. It is questionable whether individual lawful distributors of Mifeprex, who tend to be outside the mainstream pharmaceutical wholesale distribution industry, will routinely report adverse events to FDA.[93] Also, because the drug is intended to be administered in physicians' offices, a pharmacist is unlikely to dispense the product or hear of drug-drug and drug-food interactions, or other adverse events. Moreover, the types of facilities that provide medical and surgical abortions are often staffed with social-work counselors and health care workers who are not medical doctors and have limited medical training. As such, they may be unfamiliar with the adverse event reporting procedure for medical professionals (*i.e.*, MedWatch).

Even for properly-licensed physicians, FDA's MedWatch reporting is voluntary.[94] Since privacy issues are often the primary concern of women who seek abortions, a physician may not file a MedWatch report in order to protect patient confidentiality. Accordingly, the Petitioners are concerned about the possibility that medical complications are not being reported. Finally, it is possible that other women who have suffered adverse events during a mifepristone-misoprostol abortion have sought assistance from crisis pregnancy centers, counselors, and charitable organizations,[95] which may not be familiar with the MedWatch reporting system. Given the foregoing, the Petitioners believe that FDA's continuing review of the safety profile of Mifeprex relies improperly on an incomplete database of post-approval adverse events.

3. The Sponsor Has Failed to Require Adherence to the Restrictions.

The Sponsor insisted that it "will continue, as [it] always intended, to honor [its] commitments to carry out the program of restrictions imposed in the approval letter."[96] Yet, the Sponsor has broken its promise. The Sponsor apparently has not taken steps to ensure that Mifeprex is used in accordance with the approved Regimen and has continued to distribute the drug to providers that depart from the Mifeprex Regimen. For instance, the Sponsor has asserted, in its Opposition Comments, the erroneous position that the guidelines in the Prescriber's Agreement "do not state any specific dose or regimen for prescribing Mifeprex … ."[97] The Sponsor's statement reflects only one example of its continuing refusal to accept even FDA's minimal restrictions issued pursuant to Subpart H.

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[93] Obviously, distributors of mifepristone who are outside the lawful channels of distribution are even less likely to report adverse events.

[94] *See* <http://www.fda.gov/medwatch/report/hcp.htm>.

[95] *Consider Estate of Brenda Vise vs. Volunteer Women's Medical Clinic, L.L.C., et al.* (Circuit Court of Hamilton County, Tennessee, filed August 14, 2002); *Danlin Tang, Albert Ng vs. Dr. Soon Chon Sohn, Family Planning Associates Medical Group, and Does 1 – 50* (Superior Court of the State of California for the County of Los Angeles, Central District, notice to file dated December 13, 2002).

[96] Opposition Comments at 6.

[97] Opposition Comments at 14.

In the face of this recalcitrance, FDA should exercise its enforcement authority, investigate the Sponsor's failed commitments under its NDA approval, and take appropriate action, as it has in other cases where risk management programs were deemed insufficient to protect patients.[98] We note that, contemporaneous with the issuance of the Sponsor's Dear Doctor Letter, FDA underscored the possibility that if providers "do not follow the agreement, the distributor may discontinue distribution of the drug to them."[99] Shortly after approving Mifeprex, the Agency wrote to a member of Congress and stated, "If restrictions are not adhered to, FDA may withdraw approval."[100]

Even assuming that the Sponsor's responsibilities extend only as far as ensuring that the prescriber is adhering to the Prescriber's Agreement, the Sponsor is failing to meet its due diligence obligation.[101] The Prescriber's Agreement requires, *inter alia*, that the prescriber "must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself."[102] The Patient Agreement, which both the patient and the prescriber sign, states that the patient "believe[s] I am no more than 49 days (7 weeks) pregnant."[103] Yet numerous prescriber websites advertise the Mifeprex Regimen as being available for patients whose pregnancies have progressed beyond 49 days.[104] The Patient

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[98] For example, GlaxoSmithKline voluntarily withdrew its NDA for Lotronex (alosetron hydrochloride) rather than accept restrictive risk management guidelines involving informing patients of risks, limiting access to closely monitored patients, and continued clinical research. *See* "FDA and Glaxo Still Working on Lotronex's Return," *Dickinson's FDA Webview* (Jan. 24, 2002). Bayer voluntarily withdrew Baycol (cerivastatin) after reports of deaths due to severe rhabdomyolysis, when risk management efforts of labeling changes and "Dear Healthcare Provider" letters had little impact on physicians who continued to prescribe the drug at unrecommended higher doses. *See* "31 Baycol-related Deaths Cause the Drug's Withdrawal," *Dickinson's FDA Webview* (Aug. 8, 2001). Warner Lambert withdrew Rezulin (troglitzone) at FDA's urging after label restrictions and recommended monitoring of liver function failed to control inappropriate prescribing. *See* "Rezulin Withdrawal a Defeat for FDA 'Labeling Can Do It' Theory", *Dickinson's FDA Webview* (Mar. 21,2000).

[99] *See* FDA Q & As at Question 12.

[100] *See* Letter, Melinda K. Plaisier, Associate Commissioner for Legislation (FDA) to Senator Tim Hutchinson (Oct. 20, 2000): at 2 [FDA FOIA Release: MIF 002648-52].

[101] *See* Opposition Comments at 14-15.

[102] Mifeprex™ (Mifepristone) Tablets, 200 mg Prescriber's Agreement ("Prescriber's Agreement").

[103] *See* Item 4 of the Patient Agreement Mifeprex (mifepristone) Tablets ("Patient Agreement"). In addition, the Mifepristone Medication Guide ("Medication Guide") states that you should not take Mifeprex if "[i]t has been more than 49 days (7 weeks) since your last menstrual period began."

[104] *See, e.g.,* All Women's Health Centers website (available at: <http://www.floridaabortion.com/services_abortion/nonsurgical.shtml>) (visited Sept. 5, 2003) ("Non-surgical abortions, sometimes called 'medical abortions,' are performed in the first 9 weeks of pregnancy. Non-surgical abortion can be administered in pill form (otherwise known as Mifeprex or RU-486)."); Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <http://www.fpamg.com/medical.html>) (visited Sept. 5, 2003) (noting that Mifeprex Regimens are "done until the 56th day of pregnancy"); Planned Parenthood Golden Gate (available at: http://www.ppgg.org/medical/abortion_medical.asp) (visited Oct. 1, 2003) ("Medical abortion is a way to end pregnancy without surgery. It is done with medications up to 63 days after the last period begins."; Seattle Medical and Wellness Clinic (available at: <http://www.smawc.com/html/services.html>) (visited Sept. 5, 2003) (including following description: "**Medical Abortion (9 weeks LMP or less):** We offer non-surgical abortion with Mifeprex (a.k.a. the Abortion Pill, RU486) and Cytotec (misoprostol).").

Agreement also states that the patient "will take misoprostol in [her] provider's office two days after [she] take[s] Mifeprex (Day 3)."[105] Yet many prescribers' websites indicate that patients take misoprostol at home rather than at the provider's office.[106] The discrepancies between the marketplace regimen being prescribed and the approved Regimen that the patient agrees to follow indicate that many prescribers are allowing patients to make false statements. Under its NDA duties, the Sponsor has an obligation to conduct due diligence about the prescribers to whom it sells Mifeprex, and it must stop those sales if the approved Regimen is breached. Furthermore, the Sponsor has a duty to keep records of these stopped distributions.[107]

Given that these discrepancies are freely published on prescriber websites, the Sponsor should be aware of them.[108] Therefore, the Sponsor knowingly continues to supply prescribers who are not following the guidelines in the Prescriber's Agreement. These prescribers are knowingly eviscerating the requirements to provide patients with the Medication Guide, to

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[105] *See* Patient Agreement, Item 6. In addition, the Medication Guide states that the patient "**must return** to [her] provider on Day 3 and about Day 14" (emphasis in original).

[106] *See, e.g.,* Family Planning Associates Medical Group, Phoenix and Tempe Arizona, (available at: <http://www.fpamg.com/medical.html>) (visited Sept. 5, 2003) (explaining that "[t]he patient inserts 4 tablets of Misoprostol into the vagina at home 2-3 days" after ingestion of Mifeprex); Little Rock Family Planning website < http://www.lrfps.com/RU486.html > (visited Sept. 5, 2003) (describing the regimen employed by the clinic, which is "one of these regimes [sic] which has been shown to be safe and is more convenient for women using the method": "**Step Two, at home (or motel)** … Six to 8 hours after the mifepristone pills have been swallowed 8 Cytotec tablets are placed in the vagina. **Step Three, this will depend on how far you live from our clinic:** A) *If you live within one hour of Little Rock* … If you have not passed the pregnancy by 24 hours after you put the Cytotec tablets in your vagina, you will put a [sic] 4 tablets in your vagina and still plan to keep your appointment for the following week. B) *If you live outside the Little Rock Area* … You will return at 9AM the following morning to have an ultrasound to see if the abortion is complete. If the abortion is complete you will be discharged home and asked to take a urine pregnancy test in 3 weeks. … If you have not had a complete abortion you will be given 4 Cytotec [sic] to place in your vagina … ."); Planned Parenthood Golden Gate (available at: <http://www.ppgg.org/medical/abortion_medical.asp>) (visited Oct. 1, 2003) ("Medical abortion using Mifepristone involves three steps. First, the doctor will give you mifepristone pills, which block progesterone, a hormone needed to maintain pregnancy. Two days later, as directed by your clinician, you will insert another medication called misoprostol as a vaginal suppository. Misoprostol causes the uterus to contract and empty which completes the abortion. Finally, women must return to the clinic a few days after taking the misoprostol for a follow-up."); Women's Health Practice website (available at: <http://www.womenshealthpractice.com/abortion.htm>) (visited Sept. 5, 2003) (explaining, as part of the medical abortion regimen that the clinic describes as "most similar to the FDA-approved regimen," that "[t]he misoprostol will be provided to you with medication instructions that carefully explain the timing and route of administration.").

[107] 21 C.F.R. § 314.81(b)(2) (requiring NDA sponsors to submit an annual report describing distribution data). State or federal agencies may need these data if patient deaths continue and the public outcry (and/or the plaintiffs' lawyers bar) demand investigations.

[108] The Petition set forth a number of examples of Mifeprex provider websites that advertised noncompliance with the approved Mifeprex Regimen. *See* Petition at nn. 309, 313, 315, 317. Since the submission of the Petition, these websites have not been altered. (These websites were visited most recently on September 5-7, 2003. One of the website addresses changed and its content was updated, but it still states that "at home, the patient will insert four tablets [of misoprostol] into her vagina." *See* <http://www.presidentialcenter.com/services_nonsurgical.html> (visited Sept. 7, 2003)). It appears, therefore, that the Sponsor, alerted by the Petition to these instances of noncompliance, has not taken any steps to require compliance with the approved regimen. Dr. Hausknecht, the medical director of Danco, operates one of the websites that continues to advertise a regimen that differs from the approved regimen. *See* <http://www.safeabortion.com/procedure.htm> (visited Sept. 7, 2003).

obtain their signatures on the Patient Agreement, and to give them the opportunity to read and discuss these documents. The Patient Agreement is intended by FDA to describe the Mifeprex Regimen as approved and to obtain the patient's informed consent to adhere to the approved Regimen, all for the protection of the patient. Instead, some prescribers, with the Sponsor's tacit approval, are permitting patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements. In the face of such evidence, the Sponsor cannot be described as meeting its obligations with respect to the restrictions on Mifeprex.

Conclusion

Women are being told that Mifeprex is safe even if it is used in a manner different from the Regimen approved by FDA. This is a cavalier approach to distributing a drug that was deemed by FDA to be too dangerous to approve without restrictions. The Sponsor's refusal to restrict distribution to physicians who adhere to the approved Regimen represents the continuation of a pattern of overlooking the risks to women's health posed by Mifeprex. FDA should halt the marketing of this unsafe drug.

E. The Sponsor's Revised Phase IV Commitments Are Inadequate.[109]

The Sponsor's Opposition Comments downplayed the significance of the changes prior to approval in the Sponsor's Phase IV commitments.[110] As noted in the Petition, those changes by the Sponsor relegated certain study objectives to secondary status, eliminated the commitment to study the long-term effects of multiple uses of the Regimen, and weakened the commitment to monitor the adequacy of the distribution and credentialing system.[111]

The Sponsor's insistence that the range of topics to be studied was not narrowed contradicts statements made by the Sponsor when it proposed modifications of its Phase IV commitments in September 2000.[112] The Sponsor, citing feasibility concerns, decided not to study the long-term effects of multiple uses of the Mifeprex Regimen.[113] Moreover, combining multiple study objectives into one study reduced the value of the data that would be generated

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[109] The Petitioners requested, pursuant to FOIA, information about the Phase IV Mifeprex study protocols and any data arising from the Phase IV studies submitted by the Sponsor. *See* FOIA Request, filed by Wendy Wright, Director of Communications, CWA (Sept. 14, 2001). To date, the Petitioners have not received any responsive information.

[110] *See* Opposition Comments at 15-16. *See also* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 15, 2000): at 1 [FDA FOIA Release: MIF 001326] (committing to conducting two Phase IV studies).

[111] *See* Petition at 84-88.

[112] *See* Letter, Sandra Arnold to FDA/CDER, Office of Drug Evaluation III, Division of Reproductive and Urologic Products (Sept. 6, 2000): at 5 [FDA FOIA Release: MIF 001333-49] ("As new data have become available, some of the studies originally proposed have become unnecessary. Other studies, on reflection, seem unlikely to gather useful data at any reasonable cost or, in some cases, at any cost.").

[113] *See* Memorandum, FDA/CDER to "NDA 20-687 MIFEPREX (mifepristone) Population Council" (Sept. 28, 2000): at 7 ("Mifeprex Approval Memo"). As discussed in the Petition, the Sponsor, in asking for the elimination of this commitment, was motivated in part by concerns that conducting such a study would be burdensome for the Sponsor – a reason that is not generally persuasive with FDA. *See* Petition at 87.

with respect to the secondary study objectives.[114] Given the importance of understanding the effect of a patient's age, the effect of a patient's smoking status, the rate of patient follow-up on Day 14, and the adequacy of the distribution and credentialing system, the Sponsor should not have been permitted to accord these study objectives secondary status.

The Sponsor defended the changes in the study requirements by citing FDA's approval memorandum for the proposition that the changes in the Phase IV Study commitments reflected changes to the distribution system and labeling.[115] The Sponsor's argument is misleading. By allowing the distribution of mifepristone to physicians who could not provide surgical intervention, an immediate need arose to study the effect of that major change; [116] accordingly, FDA added a primary study requirement.[117] However, the September 2000 changes in distribution and labeling should have not have reduced or eliminated other primary Phase IV study commitments that were not related to the distribution or labeling changes.

Conclusion

FDA inappropriately granted the Sponsor's request to reduce its original Phase IV commitments. As a consequence, key questions about the safety of the Mifeprex Regimen will remain unanswered.

F. The Approval of Mifeprex Without Supporting Pediatric Data Was Both Unlawful And Imprudent.

In its Opposition Comments, the Sponsor admitted that it did not conduct clinical studies in the pediatric population, but relied instead on an FDA "waiver" of pediatric testing. Yet, the FD&C Act and FDA's approval regulations for NDAs require safety and effectiveness testing to support a new drug's indications for use. In a case where the Sponsor does not intend to restrict the drug's use in the pediatric population, FDA has only limited authority to cede the requirement for pediatric testing. In the case of Mifeprex, FDA's decision to approve the NDA without pediatric data was arbitrary, capricious and unlawful agency action.

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[114] Specifically, the effects of age and smoking status and the frequency with which patients return for follow-up on Day 14 were to be studied as part of "[a] cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compare to physicians who refer their patients for surgical intervention." *See* Petition at 86 (citing Mifeprex Approval Letter at 3). Furthermore, this study would be the only Phase IV study of another objective originally slated to be the focus of a separate Phase IV study, namely the adequacy of the distribution and credentialing system. *See generally* Mifeprex Approval Memo at 7.

[115] *See* Opposition Comments at 15-16 (citing Mifeprex Approval Memo at 7).

[116] This change was deemed significant enough to require the addition of a "black box" warning to physicians who could not perform surgical abortions. The black box warning directed them to make arrangements for the provision of emergency surgical intervention.

[117] FDA correctly noted the need for a new study objective when it approved this change: "To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study." Mifeprex Approval Memo at 5.

1. FDA's NDA Approval Regulations Required Pediatric Data.

The law is clear that the clinical studies used to support an NDA must establish the drug's safety and efficacy for the proposed conditions of use. Under the FD&C Act, a person may file an NDA requesting FDA approval of a new drug provided that the NDA contains, in relevant part, "full reports of investigations which have been made to show whether or not such drug is safe *for use* and such drug is effective *in use* . . . ."[118] Likewise, FDA's NDA approval regulations require "a description and analysis of each controlled clinical study *pertinent to a proposed use* of the drug."[119] This testing requirement exists separately from the so-called "Pediatric Rule,"[120] which also delineates pediatric testing requirements.

The Petitioners acknowledge that, as of October 17, 2002 and for the time being, FDA is enjoined from enforcing the Pediatric Rule.[121] However, the Petitioners challenge the Sponsor's contention that the issue of FDA's proper administration of the Rule is moot, in light of the *AAPS* court's decision to grant an appeal of the case, which is now pending.[122] Rather, the Mifeprex NDA was subject to the Pediatric Rule, which was finalized and became effective while FDA was reviewing the NDA,[123] and FDA should have administered it properly[124] or waived it properly.[125]

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[118] 21 USC § 355(b)(1)(A) (emphasis added).

[119] 21 C.F.R. § 314.50(d)(5)(ii) (emphasis added).

[120] *See* Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, *Final Rule*, 63 Fed. Reg. 66632 (Dec. 2, 1998) (testing requirements set forth in 21 C.F.R. § 314.55). *See also* Petition at 76-83 (discussing Pediatric Rule).

[121] *Association of American Physicians and Surgeons v. FDA*, 226 F. Supp. 2d 204 (D.D.C. 2002) ("*AAPS*").

[122] The Elizabeth Glaser Pediatric AIDS Foundation and the American Academy of Pediatrics filed a motion to appeal on December 16, 2002. *See* Docket for Case No. 00-CV-2898 (entry no. 73).

[123] The Pediatric Rule was promulgated on December 2, 1998 and became effective on April 1, 1999. FDA reviewed the Mifeprex NDA from March 18, 1996 until September 28, 2000, when it was approved.

[124] Under the Pediatric Rule, FDA's treatment of the Mifeprex NDA was improper, in part, because the agency did not require the Sponsor to submit supporting pediatric data. The regulation stated that, "where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults *usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies*." 21 C.F.R. § 314.55(a) (emphasis added). This requirement also was articulated earlier by FDA in the Prescription Labeling regulation. *See* 59 Fed. Reg. 64240 (Dec.13, 1994); 21 C.F.R. § 201.57(f)(9)(iv). As noted elsewhere in this Response, the Petitioners also question whether the Sponsor's adult data were derived "from adequate and well-controlled studies."

[125] It should be noted that even if FDA concluded that pediatric effectiveness of the Mifeprex Regimen could be extrapolated from adult studies, this would not be an appropriate ground for an actual *waiver* of the Pediatric Rule. The Pediatric Rule provides three grounds for waiver from the obligation imposed by the rule on drug sponsors to demonstrate that their drug is safe and effective for pediatric patients. 21 C.F.R. § 314.55(c). In some instances, drug sponsors are able to provide sufficient adult data, usually supplemented by pediatric-specific data, from which pediatric safety and efficacy can be extrapolated. 21 C.F.R. § 314.55(a). FDA stated that it was waiving the pediatric rule with respect to Mifeprex, yet did not cite to any of the bases for waiver provided in paragraph (c) of the Pediatric Rule. Mifeprex Approval Letter at 3. For a comprehensive discussion on the ineligibility of Mifeprex for a waiver from the Pediatric Rule, *see* the Petition at 78-82.

Irrespective of the current status of the *AAPS* case, at the time of the approval of the Mifeprex NDA the Agency was obligated to meet the requirements of its NDA approval regulations. FDA erred in its failure to require the Sponsor to submit pertinent pediatric data and to assess those data in its review of the NDA for Mifeprex. In so doing, the Agency abrogated its role of protecting and promoting the public health and safety. This constitutes the type of "arbitrary and capricious" action that is generally prohibited under the Administrative Procedures Act ("APA").[126]

2. The Drug's Expected Conditions of Use Included the Pediatric Population.

Mifeprex is intended for use by menstruating females. The drug's labeling states "Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy." Nothing in the "Indication and Usage" section of the labeling limits the drug's use to adults.[127] Likewise, Danco's marketing claims are not targeted to a particular age group, such as women "over age 18." The patient population therefore logically includes all females who can become pregnant – that is, as of the age their first menstrual period begins (*i.e.*, "menarche") until they no longer have a menstrual period (*i.e.*, "menopause"). According to FDA, the average age of menarche in the United States is 12 years, although menstruation may commence in healthy females as early as age 10.[128]

Under the pediatric labeling regulations, the Agency defines "pediatric population(s)" and "pediatric patient(s)" as the age group "from birth to 16 years, including age groups often called … adolescents."[129] Therefore, the population of menstruating females (*i.e.*, 10 or 12 and older) and the pediatric population (*i.e.*, up to 16) overlap by up to 6 years. Based on Danco's labeling and marketing to the menstruating female population without any age restriction, pediatric use of this product was clearly contemplated. Because Mifeprex will be used by some number of adolescent girls who become pregnant, FDA should have required the Sponsor to produce safety and effectiveness data for the pediatric population.

3. FDA Should Have Required the Submission of Pediatric Study Data Prior to Approving Mifeprex.

Under its broad authority granted by the FD&C Act, not only may FDA require the submission of pediatric data as part of a product's NDA, but the Agency *must* require such data when the product's conditions of use warrant pediatric testing. However, the Agency approved

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[126] 5 USC § 706(2)(A).

[127] Instead, the drug's labeling contains one non-constructive statement in the "Precautions" section of the labeling: "Safety and effectiveness in pediatric patients have not been established." Given the logical reading of the drug's indication and the medical information on the age range of menstruation, this one sentence in a package insert of 15 pages is valueless.

[128] *See On the Teen Scene: A Balanced Look at the Menstrual Cycle*, FDA Consumer Magazine (Dec. 1993) (available at: <http://www.fda.gov/fdac/reprints/ots_mens.html>). In the U.S., the average age of the start of menopause is 51. *See Taking Charge of Menopause*, FDA Consumer Magazine (Nov.-Dec. 1999) (available at: <http://www.fda.gov/fdac/features/1999/699_meno.html>).

[129] 21 C.F.R. § 201.57(f)(9).

Mifeprex without requiring the Sponsor to submit pediatric data or, apparently, any review of the pertinent scientific literature. When approving Mifeprex based solely on the data submitted in the NDA (*i.e.*, studies conducted in an adult population), FDA made the unsupported assumption that younger females (*i.e.*, children and adolescents) would have the same physiological response to this product as adult females.[130] Specifically, the Sponsor cited FDA's conclusion that "the drug regimen is expected to be as safe and effective for pregnant women under the age of 18 years as it is for those of the age of 18 ... ," despite the Agency's concession that most of the available data are from women 18 years and older.[131] Further, the Sponsor noted that FDA has not found any "biological reason to expect that menstruating females under age 18 to have a different physiological outcome with the regimen."[132]

As stated in the Petition, however, FDA's conclusion misreads the science. To assume, without specific data, that the effects of a potent antiprogesterone and a powerful prostaglandin analogue in pregnant adults will be the same for adolescents who are still developing in their physiologic, anatomic, and reproductive functions, is medically unsound. The relevant scientific evidence suggests that an assumption *cannot* be made that the effectiveness or safety of Mifeprex for adolescent girls is the same as for fully-developed adult women. Therefore, FDA's decision to the contrary lacks a sound and justified scientific basis.

Moreover, the Agency decision disregards decades of its own medical judgment. In the past, FDA has said that drugs should be studied directly in the pediatric population because "the action and adverse actions of pharmaceutical agents will vary as absorption, distribution, metabolism, and excretion, and receptor sensitivity are altered by the changes associated with growth and development."[133] For Mifeprex, these factors were not directly studied in children.

Studying the subpopulation of adolescents is even more important, according to FDA. For example, "[t]he development of puberty and the known effects of sex hormones on drug metabolism warrant consideration in drug evaluation in the adolescent."[134] Other "special problems" arise from the intense concern with self-image, leading to increased use (both admitted and denied) of prescription and over-the-counter drugs, dietary supplements, and cosmetics for such purposes as altering physical growth and sexual development, regulating mood and behavior, and influencing physical appearance.[135] FDA did not require a review of these adolescent-specific considerations with respect to the Mifeprex Regimen.

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[130] *See* Mifeprex Approval Memo at 7.

[131] Opposition Comments at 15 (citing FDA, "Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments," at 28).

[132] Opposition Comments at 15 (citing Mifeprex Approval Memo at 7).

[133] FDA Guidance for Industry, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children" (Sept. 1977), at 6 (hereafter, "Pediatric Study Guidance").

[134] Pediatric Study Guidance at 15.

[135] *See* Pediatric Study Guidance at 16-17.

In addition, FDA has said previously that a drug's safety profile may be different for adolescents because "medication may not be taken as prescribed. The adolescent frequently omits doses of medication, takes it at erratic intervals, and may take more than prescribed. Safety considerations should be addressed not only to the therapeutic dosage, but also to the consequences of suboptimal dosage and overdosage."[136] Given the two-drug-regimen and three-doctor-visit administration of the Mifeprex Regimen, a study of patient compliance issues in adolescents was warranted.

Conclusion

In summary, it is logical to conclude that Mifeprex is intended for use by a female population that, under the pertinent definitions adopted by FDA, includes pediatric females. Therefore, FDA should have required the submission of pediatric data with the NDA. Without any consideration of pediatric data, FDA's approval of Mifeprex is an abrogation of its fundamental duty to conduct the drug approval process in a way that protects and promotes the public health and safety. In so doing, the Agency acted in a way that was arbitrary, capricious, and contrary to law and its own regulations.

II. FDA Is Both Statutorily Empowered and Obligated to Grant an Administrative Stay of the Mifeprex NDA Approval.

The Sponsor's Opposition Comments contain three technical objections to the request for an administrative stay of the Mifeprex NDA approval.[137] First, the Sponsor alleges that an administrative stay is not the appropriate method by which FDA could withdraw the Mifeprex NDA. Second, the Sponsor alleges that the request is "untimely" because it was not filed within 30 days of the effective date for the Mifeprex NDA approval. Third, the Sponsor makes a general allegation that the Petitioners do not meet the criteria for an administrative stay under FDA's regulations. As described below, these allegations stem from an incorrect and overly restrictive reading of the Petitioners' request. Instead of answering the serious substantive issues raised in the Petition, the Sponsor has focused on the way in which the Petitioners framed their request for FDA action. Even more disconcerting, the Sponsor asks FDA to place administrative procedures above the Agency's statutory obligation to protect the public health.

A. FDA Has the Statutory Authority to Suspend the Mifeprex NDA Pending the Outcome of a Decision to Withdraw the Application.

The Petitioners' request for administrative stay of the Mifeprex NDA approval is equivalent to a request for FDA to use its authority under section 505(e) of the FD&C Act to "suspend the approval of [the] application immediately."[138] The FD&C Act states that an NDA may be "suspended" whenever FDA makes a finding of "imminent hazard to the public

[136] Pediatric Study Guidance at 15.

[137] *See* Opposition Comments at 16-24.

[138] 21 U.S.C. § 355(e); *see also* 21 C.F.R. § 314.150(a)(1).

health."[139] In the Petition and in this Response, the Petitioners have provided extensive evidence that Mifeprex poses, under FDA's definition, "a significant threat of danger to health, [and] creates a public health situation . . . that should be corrected immediately to prevent injury."[140] Furthermore, an emergency or "crisis" situation is not required, but merely a "substantial likelihood that serious harm will be experienced during . . . any realistic projection of the administrative process."[141] In interpreting this definition, a court upheld an FDA decision similar to that which the Petitioners are requesting. Specifically, even though "respectable scientific authority [could] be found on both sides of this question", and "much of the raw data used by the [Agency] in arriving at its conclusion had been available for some length of time," these facts did not preclude FDA's use of the data in finding an imminent hazard when "the magnitude of [the drug's] risk was determined only after an extensive *re-evaluation of the data*."[142]

FDA's authority is resolute and can be exercised immediately, notwithstanding any related issues regarding how the matter was initially raised (*e.g.*, a Citizen Petition), who exercised the authority (*e.g.*, HHS Secretary or FDA), and what actions follow it (*e.g.*, notice and hearing).[143] FDA should disregard the Sponsor's attempt to redirect the Agency away from the substance of the Petition toward a focus on the administrative requirements of delegating authority, providing notice, and holding a hearing. Clearly, FDA's suspension of the Mifeprex approval could occur during the pendency of any notice period or hearing which the Sponsor so forcefully claims to be entitled to under the FD&C Act, the APA and Constitutional due process provisions. Given the situation, the Petitioners are dismayed at the Sponsor's insistence that its "property right to produce and market Mifeprex,"[144] outweighs any concern for the safety of the patients that the Sponsor is seeking to "treat."

Furthermore, even if FDA finds that an imminent hazard does not exist in this case, FDA may still summarily withdraw approval of an NDA in certain circumstances. During its four-page discussion on notice and hearings, the Sponsor fails to mention that the FD&C Act's "due notice and hearing" provision does not guarantee an NDA Sponsor a hearing, and also leaves FDA with discretion regarding the type of notice that is provided.[145] Rather, FDA may proceed by summary judgment to withdraw an NDA in certain circumstances – for example, when there

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[139] *See id.*

[140] 21 C.F.R. § 2.5.

[141] *Forsham v. Califano*, 442 F. Supp. 203, 208 (D.D.C. 1977) (citing *Environmental Defense Fund v. EPA*, 510 F.2d 1292, 1297 (D.C. Cir 1975)).

[142] *Forsham v. Califano*, 442 F. Supp. 203, 209 (D.D.C. 1977) (emphasis added).

[143] *Forsham v. Califano*, 442 F. Supp. 203 (D.D.C. 1977) (on petition raised by a consumer health organization, the HHS Secretary referred the matter to FDA, which withdrew approval of a drug with notice but no formal hearing, based on a finding of imminent hazard to the public health).

[144] Opposition Comments at 18. When the Sponsor included misoprostol as part of the Mifeprex Regimen, it did not demonstrate any concern for the property rights of Searle over misoprostol.

[145] *See John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518, 520 (D.C. Cir. 1988) ("It is well settled that this [notice and hearing] provision does not guarantee the applicant a hearing in all circumstances." and "The requirements of 'due notice' must depend upon the context of the agency's action."); *Brandenfels v. Heckler*, 716 F.2d 553, 555 (9th Cir. 1983) ("The FDA is authorized to satisfy its own notice requirements by providing holders of new drug applications with either general or specific notice of opportunity for hearing.").

is no genuine and substantial issue of fact, when the applicant does not meet the minimum regulatory requirements, or when it appears conclusively from the applicant's pleadings that the applicant cannot succeed.[146]

The Petitioners' request for administrative stay contains ample evidence to support a finding in this case of imminent hazard or the requisite basis for summary withdrawal. Millions of women are being misled to believe that the Mifeprex Regimen is safe, while in actuality neither the data submitted in the original NDA nor the subsequent marketing history can support a safety profile that justifies the continued marketing of the drug product. There is simply no legal basis to assert that FDA lacks the authority to grant the requested remedy of a "stay" (*i.e.*, suspension) of the NDA pending resolution of a formal NDA withdrawal process.

B. <u>The Request for Administrative Stay Was Timely Filed.</u>

An NDA is not a "static" document. Rather, it is a "living" document that is constantly being supplemented, updated, and reviewed by FDA.[147] Therefore, FDA is constantly making a "decision" to allow an NDA approval to stand in light of new information that is submitted to the Agency. Likewise, a drug's safety and efficacy profile and risk/benefit profile also require constant re-analysis by FDA. For example, over time "newer" medical evidence comes to light and adverse reactions are recorded in the patient population. FDA's approval decisions on NDAs are not "stuck in time." Instead, "FDA has an obligation to judge a drug's effectiveness by contemporary scientific standards. If those standards change to the extent that it is questionable whether a drug can be regarded as having been shown to be effective, FDA may under the act appropriately review the drug's status."[148]

FDA's regulations state that a stay of action must be filed within 30 days of the "date of the *decision involved*" unless FDA permits a later filing for "good cause."[149] In this instance, the "decision involved" is FDA's decision to uphold the Mifeprex NDA and to *not* suspend the approval despite the influx of new information. This decision is ongoing. The Petitioners are requesting that FDA "stay" that decision and suspend the NDA approval immediately in response to the imminent hazard presented by the Mifeprex Regimen.

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[146] *See Weinberger v. Hynson, Westcott & Dunning, Inc*., 412 U.S. 609, 620-1 (1973) (withdrawing approval of NDA without a hearing based on lack of evidence negating "new drug" status); *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 518 (D.C. Cir. 1988) (withdrawing approval of NDA without a hearing based on failure to comply with current good manufacturing practices); *Cooper Laboratories, Inc. v. FDA*, 501 F.2d 772, 780 (D.C. Cir 1974) (withdrawing approval of NDA without a hearing based on insufficient evidence of efficacy).

[147] *See, e.g.*, 21 C.F.R. §§ 314.70, 314.72, 314.80, 314.81. At the very least, the Sponsor of the Mifeprex NDA is required to submit an annual report to FDA each year. 21 C.F.R. § 314.81(b)(2). The Sponsor's misdirection on this matter is revealed by the fact that, under their interpretation of the "30 days" filing requirement, the Petitioners could "cure" the alleged timeliness defect by merely submitting the Petition within 30 days of any Mifeprex NDA Supplement or Annual Report.

[148] 50 Fed. Reg. 7452, 7488 (Feb. 22, 1985) (FDA's rejection of an industry suggestion, on withdrawal of approval of an application under 21 C.F.R. § 314.150, that FDA's conclusion concerning a drug product "should remain unchanged even if FDA later adopted new standards").

[149] 21 C.F.R. § 10.35(b) (emphasis added).

Even if the request were considered to be "untimely" from a technical perspective, FDA should nevertheless still grant the requested stay pursuant to either (1) the Agency's "imminent hazard" authority under section 505(e), which contains no time limitation; or (2) the "good cause" exception of 21 C.F.R. § 10.35(b). In fact, the "imminent hazard" authority and the "good cause" exception were included in the statute and regulations for the very reasons outlined in the Petitioners' request. Namely, these provisions allow FDA to move quickly to protect the public from unsafe drug products without being slowed by overly technical readings of the regulations. Additionally, if FDA deemed the request to be untimely filed, the Agency still may stay its action on the NDA on its own initiative *at any time*. In other words, if FDA determines that the Petition's underlying request has merit, FDA may suspend approval and/or initiate withdrawal proceedings independent of the Petitioners' request.

C. The Petitioners Comply with the Spirit and Letter of the Requirements for an Administrative Stay.

As supported by the original submission, the Petitioners' request for an administrative stay meets all of the requirements of 21 C.F.R. § 10.35(e). In particular, the Petitioners have demonstrated irreparable harm to American women and an overwhelming public policy reason for removing the Mifeprex drug product from the market. The Petitioners' request is clearly not frivolous, and is being pursued in good faith. In response, the Sponsor has raised minor technical challenges that obfuscate and mischaracterize the issues raised by the Petitioners. Despite the evidence contained in the Petition concerning the harm that Mifeprex is inflicting on American women, and the Petitioners' direct interest as their physicians in speaking for these women, the Sponsor has alleged that there is insufficient injury to justify an administrative stay. Specifically, the Sponsor argued that the Petitioners are not the *actual* injured party.[150] Yet, that response is a mischaracterization of the Petitioners' request. The Petition clearly stated that the Petitioners were seeking Agency action to prevent further injury to women seeking to terminate their pregnancies.[151] The evidence submitted in the Petition and in this submission unequivocally demonstrates that women are being harmed by this drug product. In light of this fact, FDA is obliged to investigate whether the Mifeprex NDA approval should be suspended and ultimately withdrawn.

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[150] *See* Opposition Comments at 21-22.

[151] Just as the Petitioners have with their Petition, patient advocacy groups routinely utilize the Citizen Petition process to request that FDA overturn its safety and effectiveness decision for drug products and, ultimately, withdraw them from the market. *See* Letter to FDA from AIDS Healthcare Foundation, August 19, 2003 (Docket number not assigned), requesting market removal of Trizivir (abacavir sulfate/lamivudine/zidovudine) due to poor efficacy results in post-approval clinical studies letter; Docket No. 02P-1778, Citizen Petition from Public Citizen and Arizona Arthritis Center, March 28, 2002, requesting market removal of Arava (leflunomide) due to patient deaths and severe liver failure; Docket No. 02P-0120, Citizen Petition from Public Citizen, March 19, 2002, requesting market removal of Meridia (sibutramine) due to patient deaths related to cardiovascular adverse effects. Many of these Citizen Petitions are ultimately successful. *See e.g.*, Rezulin (troglitazone), banned March 2000 after a July 1998 Petition (Docket No. 98-0622); and Lotronex (alosetron HCl), banned November 2000 after an August 2000 Petition (Docket No. 00P-1499).

III. Conclusion.

For the foregoing reasons, the Petitioners respectfully request that FDA immediately suspend the approval of the NDA for Mifeprex and enter an administrative stay to halt any further distribution and marketing of Mifeprex until final Agency action is taken to withdraw the NDA approval for Mifeprex. For copies of any of the reference materials cited herein, please contact the undersigned.

Respectfully submitted,

Gary L. Yingling

Rebecca L. Dandeker

Exhibit 27

2016 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists, Christian Medical & Dental Associations, and Concerned Women for America denying 2002 Citizen Petition, Docket No. FDA-2002-P-0364 (Mar. 29, 2016) (2016 Petition Denial)

DEPARTMENT OF HEALTH & HUMAN SERVICES

MAR 29 2016

Food and Drug Administration
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Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).[1] Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

[1] The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments[2] that the then-applicant of the Mifeprex NDA (i.e., the Population Council)[3] agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));

- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and

- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

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[2] For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

[3] Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

A. Approval of Mifeprex Was Consistent With Subpart H

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion

(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.[4] The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.[5] Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.[6] Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.[7] Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.[8] According to the

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[4] See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

[5] Id.

[6] According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, Obstet Gynecol, 119 (2, Part 1):215-219.

[7] See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf .

[8] Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[9]

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.[10] Although FDA provided several examples in the preamble to the final rule to illustrate how the term "meaningful therapeutic benefit" might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.[11] In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.[12] Complications of general or local anesthesia, or of intravenous sedation ("twilight" anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.[13]

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at http://books.nap.edu/openbook.php?record_id=13181 (stating that "[u]nintended pregnancy is highly prevalent in the United States").

[9] See Closing the Gaps, supra note 8, at 103.

[10] For a discussion of how FDA interprets the phrase "meaningful therapeutic benefit to patients over existing treatments" in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] 57 FR 58942, 58947 (Dec. 11, 1992).

[12] FDA, 1999, Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer's Review), at 11 (Table 1) and 16, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf. Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, NEJM, 338:1241-1243.

[13] CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC's calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e. Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, Contraception, 89(3):193-6). We note that one study reported a comparatively high occurance of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by

You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, Contraception, 59:153-159 (Jensen study)). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.[14] In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA ≤ 49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).[15] Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.[16]

Buccal Misoprostol: A Large Australian Observational Study, Med J Aust, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

[14] We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

[15] In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages ≤ 49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

[16] FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf

Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[17] The2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.[18] You state that the

[17] 73 FR 16313 (Mar. 27, 2008).

[18] Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).[19]

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of ≤ 49 days and were included in the efficacy evaluation.[20] Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).[21] Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination (n = 39), still pregnant (n = 8), subject request for surgical intervention (n = 5), and medical indication (bleeding, n = 13).[22] The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.[23]

In the U.S. trial, 859 subjects with an EGA of ≤ 49 days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.[24] The safety profile of the patient group in the French trials with an EGA of ≤ 49 days did not differ significantly from the safety profile of the same patient group in the U.S.

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

[19] Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy*, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.

[20] Mifeprex Approval Memorandum, supra note 16, at 1; Medical Officer's Review, supra note 12, at 10.

[21] Medical Officer's Review, supra note 12, at 11 (Table 1) and 16.

[22] Id. at 11 (Table 1).

[23] Mifeprex Approval Memorandum, supra note 16, at 1.

[24] Medical Officer's Review, supra note 12, at 12-13.

trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.[25] There were no deaths in the French trials.[26]

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (id.). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.[27] Thus, in the proper setting,

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[25] Id. at 18.

[26] FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[27] 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you

historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).[28]

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).[29] Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.[30] Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).[31] The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.[32] The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."[33]

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cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

[28] You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, supra note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

[29] MacDonald, PC, NF Gant, et al., 1996, Williams Obstetrics (20th ed.), Appleton and Lange, at 151.

[30] Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, Clinical Gynecologic Endocrinology and Infertility (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, Clinical Gynecologic Endocrinology and Infertility (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, Comprehensive Gynecology (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm.

[31] E10 Guidance, available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, at 6.

[32] Id.

[33] Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.[34] In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.[35]

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

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[34] Id. at 27.

[35] We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780.

You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were "similar enough to the results of the European studies" (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.[36]

You maintain that the Mifeprex approval is not in accordance with Agency guidance[37] on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.[38] As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA's acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring "that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials" (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of "meaningful therapeutic benefit" requires concurrent testing of a proposed drug with an existing treatment.[39] We have approved other drugs

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[36] FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[37] FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[38] Petition at 31-32 (citing Effectiveness Guidance at 5-17).

[39] You state that "[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable" (Petition at 32, note 145). You add that "[t]here are study designs that would have also allowed for blinding" (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed "tainted data" to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA's reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator's observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation's effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

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were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.

approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,[40] and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.[41] The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol[42] did not submit a supplemental NDA for this new use (Petition at 41-45). You further

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[40] The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), which is the term used in the current regulations. The E6 Guidance states that GCP:

> is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

[41] Mifeprex Approval Memorandum, supra note 16, at 1.

[42] Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.[43] The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy[44]

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[43] In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C 156(f), that is, a human drug product means 'the active ingredient of a new drug * * * as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

[44] We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

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originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not "dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."

D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards

You contend that FDA "approved mifepristone for use in a deregulated regimen that lacks key safeguards" (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.[45] Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.[46] Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

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[45] We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

[46] See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, Contraception, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.

You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.[47] As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.[48] In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.[49] If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

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[47] We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

[48] Mifeprex Approval Memorandum, supra note 16, at 5.

[49] See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, Contraception, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.[50] In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."[51]

2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.[52] The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

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[50] Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

[51] Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. .

[52] Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).

necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:[53]

> Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex….

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.[54] Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.[55] These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.[56] The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.[57]

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

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[53] Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf.

[54] Mifeprex Approval Memorandum, supra note 16, at 5.

[55] Id.

[56] Id.

[57] Id.

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.[58]

3. "Dear Health Care Provider" Letter and FDA "Mifepristone Questions and Answers"; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, "Dear Health Care Provider" letter issued by Danco and by statements in the "Mifepristone Questions and Answers" (Mifepristone Q&A) document (placed on FDA's Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."[59] The intent of the two "Dear Health Care Provider" letters and the "Dear Emergency Room Director" letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

[58] Mifeprex REMS, available at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=35

[59] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm.

address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way "inappropriately attempted to link" the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,[60] the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency's scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson's apparent death from a serious systemic bacterial infection after taking Mifeprex is "not the first such death since FDA approved Mifeprex," referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 "Dear Health Care Provider Letter" (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005[61] and one in March 2006[62]) and posted multiple MedWatch safety alerts (in November 2004[63] and July 2005, the latter with updates in November 2005 and March 2006[64]). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

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[60] The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

[61] Available at, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm.

[62] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm.

[63] Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm.

[64] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm.

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009[65] to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

> Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.
>
> • Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
>
> • Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.
>
> Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.
>
> Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.
>
> Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

[65] The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

The WARNINGS section of the Mifeprex labeling states, in part, the following:

[With respect to infection and sepsis:]

> As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.
>
> A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

[With respect to uterine bleeding:]

> Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.
>
> Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.
>
> Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.
>
> Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfu¬sions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to $\leq 0.1\%$ of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

> MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.
>
> Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,[66] including 57 reports of severe infections[67] and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.[68] As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).[69] Seven of the eight fatal sepsis case reported vaginal misoprostol use;

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[66] This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

[67] Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

[68] This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

[69] We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death. [70]

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

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published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

[70] FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen "without any reaction from FDA, the Population Council, or Danco" (Petition at 71). You also claim that "common departures from the approved regimen" have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider's office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (id. at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (id. at 20-21). You state that because some prescribers, with the applicant's tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (id. at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber's Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber's Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.[71] The Prescriber's Agreement also contained responsibilities that prescribers must carry out.[72] The Prescriber's Agreement stated that prescribers must have read and understood the prescribing materials.[73]

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[71] Prescriber's Agreement, supra note 53, at 1.

[72] Id. at 1-2.

[73] Id. at 1.

The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.[74] The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (id.).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

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[74] Id.

G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.

- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.

- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.[75] We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.[76]

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[75] FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians& Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

[76] FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.[77]

H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).[78]

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.[79] It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

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[77] In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, supra note 16, at 7).

[78] We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

[79] You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

(1) Monitor the adequacy of the distribution and credentialing system.

(2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.

(3) Assess the long-term effects of multiple use of the regimen.

(4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

(5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.

(6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.

In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.[80]

III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.[81] Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

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[80] See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, Int J Womens Health, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, Fertil Steril, 84:1719; Blasey, CM, TS Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, J Clin Psychopharmacol, 31:436; Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome, J Clin Endocrinol Metab, 97:2039.

[81] You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.[82]

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[82] As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.

Exhibit 28

Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 1631316314 (Mar. 27, 2008)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2008–N–0174]

Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing this notice to notify holders of certain prescription new drug and biological license applications that they will be deemed to have in effect an approved risk evaluation and mitigation strategy (REMS) under the Food and Drug Administration Amendments Act of 2007 (FDAAA). Holders of applications deemed to have in effect an approved REMS are required to submit a proposed REMS to FDA.

DATES: Submit proposed REMSs to FDA by September 21, 2008.

ADDRESSES: Written communications regarding the applicability of this notice to a specific product should be identified with Docket Number FDA–2008–N–0174 and submitted to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic communications to *http://www.regulations.gov*. Information about FDA implementation of FDAAA is available on the Internet at *http://www.fda.gov/oc/initiatives/advance/fdaaa.html*.

FOR FURTHER INFORMATION CONTACT: Mary Dempsey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 4326, Silver Spring, MD 20993–0002, 301–796–0147.

SUPPLEMENTARY INFORMATION:

I. Introduction

On September 27, 2007, the President signed into law FDAAA (Public Law 110–85). Title IX, subtitle A, section 901 of FDAAA created new section 505–1 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355–1). Section 505–1(a) of the act authorizes FDA to require persons submitting certain applications[1] to submit and implement a REMS if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug and informs the holder of the application for the drug of the determination. Section 909 of FDAAA provides that Title IX, subtitle A takes effect 180 days after its enactment, which is March 25, 2008.

FDAAA also contains REMS requirements for drug and biological products approved before the effective date of Title IX, subtitle A. Section 909(b)(1) of FDAAA specifies that a ''drug that was approved before the effective date of this Act is * * * deemed to have in effect an approved risk evaluation and mitigation strategy under section 505–1 of the Federal Food, Drug, and Cosmetic Act * * * if there are in effect on the effective date of this Act elements to assure safe use—(A) required under section 314.520 or section 601.42 of title 21, Code of Federal Regulations; or (B) otherwise agreed to by the applicant and the Secretary [of Health and Human Services] for such drug.''

Section 909(b)(3) of FDAAA states: ''Not later than 180 days after the effective date of this Act, the holder of an approved application for which a risk evaluation and mitigation strategy is deemed to be in effect * * * shall submit to the Secretary a proposed risk evaluation and mitigation strategy. Such proposed strategy is subject to section 505–1 of the Act as if included in such application at the time of submission of the application to the Secretary.''[2]

Section 909(b)(2) of FDAAA states that a REMS for a drug deemed to have a REMS consists of the timetable required under section 505–1(d) of the act and any additional elements under section 505–1(e) and (f) of the act in effect for the drug on the effective date of FDAAA.

The purpose of this notice is to identify those drugs that FDA has determined will be deemed to have in effect an approved REMS and to notify holders of applications for such drugs that they are required to submit a proposed REMS by September 21, 2008. FDA is developing guidance on the preferred content and format of a proposed REMS required to be submitted under section 909(b) of FDAAA and will issue it as soon as possible.

II. List of Drug and Biological Products Deemed to Have a REMS

Drug and biological products deemed to have in effect an approved REMS are those that on March 25, 2008 (the effective date of Title IX, subtitle A of FDAAA), had in effect ''elements to assure safe use.'' ''Elements to assure safe use'' include the following: (1) Health care providers who prescribe the drug have particular training or experience, or are specially certified; (2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified; (3) the drug is dispensed to patients only in certain health care settings, such as hospitals; (4) the drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results; (5) each patient using the drug is subject to certain monitoring; or (6) each patient using the drug is enrolled in a registry (see section 505–1(f)(3) of the act).

Some applications approved before the effective date of FDAAA Title IX, subtitle A contain these elements to assure safe use.[3] Some of these applications were approved under § 314.520 (21 CFR 314.520) or § 601.42 (21 CFR 601.42). Others were not approved under part 314, subpart H or part 601, subpart E, but still contain elements to assure safe use that were agreed to by the applicant and the Secretary for such drug. Since 2005, these elements typically appeared in approved risk minimization action plans (RiskMAPs) (see the guidance for industry entitled ''Development and Use of Risk Minimization Action Plans'' (70 FR 15866, March 29, 2005)).

FDA has reviewed its records to identify applications that were approved before the effective date of Title IX of FDAAA with elements to assure safe use and has identified the drug and biological products listed in table 1 of this document as those that will be deemed to have in effect an approved REMS.

[1] Section 505(p)(1) of the act (21 U.S.C. 355(p)(1)) states that section 505–1 of the act applies to applications for prescription drugs approved under section 505(b) or (j) of the act and applications approved under section 351 of the Public Health Service Act (42 U.S.C. 262).

[2] Title IX, subtitle A of FDAAA, which includes section 909, takes effect March 25, 2008; 180 days after that date is September 21, 2008.

[3] These plans sometimes contain other elements to minimize risk such as a Medication Guide (21 CFR part 208) or a communication/educational plan for health care providers or patients. A drug will not be deemed to have a REMS if it has only a Medication Guide, patient package insert, and/or communication plan (see section 505–1(e)(2) and (e)(3) of the act).

TABLE 1.—PRODUCTS DEEMED TO HAVE IN EFFECT AN APPROVED REMS

Generic or Proper Name	Brand Name	Application Number[1]	Date of Approval[2]
Abarelix	Plenaxis[3]	NDA 21–320	11/25/2003
Alosetron	Lotronex	NDA 21–107	02/09/2000
Ambrisentan	Letairis	NDA 22–081	06/15/2007
Bosentan	Tracleer	NDA 21–290	11/20/2001
Clozapine	Clozaril	NDA 19–758 ANDA 74–949 ANDA 75–417 ANDA 75–713 ANDA 75–162 ANDA 76–809	09/26/1989 11/26/97 5/27/99 11/15/02 4/26/05 12/16/05
	Fazaclo ODT	NDA 21–590	02/09/2004
Dofetilide	Tikosyn	NDA 20–931	10/01/1999
Eculizumab	Soliris	BLA 125166	03/16/2007
Fentanyl PCA	Ionsys[3]	NDA 21–338	05/22/2006
Fentanyl citrate	Actiq	NDA 20–747	11/04/1998
Isotretinoin	Accutane Amnesteem Claravis	NDA 18–662 ANDA 75–945 ANDA 76–135 ANDA 76–356	05/07/1982 11/2002 04/2003 04/2003
	Sotret	ANDA 76–041 ANDA 76–503	12/2002 06/2003
Lenalidomide	Revlimid	NDA 21–880	12/27/2005
Mifepristone	Mifeprex	NDA 20–687	09/28/2000
Natalizumab	Tysabri	BLA 125104	11/23/2004
Small pox (Vaccinia) Vaccine, Live	ACAM2000	BLA 125158	08/31/2007
Sodium oxybate	Xyrem	NDA 21–196	07/17/2002
Thalidomide	Thalomid	NDA 20–785 NDA 21–430	07/16/1998

[1] New drug application (NDA), abbreviated new drug application (ANDA), biologics license application (BLA).
[2] The original date of approval of the drug. FDA may have required elements to assure safe use at a later date.
[3] Product is not currently marketed in the United States.

FDA is further asking members of the public to please notify the agency if they are aware of applications that have not been identified in this document and that they believe should be deemed to have in effect an approved REMS. Please provide the information to Mary Dempsey, Risk Management Coordinator (see the **FOR FURTHER INFORMATION CONTACT** section of this document).

Any application holder that believes its product identified in this notice should not be on the list of drug or biological products that will be deemed to have in effect an approved REMS should submit a letter identified with Docket Number FDA–2008–N–0174 to the Division of Dockets Management (see **ADDRESSES**) stating why the application holder believes its product was improperly identified in this notice. FDA will notify the application holder within 30 days of receipt of the letter of its determination.

Dated: March 19, 2008.

Jeffrey Shuren,

Associate Commissioner for Policy and Planning.

[FR Doc. E8–6201 Filed 3–26–08; 8:45 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Notice of Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

This notice announces a forthcoming of a public advisory committee of the Food and Drug Administration (FDA). The meeting will be open to the public.

Name of Committees: Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

Exhibit 29

2011 FDA Supplemental Approval Letter to Danco Laboratories, LLC (June 6, 2011)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX® (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

ENCLOSURES:
REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

Exhibit 30

2011 REMS for NDA 20-687 Mifeprex (mifepristone) Tablets, 200mg (June 8, 2011)

Please see REMS updated 3/29/2016

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

A. To provide information to patients about the benefits and risks of MIFEPREX before they make a decision whether to take the drug.

B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX and are able to assure patient access to appropriate medical facilities to manage any complications.

II. REMS ELEMENTS

A. Medication Guide

1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.

2. Please see the appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe MIFEPREX will be specially certified.

   Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

   a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.

   b. The following materials are part of the REMS and are appended:

      i. Prescriber's Agreement.

      ii. Patient Agreement.

2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

   Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

   Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

   a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.

   b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:

   a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

   b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

2. Danco will assess the performance of the certified distributors with regard to the following:

   a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

   b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

Please see REMS updated 3/29/2016

3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

Please see REMS updated 3/29/2016

MEDICATION GUIDE

Mifeprex® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

Please see REMS updated 3/29/2016

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

Please see REMS updated 3/29/2016

M I F E P R E X®
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.

- Ability to diagnose ectopic pregnancies.

- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.

- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com
*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

Please see REMS updated 3/29/2016

ACCOUNT SETUP FORM

MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

To set up your account:

1. Read the Prescriber's Agreement on the back of this Account Setup Form.
2. Complete and sign this form.
3. Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned in and are usually shipped within 24 hours.
6. Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (❑ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

❑ Medication Guides ❑ Patient Agreements

❑ State Abortion Guidelines ❑ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.

MIFEPREX™ (Mifepristone) Tablets, 200 mg

Reference ID: 2957855

Please see REMS updated 3/29/2016

Mifeprex® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:
    - contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
    - contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
    - contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
    - take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
    - return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
    - return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Please see REMS updated 3/29/2016

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

Please see REMS updated 3/29/2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

Exhibit 31

2016 FDA Letter to Danco Laboratories re: NDA 020687, Supp 20 (Mar. 29, 2016)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6) .

Sincerely,

{See appended electronic signature page}

(b) (6)
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

Exhibit 32

FDA, Center for Drug Evaluation and Research, Summary Review of Application Number: 020687Orig1s020 (March 29, 2016)

(2016 Summary Review)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020687Orig1s020

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 29, 2016
Subject	Summary Review
NDA #/Supplement #	20687/S-020
Applicant name	Danco Laboratories, LLC
Date of submission	May 28, 2015
Date of submission receipt	May 29, 2015
PDUFA goal date	March 29, 2016
Proprietary name/established name	Mifeprex/mifepristone
Dosage form/strength	Oral tablet/200 mg
Dosage regimen	Mifeprex 200 mg tablet orally followed in 24-48 hours by 800 mcg buccal misoprostol
Proposed indication	Mifeprex is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation
Action	Approval

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

1. Introduction

Danco Laboratories, LLC, referred to hereafter as the Applicant, submitted an efficacy supplement (S-020) to NDA 20687 for Mifeprex (mifepristone). The Applicant sought the following changes to its approved application:

1. (b) (4) Decrease mifepristone dose from 600 to 200 mg, followed by misoprostol at a dose increased from 400 mcg to 800 mcg, administered buccally instead of orally; see below:
   - Day One: Mifeprex Administration (oral)
     One 200 mg tablet of Mifeprex is taken in a single oral dose
   - After a 24-48 hour interval: Misoprostol Administration (buccal)(minimum 24-hour interval between Mifeprex and misoprostol)
     Four 200 mcg tablets (total dose: 800 mcg) of misoprostol are taken by the buccal route

2. Removal of the instruction that administration of misoprostol must be done in-clinic, to allow for administration at home or other location convenient for the woman
3. Administration of misoprostol at 24-48 hours instead of 48 hours after Mifeprex
4. Follow-up, although still needed, not restricted to in clinic at 14 days after Mifeprex
5. Increase in the maximum gestational age from 49 days to 70 days
6. Change of the labeled time for expected expulsion of pregnancy from 4-24 hours to 2-24 hours post misoprostol administration
7. Addition that a repeat 800 mcg buccal dose of misoprostol may be used if needed
8. Change of "physician" to "healthcare provider" in the label and Risk Evaluation and Mitigation Strategies (REMS) document
9. Change in the indication statement to add reference to use of misoprostol: "Mifeprex is indicated, in a regimen with misoprostol, for the medical termination of pregnancy through 70 days gestation."
10. Removal of references to "under Federal law" from the Prescriber's Agreement under the REMS

11. Labeling changes addressing the pediatric requirements under the Pediatric Research Equity Act

This efficacy supplement submission includes information from published studies, review articles and additional information from the authors of some of the publications. These published studies evaluated reproductive age women in the U.S. and outside the U.S. who had early medical termination with mifepristone, in a regimen with misoprostol, including women up through 70 days of gestation.

This memorandum serves as the Division's decisional memorandum for the efficacy supplement.

2. Background

The active ingredient of Mifeprex, mifepristone, is a progestin antagonist. Mifeprex, in a regimen with misoprostol, is approved for the medical termination of pregnancy up through 49 days' gestation. The approved dosing regimen is currently labeled as follows:

- Day 1: The patient takes three 200 mg tablets of Mifeprex in a single oral dose in the clinic, medical office, or hospital.
- Day 3: The patient returns to the clinic, medical office, or hospital and takes two 200 mcg tablets of misoprostol orally.
- Day 14: The patient returns for a follow-up visit to confirm that a complete termination has occurred.

At the time of the September, 2000 approval, FDA restricted distribution of Mifeprex under 21 CFR 314.520, requiring that Mifeprex be dispensed only by or under the supervision of a physician who meets certain qualifications. With the passage of FDAAA in 2007, Mifeprex was deemed to have in effect an approved REMS. The Applicant submitted a formal REMS, which was approved on June 8, 2011 and consisted of the following: a Medication Guide, elements to assure safe use (ETASU A [special certification of healthcare providers who prescribe Mifeprex], ETASU C [dispensing only in certain healthcare settings], and ETASU D [safe use condition of a signed Patient Agreement]), an implementation system and a timetable for assessments. The goals of the REMS were 1) To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and 2) To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. The REMS for Mifeprex incorporated the restrictions under which the drug was originally approved.

Since 2011, the Applicant has submitted two REMS assessment reports. The Agency review of these reports determined that the REMS goals were being met and that no modifications were required to the REMS at that time.

FDA held a pre-NDA meeting with the Applicant on January 29, 2015, to discuss proposed labeling and REMS changes to be submitted in this efficacy supplement. These changes were submitted with the efficacy supplement.

The Applicant submitted published literature and supportive information to support changes to the dose, dosing regimen, gestational age, revisions to labeling, modifications to the REMS document, and to address PREA requirements. The Agency accepts the use of peer reviewed literature as primary data for an application under the framework of a 505(b)(2) application.

3. CMC

No new CMC information was submitted with this efficacy supplement. The CMC team determined no additional review or inspections were required. The CMC team completed a review of the labeling and found the CMC sections of labeling (sections 3, 11 and 16) acceptable (See review dated March 29, 2016). The CMC review team recommends approval of the efficacy supplement; refer also to the CMC review of the separate supplement proposing a single tablet blister pack for Mifeprex, dated January 11, 2016. There are no outstanding CMC issues or postmarketing commitments or requirements.

***Comment**: On March 10, 2016, a separate CMC supplement was approved that allowed the packaging of individual 200 mg tablets of mifepristone; previously packaging consisted of three 200 mg tablets per blister pack (a total of 600 mg Mifeprex as administered under the originally approved dosing regimen).*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was submitted in this supplement. The Pharmacology/Toxicology team revised labeling to conform to the Pregnancy and Lactation Labeling Rule. There are no outstanding nonclinical issues. The Pharmacology/Toxicology review team recommends approval of the efficacy supplement; refer to the Pharmacology/Toxicology review dated March 4, 2016.

5. Clinical Pharmacology

The Applicant did not conduct any new clinical pharmacology studies pertaining to the proposed (b) (4) regimen, but provided information on pharmacokinetics (PK) of misoprostol following various routes of administration. The PK of the 200 mg Mifeprex tablet has not been characterized in women, but data are available in men and were submitted in the original NDA. The Clinical Pharmacology review team determined that the PK data were appropriate for inclusion in labeling. Review of the labeling pertinent to the Clinical Pharmacology sections is complete and labeling relevant to pharmacokinetics and pharmacodynamics is acceptable. There are no outstanding Clinical Pharmacology issues or postmarketing commitments or requirements. The clinical pharmacology review team recommends approval of the efficacy supplement; refer to the Clinical Pharmacology review dated March 29, 2016.

6. Clinical Microbiology

Not applicable.

7. Efficacy/Statistics

The Applicant submitted published literature as the primary evidence to support the efficacy (and safety) of the proposed dosing regimen (refer to the Clinical Review dated March 29, 2016, Section 9.5 for a list of submitted references). Most published articles submitted by the Applicant and reviewed by the clinical review team reported the primary efficacy endpoint as complete termination of pregnancy without further medical or surgical intervention; the Division considers this to be a clinically relevant endpoint.

The majority of the publications included a statement that the study was conducted under institutional review board (IRB) or Ethical Review Committee approval and the women gave informed consent. The clinical review team concluded that the published literature was adequate as the primary information source to support the changes proposed in the efficacy supplement. During the course of the review, the team also requested and received more detailed information from select publications from their authors via communication with the Applicant.

Although there were slight demographic differences among the published studies from the database, these differences were not expected to alter the efficacy or safety of Mifeprex. Therefore, for the majority of the proposed efficacy changes, the clinical team assessed efficacy information from a subset of publications that evaluated a given proposed change. An independent statistical review was not needed for this review of published literature.

The clinical review team identified several major proposed clinical changes in the efficacy supplement. As these major changes are interrelated, in some cases data from a given study were relied on to provide evidence to support multiple changes. These major changes as considered by the clinical team included:

1. A proposed dosing regimen consisting of mifepristone 200 mg orally followed by the buccal administration of 800 mcg misoprostol including:
    a. Use of a revised interval between mifepristone and misoprostol from 48 hours to 24-48 hours
    b. Allowing home administration of misoprostol
    c. Use of an additional dose of misoprostol
2. Support for extending the gestation age through 70 days
3. Flexibility in follow-up visit: follow-up is needed in the range of 7-14 days after Mifeprex administration; the specific nature and exact timing of the follow-up to be agreed upon by the healthcare provider and patient.
4. Change in who can provide Mifeprex from physician to healthcare provider who prescribes

The following section summarizes the clinical review team's evaluations that supported the above proposed changes:

1. *Support for the proposed dose and dosing regimen of 200 mg of Mifeprex orally and 800 mcg of misoprostol buccally 24-48 hours after Mifeprex administration:* The clinical review team reviewed the submission and identified studies and review articles that evaluated over 35,000 women who were treated with efficacy in the 91-98% range. For additional details on the efficacy from these studies, please refer to Section 6 of the Clinical Review.

2. *Support for extending the gestational age to 70 days:*
The Applicant submitted a number of published articles and systematic reviews that supported the proposed dose and dosing regimen. Four studies and one systematic review evaluated the exact proposed dosing regimen through 70 days gestation. These include three prospective observational studies (Winikoff et al 2012[1], Boersma et al[2] , Sanhueza Smith et al[3]) and one randomized controlled trial (RCT) (Olavarrieta et al[4]) that had a primary objective of evaluating medical abortion provision by non-physicians. The systematic review by Chen and Creinin[5] covered 20 studies including over 30,000 women; all but one of the studies used the proposed regimen in gestations through 70 days (the remaining study used 400 mcg of buccal misoprostol). For those publications that provided overall success rates, these were in the range of 97-98%. Other relevant publications include the systematic review by Raymond[6] of 87 studies, which covered a variety of misoprostol doses and routes of administration used with 200 mg of mifepristone. Assessing the efficacy by misoprostol dose, the paper noted that doses ≥ 800 mcg had a success rate of 96.8%, with an ongoing pregnancy rate of 0.7%.

[1] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[2] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[3] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015; 22: 75-82
[4] Olavarrieta CD, Ganatra B, Sorhaindo A, Karver TS, Seuc A, Villalobos A, Garcia SG, Pérez M, Bousieguez M, Sanhueza P. Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial. Bull World Health Organ 2015; 93: 249-258
[5] Chen MJ, Creinin MD. Mifepristone with Buccal Misoprostol for Medical Abortion Obstet Gynecol: a Systematic Review. Obstet Gynecol 2015; 126(1): 12-21
[6] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

The original dosing regimen specifies taking misoprostol 2 days after Mifeprex. This efficacy supplement proposes a more flexible time frame of 24 to 48 hours between Mifeprex and misoprostol administration. Data from a review article by Wedisinghe et al[7] evaluated different time intervals using administration of misoprostol after Mifeprex. A meta-analysis of all five studies found a non-significant odds ratio for failure for shorter vs. longer dosing intervals, but a trend for lower success if a dosing interval < 8 hours is used. Chen & Creinin's systematic review[8] of 20 studies including over 33,000 women, all but one using the proposed regimen, compared the success of dosing intervals of 24 hours with intervals ranging from 24-48 hours. The success rate in six studies that used a 24-hour interval through 63 days gestation was 94.2%, compared to the rate of 96.8% in 14 studies that used a 24-48 hour interval, and this difference was statistically significant. The clinical team concluded that the efficacy of the revised dosing regimen was not compromised by revising the dosing interval to 24-48 hours. In addition, they noted that the overall rate of ongoing pregnancies did not differ significantly by dosing interval.

3. *Administration of misoprostol after Mifeprex administration at home:* Currently, the dosing regimen specifies that misoprostol is taken in the clinic setting following Mifeprex administration. No specific publication evaluated treatment outcomes with use of misoprostol at home compared to in-clinic dosing. However, one large literature review (Raymond et al[9]) evaluated a variety of mifepristone treatment regimens with different misoprostol doses, routes of administration and dosing intervals used in gestations through 63 days. Roughly half of the studies included in this review did not require women to take misoprostol in-clinic. Rates of treatment failure and of ongoing pregnancy were very similar regardless of whether misoprostol was taken in-clinic or at another location. The clinical review team concluded that the review provided sufficient data to support labeling that misoprostol does not need to be restricted to in-clinic administration.

4. *Use of a repeat misoprostol dose, if necessary:* The Applicant submitted several published studies that supported use of a repeat misoprostol dose, when complete uterine expulsion did not occur after the initial misoprostol dose following Mifeprex. In clinical practice, the usual treatment for incomplete expulsion (retained products of conception) may include either a repeat dose of misoprostol, expectant management or a surgical procedure (suction aspiration or a dilation and curettage). Studies that specifically report the success rate of a repeat dose of misoprostol are:

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[7] Wedisinghe L and Elsandabesee D. Flexible mifepristone and misoprostol administration interval for first-trimester medical termination. Contraception 2010; 81(4): 269-74. doi: 10.1016/ j.contraception.2009.09.007. Epub Oct 29, 2009

[8] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859

[9] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

- Winikoff et al[10] – studied the proposed regimen through 70 days gestation; of the few women who received a second dose for an incomplete abortion at follow-up, the success rate was 91% at 57-63 days and 67% at 64-70 days.
- Chen and Creinin [11] – a systematic review of 20 studies, all but one of which used the proposed regimen up through 70 days; success of a second dose ranged from 91-100%
- Boersma et al[12] – included pregnancies through 70 days treated with the proposed regimen; five of 330 women took a second dose due to absence of bleeding 48 hours after first dose; the success rate was 80%
- Louie et al[13] – studied the proposed regimen to 63 days; in 16 women (of 863) who took a second dose of misoprostol, the success rate was 100%
- Chong et al[14] – compared the proposed regimen to a lower dose of misoprostol; the success of a second dose of misoprostol was 92% overall, but the number of women in each dose arm getting a second dose was not specified.
- Winikoff et al[15] – 14 women in the proposed regimen took a second dose of misoprostol with a success rate of 92.9%.

Using the information from the above studies and other supportive data, the clinical team concluded that the available data support the efficacy of a repeat dose of misoprostol if complete expulsion has not occurred. The relatively high complete pregnancy termination rates indicate that this option is likely to reduce the need for a surgical intervention.

5. *Requirements regarding follow-up care:* Current labeling states that women will return to the clinic 14 days after Mifeprex administration for follow-up. This provision was based on the follow up regimen in the U.S. phase 3 trial that supported the initial approval in 2000. Although the Applicant submitted several studies that evaluated flexibility in the time of follow-up, the key publication identified by the review team that addressed this issue was a 2013 article by

[10] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6
[11] Creinin MD, Fox MC, Teal S, Chen A, Schaff EA, Meyn LA. MOD Study Trial Group: A randomized comparison of misoprostol 6-8 hours versus 24 hours after mifepristone for abortion. Obstet Gynecol 2004; 103: 851-859
[12]Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of amenorrhoea in a general practice in Curacao. Eur J Contracept Reprod Health Care 2011; 16: 61-6
[13] Louie KS, Tsereteli T, Chong E, Ailyeva F, Rzayeva G, Winikoff B. Acceptability and feasibility of mifepristone medical abortion in the early first trimester in Azerbaijan. Eur J Contracept Reprod Health Care 2014; 19(6): 457-464
[14] Chong E, Tsereteli T, Nguyen NN, Winikoff B. A randomized controlled trial of different buccal misoprostol doses in mifepristone medical abortion. Contraception 2012; 86: 251-256
[15] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

Raymond[16]. The impact of the timing of follow-up was assessed in Raymond's systematic review of studies using various treatment regimens. While some have posited that earlier follow-up may result in a higher rate of surgical intervention (for women who would have had complete expulsion had they been given a bit more time), Raymond's analyses found no difference in failure rates for women followed less than one week after mifepristone as compared to a week or more after mifepristone. As follow-up was anticipated to not alter the efficacy of the proposing dosing regimen, this change is also discussed below in Section 7.

6. *Allowing qualified healthcare providers to use Mifeprex.*

The Applicant provided data on the efficacy of medical abortion provided by non-physician healthcare providers, including four studies with 3,200 women in randomized controlled clinical trials and 596 women in prospective cohorts. These studies included a study by Warriner et al[17] that showed efficacy of 97.4% with nurses versus 96.3% by physicians.

Conclusions: I concur with the clinical review team's assessments and conclusions and these conclusions will be reflected in labeling. The data and information reviewed constitute substantial evidence of efficacy to support the proposed dosing regimen for Mifeprex for pregnancy termination through 70 days gestation. Other proposed changes to the Mifeprex labeling, including the time interval between Mifeprex and misoprostol dosing, and use of a repeat dose, were also adequately supported by evidence. Finally, I concur with the clinical review team that the information from the published literature also supported efficacious use of Mifeprex by non-physician providers.

Comment: Discussion was held as to whether the original dosing regimen approved in 2000 (i.e., Mifeprex 600 mg and misoprostol 400 mcg up to 49 days gestation) should remain in labeling. (b) (4) the clinical review team and I concur with their (b) (4) request to remove the current regimen from the labeling. Removal of the original dosing regimen simplifies labeling, and avoids any confusion regarding instructions. Therefore, the revised labeling, and REMS materials accompanying the approval of this efficacy supplement, will include only the proposed dosing regimen and instructions. It should be noted that there are no safety or efficacy concerns about the originally approved dosing regimen that led to removing it from the labeling.

[16]Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.
[17] Warriner IK, Wang D, Huong NTM, Thapa K, Tamang A, Shah I et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet 2011; 377: 1155-61.

8. Safety

The safety of the proposed dosing regimen for Mifeprex was supported by the evidence from submitted published literature and postmarketing experience. The focus of the safety analysis was on published studies that evaluated the proposed dosing regimen (Mifeprex 200 mg followed by 800 mcg misoprostol buccally 24-48 hours later), with comparison to the known safety profile of the currently approved dosing regimen.

Exposure: Per the Applicant's submission, the clinical review concluded that there have been approximately 2.5 million uses of Mifeprex by U.S. women since the drug's approval in 2000. The clinical review team estimated that exposure to the proposed dosing regimen for their safety analysis was based on approximately 30,000 patients (refer to Table 11 for a list of references used to evaluate safety). Such exposure volume is sufficient to characterize the safety profile of the proposed dosing regimen and other proposed changes in this efficacy supplement.

Deaths: Deaths with medical abortion rarely occur and causality can be difficult to determine. Most of the publications did not specifically report any deaths with medical abortion with Mifeprex. Among the seven U.S. studies submitted to support the safety profile of Mifeprex and misoprostol, only one (Grossman, et al[18]) explicitly addressed deaths and noted that there were no deaths among 578 subjects evaluated in the study. Only one observational study (Goldstone, et al[19]) from Australia contained a report of a death after a mifepristone and misoprostol dosing regimen. In this retrospective review of 13,345 pregnancy terminations, the authors identified one death from sepsis. The article stated that the death was in an individual who failed to follow-up with her healthcare provider despite showing signs of illness. Based on this information, deaths in association with abortion are extremely rare.

Deaths reported from the postmarketing experience of Mifeprex are summarized below in the Postmarketing Experience section.

Nonfatal serious adverse events: The clinical review team identified key nonfatal serious adverse events (SAEs) associated with the proposed dosing regimen for Mifeprex. These SAEs include: hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. Section 7 of the clinical review dated March 29, 2016, provides a detailed discussion of reported rates of hospitalization, serious infection, bleeding requiring transfusion and ectopic pregnancy. The latter is not an adverse reaction because an ectopic pregnancy would exist prior to the Mifeprex regimen; it represents instead a failure to diagnose an ectopic pregnancy. Overall rates identified by the clinical review team from the published literature are as follows:

- Hospitalization: 0.04-0.6% in U.S. studies of over 14,000 women; 0-0.7% in international studies of over 1,200 women

[18]Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.
[19]Goldstone P, Michelson J, Williamson E. Early medical abortion using low-dose mifepristone followed by buccal misoprostol: A large Australian observational study. Med J Austral 2012; 197: 282-6.

- Serious infection/sepsis: 0-0.2% in U.S. and international studies of over 12,000 women
- Transfusion: 0.03-0.5% in U.S. studies of over 17,000 women; 0-0.1% in international studies of over 12,000 women

A study by Upadhyay et al[20] reported a 0.31% rate of major complications (including incomplete or failed abortion, hemorrhage, infection or uterine perforation that required hospitalization, surgery or transfusion) for medical abortions (dosing regimen unspecified) through 63 days; this was about double the rate reported for first trimester aspiration abortions and statistically significantly higher. However, these rates were driven by higher rates of incomplete/failed abortion; rates of hemorrhage (0.14%) and infection (0.23%) did not differ from those associated with aspirations.

Only one submitted study reported an ectopic pregnancy. This study (Winikoff et al[21]) reported one ectopic among 847 women (0.12%).

Comment: The proposed dosing regimen has been studied extensively in the literature using U.S. and global sites. Serious adverse events including deaths, hospitalization, serious infections, bleeding requiring transfusion and ectopic pregnancy are rarely reported. The rates of these serious adverse events are well below 1% and do not suggest a safety profile different from the original approved Mifeprex dosing regimen. Although there is less serious adverse event data on women who received Mifeprex and misoprostol between 64-70 days of gestation, the data from a U.S. study of 379 women (Winikoff et al)[22] in that gestational age is reassuring that the rates of these serious adverse events are not clinically different from that of other gestational age ranges.

In summary, based on the published literature, nonfatal serious adverse events occur with Mifeprex and misoprostol use with rates generally less than 1%. Increased gestational age (64-70 weeks) was not associated with an increased incidence of nonfatal SAEs. Other submission- specific safety issues that were evaluated including uterine rupture and angioedema/anaphylaxis are discussed in the Postmarketing Experience section below.

Loss to follow-up: The studies included in this safety review revealed a wide range of loss to follow-up, from 0.6% loss to follow-up in the study with telephone follow-up (Ngoc et al[23]) to 22% in the Grossman et al[24] study using telemedicine to deliver medical

[20]Upadhyay UD, Desai S, Lidar V, Waits TA, Grossman D, Anderson P, Taylor D. Incidence of emergency department visits and complications after abortion. Obstet Gynecol 2015;125(1):175-183.
[21]Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008;112(6):1303-1310.
[22]Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070-6.
[23] Ngoc NTN, et al. Acceptability and feasibility of phone follow-up after early medical abortion in Vietnam: A randomized controlled trial. Obstet Gynecol 2014;123:88-95.
[24] Grossman D, Grindlay K, Buchacker T, Lane K, Blanchard K. Effectivenesss and acceptability of medical abortion provided thorugh telemedicine. Obstet Gynecol 2011;118:296-303.

abortion services.

Comment: Based on these data reviewed by the clinical review team, there is no literature that suggests that follow-up modality alters safety. Therefore, labeling will not be directive regarding follow-up; that will be a decision left to the patient and provider.

Common adverse events: The clinical review team evaluated common adverse reaction data and compared U.S. and global study locations. The comparison revealed that there were differences in the frequency of common adverse reactions, with the reporting rates considerably higher among the U.S. studies. There is no reason to anticipate regional differences in the safety profile for the same treatment regimen, so these differences likely reflect lower ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data in labeling would not be appropriate, as it is unlikely to be informative to the U.S. population of users. The data to be reported in labeling is outlined in Table 1 below:

Table 1: Common Adverse Events (≥ 15%) in U.S. Studies of the Proposed Dosing Regimen

Adverse Reaction	# U.S. studies	Number of Evaluable Women	Range of frequency (%)	Upper Gestational Age of Studies Reporting Outcome
Nausea	3	1,248	51-75%	70 days
Weakness	2	630	55-58%	63 days
Fever/chills	1	414	48%	63 days
Vomiting	3	1,248	37-48%	70 days
Headache	2	630	41-44%	63 days
Diarrhea	3	1,248	18-43%	70 days
Dizziness	2	630	39-41%	63 days

Source: Data from Middleton[25], Winikoff[26] and Winikoff[27] as outlined in Table 2 of the CDTL review dated March 29, 2016.

One concerning adverse event is severe vaginal bleeding. Severe vaginal bleeding can result in interventions such as hospitalization and transfusion and may be associated with infection. The overall rate of bleeding across publications varied between 0.5% and 4.2%. Two publications (Sanhueza Smith et al[28] and Gatter et al[29]) evaluated clinically significant bleeding by gestational age. Although the publications reported slightly different rates, there was no trend of increased bleeding requiring intervention with Mifeprex and misoprostol use with increasing gestational age.

[25] Middleton T, et al. Randomized trial of mifepristone and buccal or vaginal misoprostol for abortion through 56 days of last menstrual period. Contraception 2005; 72: 328-32

[26] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012; 120: 1070-6

[27] Winikoff B, Dzuba IG, Creinin MD, Crowden WA, Goldberg AB, Gonzales J, Howe M, Moskowitz J, Prine L, Shannon CS. Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial. Obstet Gynecol 2008; 112(6): 1303-1310

[28] Sanhueza Smith P, Pena M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75-82.

[29] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.

Comment: While not all of the studies reported common adverse events, those that reported did not have unexpected rates of common adverse events. These common adverse events are included in labeling in section 6.1 (Clinical Trial Experience) in the ADVERSE REACTIONS section.

Postmarketing experience – Spontaneous reports:

The safety profile for Mifeprex includes over 15 years of postmarketing safety data available on Mifeprex due to the reporting requirements under the REMS. The Year 3 REMS Assessment report was submitted by the Applicant in June, 2015. The (b) (6) (b) (6) provided a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. Findings include:

- No Clostridial septic deaths reported in the U.S. since 2009, and none worldwide since 2010.
- The postmarketing rates of hospitalization, severe infection, blood loss requiring transfusion and ectopic pregnancy reported from publications and remain stable and relatively low.

Submission-specific safety issues:

- Anaphylaxis/angioedema: The (b) (6) ((b) (6) identified a safety signal of anaphylaxis and angioedema with mifepristone administration. This signal was based on a comprehensive review of adverse event reports submitted from 2000 through November 17, 2015. A FAERS search retrieved one case of anaphylaxis and six cases of angioedema with mifepristone administration. Six of the seven cases were seen in women using mifepristone for termination of pregnancy. Six of the seven cases noted some type of medical intervention, such as treatment with an antihistamine, a histamine H2 antagonist, a corticosteroid, or a combination of various medications. Hospitalization was noted in three of the seven total cases; all three hospitalization cases occurred in patients who experienced angioedema. There were no additional cases of anaphylaxis or angioedema identified in the literature.

  Comment: (b) (6) and the clinical review team recommended that anaphylaxis and angioedema be described in the Contraindications and Adverse Reactions sections of labeling. These labeling sections were discussed with the Applicant and labeling was revised for those sections to describe these serious adverse events.

- Uterine rupture: As discussed in the clinical review, the potential risk of uterine rupture was considered because the current labeling for misoprostol includes a Boxed Warning against the use of misoprostol for gestations more than 8 weeks due to the risk of uterine rupture. Although misoprostol is used alone for various obstetric indications, including induction of labor at term, it was important to consider whether labeling about this potential risk is warranted for Mifeprex. Both the clinical reviewer and the (b) (6) ((b) (6) reviewed the literature and (b) (6) searched FAERS for adverse event reports.

Published literature reported three case reports[30,31,32] of uterine rupture with mifepristone/misoprostol treatment in the first trimester. Of these three reports, two patients had a risk factor for uterine rupture (prior uterine surgery). The third case was in a patient who received more than two doses of misoprostol. After consideration, the clinical review team decided that labeling should include information about this event. The FAERS search did not identify any reports of uterine rupture with use of mifepristone alone. Of 80 reports, 77 cited use of misoprostol alone, and three of mifepristone and misoprostol. Only two reports of uterine rupture in the first trimester were identified, both using misoprostol alone; one entailed an unspecified dose and route of misoprostol at 5 weeks gestation, and one involved vaginal administration of 800 mcg misoprostol at 8 weeks gestation for cervical preparation prior to a surgical abortion in a woman with a prior uterine scar.

Based on the available safety reports of uterine rupture, the review team from (b) (6) and clinical review team concluded that these data demonstrated that uterine rupture with Mifeprex and misoprostol in the first ten weeks (70 days) of gestation is exceedingly uncommon, and occurs most often in the face of a risk factor (previous uterine surgery).

Comment: I agree with the clinical review team and the (b) (6) team that the risk of uterine rupture with first trimester use of mifepristone and misoprostol appears to be extremely rare, and most often associated with a prior uterine scar, a known risk factor for uterine rupture. Labeling of these reports is included in section 2.3 of the DOSAGE AND ADMINISTRATION and section 6.2 of the ADVERSE REACTIONS of labeling to provide additional information to healthcare providers, but no restriction of use is needed based upon this extremely rare adverse reaction.

The clinical review team also evaluated the safety for each of the following major changes proposed in this efficacy supplement:

1. Changing the dosing interval between Mifeprex and misoprostol from 48 hours to 24-48 hours
2. Home administration of misoprostol
3. Use of a repeat dose of misoprostol
4. Change in the follow-up timeframe and method of follow-up
5. Allowing providers other than physicians to provide Mifeprex

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[30] Khan S et al. Uterine rupture at 8 weeks' gestation following 600 µg of oral misoprostol for management of delayed miscarriage. Journal of Obstet Gynaecol 2007; 27: 869-870

[31] Bika O, Huned D, Jha S, Selby K Uterine rupture following termination of pregnancy in a scarred uterus J Obstet Gynaecol 2014; 34(2): 198-9. doi: 10.3109/01443615.2013.841132

[32] Willmott F, et al. Rupture of uterus in the first trimester during medical termination of pregnancy for exomphalos using mifepristone/misoprostol. BJOG 2008;15:575-77

To evaluate each of these changes, the reviewers evaluated the adverse event information regarding:

- *Changing the timing interval between Mifeprex and misoprostol and change in the gestational age to 70 days:* Support for the 24-48 hour interval and use up through 70 days was primarily based on a large systematic review by Shaw et al[33]. This review evaluated studies looking at different follow-up modalities and demonstrated that there are a variety of acceptable alternatives to in-clinic follow-up that can identify cases in which there is need for additional intervention. In addition, the systematic review did not identify any significant difference in adverse events with different time intervals. Based on these findings, labeling will not be directive regarding specific details of how follow-up should be performed; this will be a decision between the patient and her healthcare provider.

- *Home administration of misoprostol:* The Applicant supplied several published studies that supported this change including Gatter et al[34] and Ireland et al[35]. These studies reported on large numbers of women in the U.S. who took misoprostol at home. The authors showed that home administration of misoprostol, as part of the proposed regimen, is associated with exceedingly low rates of serious adverse events, and with rates of common adverse events comparable to those in the studies of clinic administration of misoprostol that supported the initial approval in 2000. Given that information is available on approximately 45,000 women from the published literature, half of which incorporated home use of misoprostol, there is no clinical reason to restrict the location in which misoprostol may be taken. Given the fact that the onset of cramping and bleeding occurs rapidly (i.e., generally within 2 hours) after misoprostol dosing, allowing dosing at home increases the chance that the woman will be in an appropriate and safe location when the process begins.

- *Use of a repeat dose of misoprostol:* Safety reporting from studies that evaluated a repeat dose of misoprostol did not specifically assess the subset of women who received a second dose, but no unexpected findings were identified. One randomized controlled trial (Coyaji et al[36]) conducted in 300 women seeking medical abortion in India looked at a single misoprostol dose as compared to two misoprostol doses. Although there was no difference in the complete pregnancy termination rate in women who received a second misoprostol dose compared to those who did not, the repeat misoprostol dose reduced the need for surgical intervention. This study was reassuring in that there was no significant difference in the adverse events observed—similar percentages of women experienced

[33] Shaw KA, Topp NJ, Shaw JG, Blumenthal PB. Mifepristone-misoprostol dosing interval and effect on induction abortion times. Obstet Gynecol 2013;121(6):1335-1347.
[34] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[35] Ireland LD, Gatter M, Chen AY. Medical compared with surgical abortion for effective pregnancy termination in the first trimester. Obstet Gynecol 2015;126:22-8.
[36] Coyaji K, Krishna U, Ambardekar S, Bracken H, Raote V, Mandlekar A, Winikoff B. Are two doses of misoprostol after mifepristone for early abortion better than one? BJOG 2007;114:271-278.

cramping (87% in the single dose group, 89% in the repeat dose group), nausea (both groups 1%), vomiting (both groups 0%), and diarrhea (0% in the single dose group versus 2% in the repeat dose group). A supportive systematic review by Gallo et al[37] also provided safety information on subjects who received repeat misoprostol. In this review, the only side effects discussed in the trials were diarrhea, which was more common on those groups receiving misoprostol orally than in those receiving it exclusively vaginally (26-27% versus 9%). Rash was reported <1%. Based on these findings, labeling will be changed because the misoprostol dose does not need to be restricted to in clinic administration to assure safe pregnancy termination using the proposed dosing regimen. Given the onset of bleeding and cramping after misoprostol, allowing home administration increases the likelihood that a woman will be in an appropriate and safe location when the pregnancy termination process begins.

- *Change in the follow-up timeframe and method of follow-up:* The Applicant submitted several articles that described different methodologies in follow-up including phone calls and standardized instructions. The clinical reviewers evaluated a study in Scotland by Cameron et al[38] that evaluated self-assessment as compared to standard follow-up methodologies (clinic visit or phone call). Most of the women chose self-assessment over an in-clinic visit or phone call, and there were no significant differences in adverse outcomes between women who underwent self-assessment of health compared to those who had a clinic visit or phone call. Among women with an ongoing pregnancy after Mifeprex and misoprostol, the majority self-identified and presented within two-weeks for care. Based on this information and the other data from the Raymond systematic article[39] that did not identify a difference in failure rate for earlier (less than one week) as compared to one week or greater of follow-up, sufficient support was provided to use a broadened window of 7 to 14 days for follow-up. This revised follow-up time frame will be included in labeling.

- *Allowing providers other than physicians to provide Mifeprex*: The current Prescriber's Agreement in the REMS specifies that "…Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…" In addition, current labeling states that Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. However, labeling states that other healthcare providers, acting under the supervision of a qualified physician, may also provide Mifeprex to patients. Several published studies submitted by the Applicant indicate that health care providers such as nurse practitioners, nurse midwives, and physician assistants are

[37] Gallo MF, Cahill S, Castelman L, Mitchell EMH. A systematic review of more than one dose of misoprostol after mifepristone for abortion up to 10 weeks gestation. Contraception 2006;74:36-41.
[38] Cameron ST, Glasier A, Johnstone A, Dewart H, Campbell A. Can women determine the success of early medical termination of pregnancy themselves? Contraception 2015;91:6-11.
[39] Raymond EG & Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol 2012; 119: 215-9

currently providing abortion services. One of these studies (Kopp Kallner et al[40]) was a randomized controlled trial of 1,068 women in Sweden who were randomized to receive medical abortion care from two nurse midwives experienced in medical terminations and trained in early pregnancy ultrasound versus a group of 34 physicians with varying training and experience. Success rates were ≥ 96% regardless of gestational age. The nurse midwife group had few complications, though this was not statistically significant (4.1% for nurse midwives, versus 6.1% for doctors, p=0.14). No serious complications were reported and no blood transfusions were administered in the study. Based on this and other supportive studies, the information supports the efficacy and safety of allowing healthcare providers other than physicians can effectively and safely provide abortion services, provided that they meet the requirements for certification described in the REMS. The clinical team also felt that the term "healthcare provider who prescribes" would be the appropriate terminology as prescribing ability is a critical factor in dispensing Mifeprex.

The clinical review team concluded that the evidence demonstrated acceptable safety for each of the above proposed changes, and I concur with their conclusion. The proposed dosing regimen has a similar safety profile as the original regimen approved in 2000. Adverse outcomes of interest, such as deaths, serious infection, transfusions, ectopic pregnancies and uterine rupture, remain rare, and are not necessarily attributable to Mifeprex use. Overall, the rate of deaths and nonfatal serious adverse events are acceptably low, and data for the proposed regimen do not suggest a safety profile that deviates from that of the originally approved regimen No association between adverse outcomes and increasing gestational age was identified. Finally, the available information supports the safety of the other proposed changes, including increasing the flexibility of the time interval between Mifeprex and misoprostol, at home use of misoprostol, use of a repeat dose of misoprostol, change in the follow-up timeframe and allowing health care providers other than physicians to prescribe and dispense Mifeprex were acceptable.

9. Advisory Committee Meeting

Mifeprex is not a new molecular entity requiring discussion before an advisory committee. In addition, an advisory committee was not necessary as the application did not raise complex scientific or other issues that would warrant holding an AC before approval.

10. Pediatrics

This efficacy supplement triggered requirements under the Pediatric Research Equity Act (PREA). The Agency granted a partial PREA waiver for pre-menarcheal females ages birth to 12 years because it would be impossible to conduct studies in this pediatric population, as pregnancy does not exist in premenarcheal females.

[40] Kopp Kallner H, Fiala C, Stephansson O, Gemzell-Danielsson K. Home self-administration of vaginal misoprostol for medical abortion at 50-63 days compared with gestation of below 50 days. Human Reprod 2010;25(5):1153-1157.

The Applicant fulfilled the remaining PREA requirement in postmenarcheal females by submitting published studies of Mifeprex for pregnancy termination in postmenarcheal females less than 17 years old. Efficacy and safety information in these adolescents was based on a U.S. study in 322 postmenarcheal adolescents (Gatter et al[41]). Of the 322 adolescents, 106 of these adolescents were under 16; see Table 2 below:

Table 2: Age and Number of Adolescents Undergoing Medical Abortion (Gatter et al[42])

Age of Subject	Number of Subjects evaluated
11	1
12	1
13	2
14	20
15	82
16	216

Source: Refer to Table 17 of the Medical Officer's review dated March 29, 2016

The Gatter et al[43] study reported that postmenarchal females less than 18 years old had a 98.7% pregnancy termination rate as compared to females aged 18-24, who had a rate of 98.1%. This article reported that loss to follow-up was slightly higher in those less than 18 years old, however, age did not adversely impact efficacy outcomes.

One issue was whether adolescents would comply with at home use of misoprostol. The Gatter[44] et al study incorporated at home use of misoprostol into the Mifeprex dose regimen given to all females, including postmenarchal females less than 18 years old. The overall efficacy in adolescents was similar to that of all older women. This information supports at home administration of misoprostol in postmenarchal females under 17.

Two other published studies provided additional efficacy on Mifeprex use by adolescents for pregnancy termination:

- Phelps et al[45] evaluated data from 28 adolescents aged 14 to 17, at ≤ 56 days gestation, using Mifeprex 200 mg followed 48 hours later by misoprostol 800 mcg vaginally. In this study, 100% of subjects had a complete pregnancy termination, with five not requiring misoprostol.

[41]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[42] Ibid.
[43]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[44]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[45]Phelps RH, et al. Mifepristone abortion in minors. Contraception 2001;64:339-343.

- Niinimaki et al[46] used data from a Finnish Registry from 2000-2006. An analysis of efficacy between adolescents under age 18 compared to the women ≥ age 18 indicated that the adolescent group had a lower rate of incomplete abortions as compared to adults. And efficacy outcomes in adolescents were similar to those of adult women.

The safety of Mifeprex in postmenarcheal adolescents was primarily supported by adverse event information from the Gatter et al[47] study. (b) (6), (b) (4) Supportive data from a Finnish registry (Niinimaki et al) from 3024 adolescent females under 18 years of age reported that, compared to adult women, the risks of hemorrhage (adjusted odds ratio 0.87 [95% confidence interval: 0.77 to 0.99]), incomplete abortion (0.69, [95% confidence interval: 0.59 to 0.82]), and surgical evacuation (0.78, [95% confidence interval: 0.67 to 0.90]) were lower in the adolescent cohort. In the Finnish registry study, a majority of adolescents and adults received both Mifeprex and misoprostol. Safety findings from the Gatter et al and Niinimaki et al studies are reassuring and indicate that the safety profile of Mifeprex is similar between postmenarcheal adolescents and adult women.

Additional details from this article and other published data on Mifeprex use in adolescents (females under 17) are described in the clinical review (Refer to the Medical Officer's review dated March 29, 2016).

(b) (6) concurred that the efficacy and safety data in postmenarcheal adolescents less than 17 years old was sufficient to support the use of Mifeprex in this pediatric population and to fulfill the PREA pediatric study requirement. The revised Mifeprex labeling will state that that efficacy and safety are similar to adult women in the Pediatric Use section (8.4).

11. Other Relevant Regulatory Issues

(b) (6)

reviewed the Medication Guide in conjunction with the (b) (6) ((b) (6) Both (b) (6) and (b) (6) found the Medication Guide to be acceptable with recommended changes (See review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in

[46]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.
[47]Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015; 91:269-273.
[48]Niinimaki M, et al. Comparison of rates of adverse events in adolescent and adult women undergoing medical abortion: population register based study. BJM 2011;342: d2111.

the Medication Guide and incorporated appropriate changes into the final agreed upon Medication Guide.

(b) (6) (b) (6)

reviewed the Prescribing Information (PI) in addition to the joint review with (b) (6) of the Medication Guide in conjunction with (b) (6) After review, (b) (6) provided recommended changes (See (b) (6) review dated March 29, 2016). The Division considered all of the recommendations from (b) (6) in revising and updating the text in the PI and incorporated appropriate changes into the final label.

(b) (6) (b) (6)

(b) (6) (b) (6) in the (b) (6)) reviewed the proposed modifications to the REMS. The (b) (6) review reflected agreement with the Applicant's proposed REMS changes which include:

- Removal of the term "under Federal law" from the Prescriber's Agreement.
- Replacement of the word "physician" with a broader term to describe appropriate healthcare professionals who may order, prescribe and administer Mifeprex. (b) (6) believes that the Applicant's proposed terminology of " (b) (4) is too broad and that a more appropriate description is "healthcare provider who prescribes," which limits acceptable healthcare providers to those who are licensed in their state to prescribe medications.
- Removal of the Medication Guide from the REMS. The Medication Guide remains an important education tool for patients. It will still be dispensed to each patient in accordance with 21 CFR part 208. As described in the Medication Guide Guidance, a Medication Guide is not necessary to ensure that the benefits outweigh the risks of Mifeprex
- Modification of Element to Assure Safe Use (ETASU) A, the Prescriber's Agreement. (b) (6) recommends changing the name of the document to the Prescriber's Agreement Form to be consistent with other REMS programs. References to "physician" should be changed to "healthcare provider who prescribes."
- (b) (6) recommends removing the Patient Agreement from the REMS for a number of reasons:
  1. The established safety profile over 15 years of experience with Mifeprex is well-characterized, stable, and known serious risks occur rarely
  2. The Medication Guide contains the same risk information addressed in the Patient Agreement, and will still be provided to patients under 21 CFR part 208
  3. The Prescriber's Agreement Form will continue to require providers to explain the treatment, its effects and risks associated with Mifeprex and to answer any questions that a patient may have
  4. Established clinical practice provides for counseling, informing the patient about follow-up, when to contact the provider/clinic, answering questions and obtaining signed informed consent before treatment. FDA has removed REMS

requirements in other programs based on the integration of the REMS safe use condition into clinical practice.

Other revisions to the REMS document will be made for consistency with changes described above and to reflect current FDA thinking and practice regarding format, language and flow in REMS documents. These changes include modification of the Mifeprex REMS goal, changes in requirements to certify prescribers (removal of the requirement to obtain a Patient Agreement) and other minor edits.

In summary, the overall (b) (6) recommendation for the REMS modification for this efficacy supplement was approval (Refer to (b) (6) review dated March 29, 2016).

12. Labeling

Carton and container labeling was reviewed by the (b) (6) ((b) (6) the (b) (6) ((b) (6) and the (b) (6) ((b) (6) (b) (6) Their comments were conveyed to the Applicant as appropriate.

The label was submitted in the format prescribed by the PLR. Although the supplement was submitted prior to when it would otherwise have been required to comply with the PLLR requirements, the review team believed it would be of value to harmonize with this labeling standard to the extent possible.

Specific issues discussed during labeling negotiations included the selection of studies for inclusion in Section 6.1 (Clinical Trial Experience in the ADVERSE REACTIONS section) and 14 (CLINICAL STUDIES section). Only studies that evaluated the specific proposed regimen were included in these sections. For the Adverse Reactions section, examination of the common adverse reaction data by U.S. compared to non-U.S. study location revealed that there were large differences in the frequency of common adverse reactions, with the reporting rate considerably higher among the U.S. studies. This may reflect differences in ascertainment or subject reporting of adverse reactions in non-U.S. studies. Regardless, inclusion of this non-U.S. data would not be appropriate, as it is unlikely to be informative to the U.S. population of users. In the case of serious adverse reactions, the reported frequency was quite similar regardless of study location; for this reason, serious adverse reaction information from global studies is reported. Agreement on labeling was reached on March 29, 2016.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

Postmarketing Requirements/Postmarketing Commitments: None.

Risk Evaluation and Mitigation Strategies (REMS): The Applicant proposed a REMS modification for the Mifeprex REMS program with the submission of this efficacy supplement. The review teams from the (b) (6) evaluated the current Mifeprex REMS program and the proposed REMS modifications to determine whether each Mifeprex REMS element remains necessary to ensure that the benefits of Mifeprex outweigh the risks. Factors that impacted the decision included findings from two REMS assessments (the more recent REMS assessment review was completed in October 2015), an unchanged safety profile, and published literature that documented adequate safeguards in clinical practice with the use of Mifeprex in a regimen with misoprostol.

The teams determined that the following REMS modifications were warranted:

1. Revisions to the Prescriber Agreement Form to reflect the new dosing regimen and to reflect current REMS formatting and language standards
2. Removal of the Medication Guide as a REMS element, as distribution of the Medication Guide is required under 21 CFR 208
3. Removal of the Patient Agreement as a Documentation of Safe Use Condition (ETASU D)
4. Updating of the REMS goals to reflect the above 3 changes.
5. Removal of the phrase "Under Federal law" from the Prescriber's Agreement
6. Replacing the term "licensed physician" with "healthcare provider who prescribes"

The above modifications to the Mifeprex REMS program were discussed with the (b) (6) (b) (6) on January 15, 2016, as per (b) (6) .

The (b) (6) concurred with conforming changes to the Prescriber's Agreement to reflect the new dosing regimen, and with removal of the Medication Guide from the REMS. The Medication Guide would remain a part of labeling to inform patients about the risks associated with Mifeprex use. The (b) (6) also concurred with revisions to the REMS goals to reflect these changes.

The (b) (6) concurred with the removal of the term "under Federal law". A rationale for the original inclusion of the phrase "Under Federal law" cannot be discerned from available historical documents, nor is it consistent with REMS materials for other products. All the conditions of approval, including the REMS materials, are under Federal law; therefore, the phrase is unnecessary and it was decided that the phrase be removed from the Prescriber's Agreement.

The (b) (6) concurred with use of the term "healthcare providers who prescribe." To support a change in the REMS that would allow qualified healthcare providers other than physicians to prescribe Mifeprex through the Mifeprex REMS program, the Applicant provided information from over 3,200 women in randomized controlled trials and 596 women in prospective cohort studies comparing medical abortion care by physicians versus other providers (nurses or nurse midwives). These studies were conducted in a variety of settings (international, urban, rural, and low-resource). No differences in serious adverse events, ongoing pregnancy or incomplete abortion were identified between the groups. Given that providers other than physicians are providing family planning and abortion care under supervision and that the approved labeling and REMS program stipulate that prescribers must be able to refer patients for additional care, including surgical management, allowing these prescribers to participate in the Mifeprex REMS program is acceptable.

The (b) (6) also concurred with the teams' recommendation to remove the Patient Agreement (ETASU D) from the REMS although some (b) (6) members commented that additional support for the review team's rationale for this modification was needed. The review team's rationale for this change was:

APPEARS THIS WAY ON ORIGINAL

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and Informed Consent, and, more specifically with Mifeprex, includes counseling on all options for termination of pregnancy, access to pain management and emergency services if needed.
- Medical abortion with Mifeprex is provided by a well-established group of organizations and their associated providers who are knowledgeable in this area of women's health. Their documents and guidelines cover all the safety information that also appears in the Patient Agreement.
- ETASUs A and C remain in place: The Prescriber's Agreement under ETASU A requires that providers "explain the procedure, follow-up, and risks to each patient and give her an opportunity to discuss them." The REMS will continue to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals. This ensures that Mifeprex can only be dispensed under the direct supervision of a certified prescriber.
- Labeling mitigates risk: The Medication Guide, which will remain a part of labeling, contains the same risk information covered under the Patient Agreement.

The Mifeprex REMS program will have a modified ETASU REMS that will continue to ensure that Mifeprex can only be prescribed by certified prescribers and be dispensed to patients in certain healthcare settings, specifically, clinics, medical offices and hospitals. The Medication Guide will continue to be distributed to patients required under 21 CFR part 208. As required for all ETASU REMS, ongoing assessments of the Mifeprex REMS program will continue to ensure that the modified Mifeprex REMS program is meeting its goals.

13. Decision/Action/Risk Benefit Assessment

Decision:

All regulatory and scientific requirements have been adequately addressed in this efficacy supplement. Review teams involved in this supplement have recommended approval of the supplement from their disciplines' perspective. The submitted efficacy and safety information supported approval of the proposed dosing regimen through 70 days gestation, and other changes discussed in this summary memo. This supplement will receive an Approval action.

Benefit Risk Assessment:

This efficacy supplement provided substantial evidence of efficacy for the proposed dosing regimen through 70 days gestation. The efficacy findings were similar to those that led to the approval of the original dosing regimen in 2000. In addition, the submitted published literature supported other changes sought in this efficacy supplement that will

be reflected in labeling: 1) a more flexible time interval of 24 to 48 hours between Mifeprex and misoprostol administration, 2) the option of at home administration of misoprostol, 3) the option of repeat misoprostol dosing, if clinically indicated, 4) flexibility in the follow–up time frame of 7 to 14 days, and 5) permitting qualified healthcare providers other than physicians to prescribe Mifeprex.

The safety findings of the proposed dosing regimen were acceptable and were similar to those seen with the original dosing regimen approved in 2000.

After review of the REMS modifications proposed by the Sponsor, I concur with the clinical team and (b) (6) recommendations that:

1. The Medication Guide can be removed from the Mifeprex REMS program. The Medication Guide requirements under 21 CFR part 208 require the Medication Guide to be distributed to patients. Mifeprex will only be dispensed by a healthcare professional who will be knowledgeable and able to provide the patient instructions on appropriate use of the drug, including what potential side effects may occur or follow-up that may be required as appropriate, and who will answer any questions the patient may have. In that setting, the Medication Guide will already be a required available tool for counseling. Therefore, given the existing requirements under 21 CFR part 208, I concur that there is no reason for the Medication Guide to specifically be a part of the REMS.

2. The Prescriber Agreement Form (ETASU A) as revised reflects current FDA format and content to conform to current REMS programs and reflect the labeling changes that will be approved in this supplement. I concur that the changes are acceptable.

3. Revision of the Mifeprex REMS goals (ETASU C) will adequately mitigate the risk of serious complications by requiring certification of healthcare providers who prescribe and ensuring the Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber.

4. Removal of the Patient Agreement Form (ETASU D): I concur with the clinical review team that the Patient Agreement Form, which requires a patient's signature, does not add to safe use conditions for the patient for this REMS and is a burden for patients. It is standard of care for patients undergoing pregnancy termination to undergo extensive counseling and informed consent. The Patient Agreement Form contains duplicative information already provided by each healthcare provider or clinic. I believe that it is much more critical for the healthcare provider who orders or prescribes Mifeprex to provide and discuss informed consent derived from their own practice so that care can be individualized for the patient.

I support that the Mifeprex REMS with ETASUs A and C remain in place to support conditions critical to the use of the drug. Therefore, the implementation system and timetable for assessments should continue.

I also agree with the clinical review team that the reporting requirements should only be required for deaths. It is important that the Agency be informed of any deaths with Mifeprex to monitor new safety signals or trends. However, after 15 years of reporting serious adverse events, the safety profile for Mifeprex is essentially unchanged. Therefore, I agree that reporting of labeled serious adverse events other than deaths can be collected in the periodic safety update reports and annual reports to the Agency.

In summary, I believe that the benefit-risk profile for Mifeprex continues to be favorable and with the agreed-to labeling changes and REMS modifications, the Mifeprex REMS program will continue to assure safe use. Therefore, I support approval of this efficacy supplement and REMS modifications.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked [redacted] (b) (6) and the [redacted] (b) (6) [redacted] to continue to include a Patient Agreement Form in the REMS for Mifeprex (see March 28, 2016 Memorandum from Janet Woodcock, MD, Director, Center for Drug Evaluation and Research, through the [redacted] (b) (6) [redacted] (6) Therefore, the Patient Agreement Form will be retained and other changes will be made in the REMS to reflect that it is being retained.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

03/29/2016

Exhibit 33

Beverly Winikoff, et al., *Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age*, 120 Obstetrics & Gynecology 1070 (2012)

Extending Outpatient Medical Abortion Services Through 70 Days of Gestational Age

Beverly Winikoff, MD, MPH, Ilana G. Dzuba, MHS, Erica Chong, MPH, Alisa B. Goldberg, MD, MPH, E. Steve Lichtenberg, MD, MPH, Carol Ball, MD, Gillian Dean, MD, MPH, Daniel Sacks, MD, William A. Crowden, BA, and Yael Swica, MD, MPH

OBJECTIVE: To estimate the efficacy and acceptability of medical abortion at 64–70 days from last menstrual period (LMP) and to compare it with the already proven 57–63 days from LMP gestational age range.

METHODS: This prospective, comparative, open-label trial enrolled 729 women with pregnancies 57–70 days from LMP requesting abortion at six U.S. clinics. Medical abortions were managed with 200 mg mifepristone and 800 micrograms buccal misoprostol and sites' service delivery protocols. Follow-up visits occurred 7–14 days after mifepristone, with an abortion considered complete if surgical intervention was not performed. Success, ongoing pregnancy, and acceptability rates were compared.

RESULTS: A total of 629 cases were analyzable for efficacy. Success rates were similar in the two groups (57–63 days group: 93.5%, 95% confidence interval [CI] 90–96; 64–70 days group: 92.8%, 95% CI 89–95). Ongoing pregnancy rates also did not differ significantly (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7). Acceptability was high and similar in both arms, with most women (57–63 days: 87.4%; 64–70 days: 88.3%) reporting that their experience was either very satisfactory or satisfactory.

CONCLUSION: Medical abortion with mifepristone and misoprostol in current outpatient settings is an efficacious and acceptable method of ending pregnancies 64–70 days from LMP and can be offered without alteration of existing services.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00997347.

(Obstet Gynecol 2012;120:1070–76)

DOI: http://10.1097/AOG.0b013e31826c315f

LEVEL OF EVIDENCE: II

From the Gynuity Health Projects, Planned Parenthood of New York City, and the Columbia University College of Physicians and Surgeons, Obstetrics/Gynecology Department, New York, New York; Planned Parenthood League of Massachusetts and Harvard University, Boston, Massachusetts; Family Planning Associates Medical Group and Northwestern University, Chicago, Illinois; Planned Parenthood of Minnesota, North Dakota, South Dakota, St. Paul, Minnesota; Presidential Women's Center, West Palm Beach, Florida; and Planned Parenthood of Waco, Waco, Texas.

The authors thank Kathryn Conkling for manuscript preparation and data entry and management, and Jennifer Fortin, Rose Ali, Michelle Arnesen, Stefanie Sanden, Lauren Porsch, Mona Reis, Ellen Kimmel, Irene Saenz, and Iris Draughn for collecting data for this study. Nancy Sloan provided technical assistance in review of the draft manuscript.

Presented at the National Abortion Federation's Annual Meeting, April 10-12, 2011, Chicago, Illinois, and at Reproductive Health 2010, September 25, 2010, Atlanta, Georgia.

The findings and conclusions in this article are those of the authors and do not necessarily represent the views of Planned Parenthood Federation of America.

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Financial Disclosure

The authors did not report any potential conflicts of interest.

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When medical abortion with mifepristone and misoprostol was approved by the U.S. Food and Drug Administration (FDA) in 2000, the regimen was recommended for outpatient use through 49 days from the last menstrual period (LMP).[1] Extensive research and more than 11 years of experience in the United States with approximately 1.75 million uses have established that medical abortion is safe and effective through 63 days from LMP when used by women at home (May 2011, Danco Laboratories, personal communication).[2–6]

Generally, women in the United States whose first-trimester pregnancies are beyond 63 days from LMP are not offered medical abortion with mifepristone and misoprostol. Medical abortion after 63 days from LMP is occasionally available outside the United States, but only on an inpatient basis using complex regimens.[7–9] Inpatient protocols typically involve redosing of medications, vaginal speculum examination, and an overnight stay, and are burdensome for women, providers, and health care systems. Data supporting use of medical abortion past 63 days from

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LMP in outpatient services are limited to one small trial, but results were not available when this study began.[10] Our study sought to estimate the efficacy and acceptability of the most common outpatient medical abortion regimen in the United States (200 mg mifepristone and 800 micrograms buccal misoprostol) through 70 days from LMP and to compare outcomes between women with pregnancies of 64–70 days' duration and women with pregnancies in the range of 57–63 days. The gestational age limit of 70 days extends the usual gestational age cutoff of 63 days by 1 week.

MATERIALS AND METHODS

The study was performed at six facilities: Family Planning Associates Medical Group (Chicago, IL), Planned Parenthood League of Massachusetts (Boston, MA), Planned Parenthood of New York City (New York, NY), Planned Parenthood of Waco (Waco, TX), Presidential Women's Center (West Palm Beach, FL), and Planned Parenthood of Minnesota, North Dakota, South Dakota (St. Paul, MN). The Quorum Review Institutional Review Board approved the protocol.

Women seeking pregnancy termination were invited to participate in the study if they were eligible for medical abortion, were at least 18 years old, and had a confirmed intrauterine pregnancy 57 through 70 days from LMP, based on routine ultrasound practices of the respective study sites (crown-rump length+42 was most commonly used). Participants had to be willing and able to provide informed consent, have access to a telephone and emergency transportation, be able to speak and read English or Spanish, and agree to follow study protocols. Screening and enrollment generally occurred during the same visit, except when a state-mandated 24-hour waiting period after informed consent required a second visit.

On day 1, participants swallowed mifepristone 200 mg (Mifeprex) in the clinic and then were provided with misoprostol 800 micrograms to take 24–48 hours later at home. Women were instructed to hold the misoprostol buccally for 30 minutes before swallowing any remains. Analgesics and antinausea medications were dispensed or prescribed according to local standards at each facility, and participants were counseled to call the clinic with questions or concerns. Participants maintained a diary for up to 15 days to record time of misoprostol administration, bleeding, expulsion time (if recognized), pain medications used, and days of missed work or school.

Participants returned to the study site 7 to 14 days after using mifepristone (according to clinic practice) for clinical assessment, which included ultrasonography. Uterine suction curettage was recommended for women with ongoing pregnancies. Women with nonviable pregnancies (eg, empty sac or static size with absent cardiac activity on ultrasonography) could opt for suction curettage, expectant management, or a second misoprostol dose. If either of the latter two options was chosen, then women were asked to return to the clinic in 1 week for further follow-up. If a persistent nonviable pregnancy was diagnosed at the extended follow-up visit, suction curettage was recommended. Providers also intervened surgically if they deemed it medically necessary or at the patient's request. After expulsion of uterine contents was confirmed, women responded to a semi-structured interview about their experiences with the medical abortion overall, the incidence of side effects and their severity (based on their own definitions of mild, moderate, and severe), and the acceptability of the procedure. If a participant failed to return for a follow-up visit, then assessment of abortion status and the interview could be conducted by telephone. Study sites were required to document at least three attempts to contact women who were lost to follow-up.

The study's primary objective was to assure that an outpatient medical abortion regimen could be used in gestations 64–70 days from LMP and achieve a success rate of at least 90%, which would characterize a clinically acceptable regimen. A cohort of women with gestations 57–63 days from LMP was also enrolled to serve as a comparison; 334 women per group were needed to detect a 5% or greater lower efficacy than the hypothesized 95% success rate in the 57–63 days group, based on previously published reports ($\alpha=0.05$, $1-\beta=0.8$, using a one-tailed test) and would allow us to estimate a success rate of 90% with a confidence interval (CI) of $\pm 3.2\%$.[2–3,11] Data were analyzed using SPSS 15.0. An independent data and safety monitoring committee reviewed the interim results for safety and efficacy after 50% of the data were available.

The primary outcome of the trial was complete abortion without surgical intervention at any point, regardless of the number of misoprostol doses used. Secondary outcomes included side effects, patient satisfaction and acceptability, days of heavy bleeding, days of missed work or school, and number of calls and unscheduled visits to the clinic. One-tailed $P<.05$ was considered to indicate statistical significance. We chose to use one-tailed P values because our objective was to determine whether use of medical abortion in

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the gestational age range of 64–70 days would result in worse outcomes than its current use in the 57- to 63-day age range. Binomial proportion CIs for efficacy rates were calculated. We used Fisher's exact test to determine differences in proportions, and for continuous variables we used the Student *t* test to determine differences in means.

RESULTS

Between August 2009 and February 2011, the study sites enrolled 729 women; 379 women in the 57–63 days group and 350 women in the 64–70 days group. Fifty-three (14%) women in the earlier and 45 (13%) in the later gestational age group were lost to follow-up, and two women, one from each group, withdrew before using mifepristone. Enrollment was continued to 729 women to compensate for loss to follow-up. Six-hundred twenty-nine cases had outcome data, short of the estimated sample size of 668. Analysis of the outcomes at that time were conducted to determine the utility of continuing the study and whether a statistically significant difference in success would be possible if the study were to continue and the remaining 39 analyzable case records were available. We analyzed the hypothetical scenario that maximized the possible difference in efficacy between the two groups by adding all 39 hypothetical additional cases to the 57–63 days group (because it had the higher efficacy rate) and assuming that every woman had a successful abortion (to model the maximum mathematical differences possible between the groups). This model improved the efficacy rate in the 57–63 days study group by 0.7 percentage points and doubled the difference in efficacy between the two gestational age groups from 0.7% to 1.4%. Comparing the projected success rates of the two gestational age groups resulted in $P=0.2$. It was therefore determined that enrolling all 688 women would not show a statistically significant or a clinically meaningful difference in success rates. The study would have required an additional 13,120 women with follow-up in each study group (total 26,240 analyzable cases) to be able to find a statistically significant difference between the observed success rates. Therefore, a total of 629 medical abortions, 325 in the 57–63 days group and 304 in the 64–70 days group, were analyzed for efficacy in the final analysis. Baseline characteristics of women in the two groups were similar for mean age, education level, gravidity, and previous abortions (Table 1).

Efficacy of the outpatient medical abortion regimen in the 57–63 days group was 93.5% (95% CI 90.1–95.9) and 92.8% (95% CI 89.1–95.3; $P=.41$) in the 64–70 days group (Table 2). Three percent of women in both groups had a surgical intervention because of ongoing pregnancy (57–63 days: 3.1%, 95% CI 1.6–5.8; 64–70 days: 3.0%, 95% CI 1.5–5.7; $P=.62$). Rates of surgical intervention attributable to persistent nonviable pregnancy or sac ($P=.33$), substantial uterine debris ($P=.29$), excessive prolonged bleeding ($P=.75$), or woman's request ($P=.86$) were comparable between study groups. There was no significant difference in efficacy by study site ($P=.137$).

Approximately 5.2% of women in the 57–63 days group and 5.3% of women in the 64–70 days group had incomplete abortion diagnosed (ie, persistent gestational sac or substantial debris) at their first follow-up visits ($P=.56$). The majority were treated with a second dose of misoprostol, with those in the 57–63 days group receiving a second dose at a higher rate than those in the 64–70 days group (76.5% compared with 56.3%; $P=.195$). Of those who received a second dose of misoprostol and underwent an extended follow-up evaluation, 91% (10 of 11) in the earlier and 66.7% (6 of 9) in the later gestational age group were determined to have a complete abortion ($P=.974$).

Almost 70% of participants in each group reported a time of expulsion at follow-up. Among women who reported a time of expulsion, those in

Table 1. Participant Demographic Characteristics

	57–63 d (n=325)	64–70 d (n=304)	*P* (Two-Tailed)
Age (y)	26 (18–42)	26 (18–42)	.66
Primigravid woman	32 (103)	31 (94)	.86
Previous abortion	47 (154)	48 (146)	.87
Previous medical abortion	21 (67)	24 (72)	.39
Education level	322	303	4 unknowns
Less than high school	8 (24)	9 (26)	.71
High school	59 (191)	60 (183)	.85
University	27 (87)	27 (83)	.99
Postgraduate	6 (20)	4 (11)	.19

Data are mean (range), n (%), or n unless otherwise specified.

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Table 2. Efficacy and Major Adverse Events by Gestational Age Group

	57–63 d (n=325)	64–70 d (n=304)	*P* (One-Sided)
Success	93.5 (304; 90–96)	92.8 (282; 89–95)	.41
Interventions	6.5 (21)	7.2 (22)	
Ongoing pregnancies	3.1 (10)	3.0 (9)	.62
Persistent nonviable sac	0.92 (3)	1.6 (5)	.33
Substantial debris in uterus	0.31 (1)	1.0 (3)	.29
Excessive prolonged bleeding	1.2 (4)	1.0 (3)	.75
Woman's request	0.61 (2)	0.33 (1)	.86
Other	0.31 (1)	0.33 (1)	.73
Major adverse events			
Went to emergency department	3.7 (12)	4.6 (14)	.36
Received blood transfusion	0.6 (2)	0.3 (1)	.52
Admitted to hospital	0.9 (3)	0.7 (2)	.53

Data are % (n; 95% confidence interval) or % (n) unless otherwise specified.

the earlier gestational age group were significantly more likely than those in the later gestational age group to expel sooner (Fig. 1; log-rank test *P*=.005). This difference in reported expulsion time was most notably seen at 3 hours after using misoprostol (37.7% in week 9 compared with 22.5% in week 10; *P*=.001), but equal numbers (93.1% compared with 92.1%, respectively; *P*=.43) reported expulsion by 24 hours (Fig. 1).

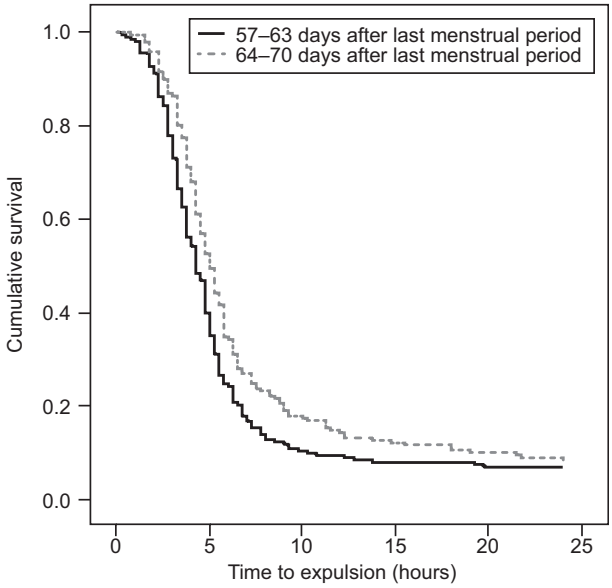

Fig. 1. Time from misoprostol administration to pregnancy expulsion. Survival curves of the number of hours since misoprostol administration until pregnancy expulsion for women 57–63 days from last menstrual period or 64–70 days from last menstrual period. Includes women who reported a time of expulsion, excluding those with ongoing pregnancies or persistent nonviable sac at follow-up. Log-rank test *P*=.005.

Winikoff. Medical Abortion Through 70 Days From LMP. Obstet Gynecol 2012.

Twenty-nine women made visits to an emergency department, primarily for pain and bleeding during the study period (3.7% from the earlier gestational age group and 4.6% from the later group (*P*=.35) (Table 2). Three women received blood transfusions, two in the 57–63 days group and one in the 64–70 days group (*P*=.52). One woman in the 57–63 days group was admitted to the hospital and was successfully treated for *Escherichia coli* sepsis, and one woman in the 57–63 days group with a history of chronic pancreatitis was admitted to the hospital for recurrence of her disease.

Eighty-five percent of participants completed and submitted the diaries they maintained for up to 15 days. Mean duration of heavy bleeding did not differ significantly by group (Table 3). There was no significant difference in mean days of work or school missed by women because of the abortion (1.85 in 57–63 days group compared with 1.80 in 64–70 days group; *P*=.81).

The side effect profiles of each study group were similar, with no significant differences except for vomiting (Table 3). A minority of women in each group experienced this side effect, but fewer in the earlier gestational age group (36% compared with 46%; *P*=.01). However, severe vomiting was no different in the two groups (10.7% for 57–63 days compared with 12.0% for 64–70 days; *P*=.35). Opiates were reportedly used more often for pain relief by women in the 64–70 days group (76% in the 57–63 days group compared with 84%; *P*=.003), but nonsteroidal anti-inflammatory drug use did not differ. Mean days of any analgesic use were the same in both groups. Fewer women in the 57–63 days group reported use of antiemetic medication (34% compared with 46%; *P*=.002). The study participants requested relatively little clinic staff time beyond the scheduled study visits. Only 20%

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Table 3. Side Effect and Bleeding Profile

Side Effects	57–63 d (n=318)	64–70 d (n=300)	*P* (One-Sided)
None	22.6 (72)	17.0 (51)	.05
Chills	24.2 (77)	22.7 (68)	.36
Fever	11.9 (38)	10.3 (31)	.31
Vomiting	35.8 (114)	45.7 (137)	.008
Nausea	50.0 (159)	51.7 (155)	.37
Diarrhea	17.9 (57)	17.3 (52)	.47
Heavy bleeding	319	298	
Days of heavy bleeding	2.5±2.06 (0–14)	2.3±1.86 (0–11)	.09
Median days of heavy bleeding	2	2	

Data are % (n), n, or mean±standard deviation (range) unless otherwise specified.

of women in both groups made phone calls because of concerns related to their abortion, and 4% of women in the earlier and 3% of women in the later gestational age groups made unanticipated clinic visits.

The majority of women in both groups (57–63 days: 87.4%; 64–70 days: 88.3%) reported being either satisfied or very satisfied with the medical abortion method, and 78% and 79% of women in the two groups, respectively, reported that they would choose medical abortion again instead of surgery. Women in the earlier gestational age group were as likely to report seeing the pregnancy or some part of it as those in the later gestational age group (64% compared with 69.3%; *P*=.10). There were no significant differences in women's reported reactions to what they saw, with the exception that women in the earlier gestational age group were more likely to report "nothing or no feeling" (13.9% compared with 8.2%; *P*=.04) and those in the later group were more likely to report that they were "relieved" (7.4% compared with 13.9%; *P*=.02).

DISCUSSION

The results show that medical abortion with an outpatient regimen of 200 mg mifepristone followed 24 to 48 hours later by 800 micrograms buccal misoprostol self-administered at home is efficacious and acceptable in women 64 to 70 days from LMP and is not statistically or clinically different from a current outpatient medical abortion protocol used with women 57–63 days from LMP. In 2000, the FDA approved mifepristone based on an efficacy of 92% for gestations up to 49 days from LMP.[12] The success rate achieved in this study during week 10 of gestation (92.8%) is similar to that rate and clinically acceptable. Based on this evidence, medical abortion using the study protocol can be extended from 63 days from LMP to 70 days from LMP without reconfiguration of existing outpatient clinical services. Our findings are consistent with those of Boersma et al,[10] who offered the same outpatient medical abortion regimen as in the current study to 26 women with gestational ages 64–70 days from LMP, but with an interval of 24–36 hours between the mifepristone and misoprostol doses. That study found 96% success in those women but was too small to provide reliable point estimates of success rates.

The study cannot reject the null hypothesis that there is no difference between the success rates of medical abortion among women with pregnancies of 9 and 10 weeks of gestation. Although the inability to reject the null hypothesis theoretically could be attributable to early cessation of the study, the observed differences between study groups are much smaller than those originally hypothesized and are not clinically meaningful. The additional analyses conducted also suggest that continuing enrollment to include 668 analyzable cases would not have affected the study conclusions.

The overall high efficacy of the medical abortion regimen used in this study through 63 days from LMP is well-documented, and only a very minimal decline in efficacy as gestational age increases has been noted.[2,13] The trend observed in the two point estimates for success in weeks 9 and 10 in this study is consistent with such a small decline (Fig. 2), alleviating concern of an abrupt decline in efficacy of the method beyond 63 days from LMP.

The study was not powered to detect a difference in safety outcomes because major adverse events attributable to medical abortion (eg, hospitalizations, emergency department visits, and blood transfusions) are rare. No medical abortion studies (including the pilot studies on which FDA approval was based) were powered to detect rates of rare occurrences such as transfusion or hospitalization. Similar to those studies, the occurrence of major adverse events in this study was very infrequent.

Many studies have explored women's experiences with outpatient medical abortion in the first trimester,[14]

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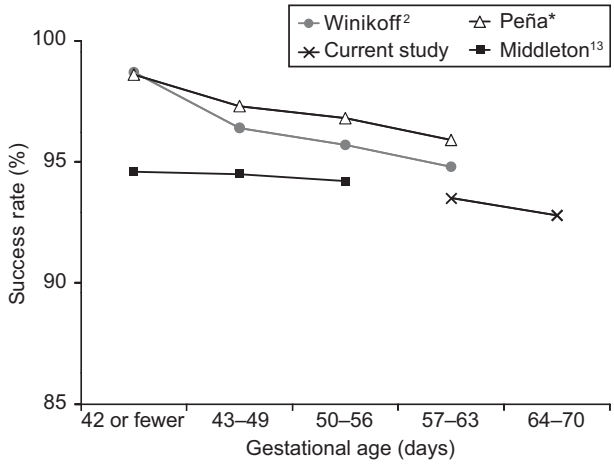

Fig. 2. Efficacy of mifepristone medical abortion with 800 micrograms buccal misoprostol from 49 to 70 days from last menstrual period. Illustration of success rates by gestational age from different studies that used the same medical abortion regimen as in this study. *Peña M. Medicamentos para la interrupción legal del embarazo: La experiencia de la Secretaría de Salud del Districto Federal (Mexico). 20th Congress of the Latin American Federation of Obstetrics and Gynecology (FLASOG) 2011; Managua, Nicaragua.

Winikoff. Medical Abortion Through 70 Days From LMP. Obstet Gynecol 2012.

but often the information is not disaggregated by week. Although our findings do not show any differences between the two study groups in such aspects as bleeding profiles, days of school or work missed, and reports of seeing the expulsion, women's experiences at these later weeks of gestational age may differ in some ways from women with earlier first-trimester pregnancies. The results from this study may help clinicians who provide medical abortion to women with pregnancies 57–70 days of gestational age to tailor counseling messages to prepare women for what to expect. For example, more than two-thirds of women reported witnessing uterine expulsion, so women should be counseled on that likelihood. Women with gestations in week 10 may expel their pregnancies less quickly after using misoprostol, but perhaps this is not surprising given the slightly larger size of the gestational sac at the later gestational age The fact that more women in week 10 expressed relief after their medical abortions could be an artifact of participating in the test group of a research trial.

Some women may have been misclassified into study groups based on usual variability in gestational age dating by ultrasonography. To be sure that such misclassification would not have affected study results, reanalysis of success among women with pregnancies at the opposite extremes of the gestational age spectrum considered in this study (ie, a comparison of the earlier half of the early age range with the latter half of the later age range), as well as by standardizing gestational age assessment, did not affect our outcomes or our conclusions (data not shown).

The content of counseling was not dictated by the study protocol and was based on usual counseling provided. Possible assumptions that pain, bleeding, and the size of the expelled fetus in week 10 may be more than at earlier weeks of gestation could have had an effect on women's perceptions. It is also possible that there were slight differences in counseling messages as a result of the counselors' knowledge of gestational age in each woman. Similarly, observations and experience amassed during the course of the study may have resulted in adjustments in counseling messages to later enrollees, better-preparing women with pregnancies in week 10 for what they might experience.

The study sites already were highly experienced at providing medical abortion and were accustomed to administering the specific regimen used in this study. Therefore, the observed efficacy rates may not be generalizable to clinics that are less experienced. Results also are not generalizable to regimens other than the one studied, for either efficacy or the side effects of misoprostol, which are known to vary by route and dose. Last, because adverse events were so rare in our study, the sample size was not sufficient to characterize adequately the occurrence of adverse events for women who terminate their pregnancies medically during the ninth or tenth week other than to say that serious events are infrequent and side effects are tolerable.

In conclusion, the regimen of 200 mg mifepristone and 800 micrograms buccal misoprostol is efficacious and acceptable for women seeking medical abortion with pregnancies of 70 days or less. The findings of this research are important for expanding the availability of this nonsurgical option to women seeking termination of pregnancy in the first trimester.

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Exhibit 34

Mary Gatter, et al., *Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days*, 91 Contraception 269 (2015)

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Contraception xx (2015) xxx–xxx

Original research article

Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days☆,☆☆

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Abstract

Objective: The aim of this study was to report on the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg misoprostol buccally 24–48 h later through 63 days estimated gestational age.
Study design: We analyzed outcomes in women presenting for medical abortion between April 1, 2006, and May 31, 2011, using an evidence-based alternative to the United States Food and Drug Administration (FDA)-approved regimen. Cases were identified for this descriptive study from our electronic practice management (EPM) database, and our electronic database on adverse events was queried for information on efficacy and safety. The primary outcome was successful abortion. Logistic regression was used to identify predictors of successful abortion.
Results: Among the 13,373 women who completed follow-up, efficacy of the regimen was 97.7%. Efficacy was highest at 29 to 35 days (98.8%) and 36 to 42 days (98.8%) of gestation and lowest at 57 to 63 days (95.5%). The odds of needing aspiration for any reason were greatest at higher gestational ages. Rates of infection requiring hospitalization and rates of transfusion were 0.01 and 0.03%, respectively.
Conclusions: An evidence-based regimen of 200 mg of mifepristone orally followed by home use of 800 mcg of buccal misoprostol 24–48 h later is safe and effective through 63 days estimated gestational age. Further, the need for aspiration for any reason was low, and hospitalization was rare.
Implications: This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion (200 mg mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later) through 63 days estimated gestational age, and contributes to the existing evidence against restrictions requiring use of the FDA-approved regimen.
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Keywords: Medical abortion; Mifepristone; First-trimester abortion; Evidence-based regimen; Buccal misoprostol; Efficacy

1. Introduction

The United States Food and Drug Administration (FDA) approved the use of mifepristone and misoprostol for pregnancy termination in 2000. The regimen, labeled for use through 49 days estimated gestational age, required a minimum of three visits to the healthcare provider. Six hundred milligrams of mifepristone was taken orally at Visit 1, followed in 2 days by misoprostol 400 mcg, also taken orally. A third follow-up visit was required in 14 days to ensure that the abortion was complete. The efficacy of this regimen ranged from 92 to 97% [1–3]. Publications soon followed providing an evidence base for alterations to the regimen. Alterations included a lower dose of mifepristone, different routes of administration of misoprostol, variations in the timing of misoprostol administration, home use of misoprostol, and increasing the gestational age limit for the regimen [4–11]. A recent publication confirmed the low rate of significant adverse events with use of the evidence-based regimen [11].

In 2008, a prospective study was published describing the use of 200 mg of mifepristone followed in 24 to 36 h by 800 mcg of buccal misoprostol for pregnancy termination to 63

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days of gestation with a success rate for the regimen of 96.2% [8]. Despite the growing literature supporting evidence-based provision of medical abortion, some providers are required by law to limit the provision of medical abortion to that regimen, which was FDA-approved more than a decade ago [12]. The goal of the current study was to assess, in a much larger cohort of patients, the safety and efficacy of an evidence-based medical abortion regimen utilizing 200 mg of mifepristone orally followed by home use of 800 mcg of misoprostol buccally 24–48 h later through 63 days estimated gestational age.

2. Materials and methods

2.1. Medical abortion protocols and monitoring

Our large network of urban healthcare centers includes 19 health centers providing approximately 15,000 abortions per year, of which about 30% are medical abortions. Demographic information, treatment dates, and diagnostic codes for all patients were retrieved using the electronic practice management (EPM) billing system. Some clinical information was retrieved from an electronic medical records (EMR) system, which was gradually implemented across all study sites between 2008 and 2010. All patients undergo an ultrasound examination for pregnancy dating prior to abortion. The clinician administering the medication abortion performed and interpreted the ultrasound. All clinicians had undergone the same standardized training and were monitored regularly to ensure accuracy and to maintain consistency. Ultrasound machines using a Hadlock scale calculated gestational age in days; herein, we analyze and report gestational age in 7-day increments (e.g., 22 to 28 days). Since April 2006, our medical abortion regimen has consisted of 200 mg of mifepristone taken orally at the health center followed by 800 mcg of buccal misoprostol used by the patient at home 24 to 48 h later. Medical protocols during the study period allowed for repeat doses of misoprostol for patients who had an incomplete medical abortion. Data on which patients received a repeat dose are not available from the EPM system, but only in the EMR system; therefore, for patients seen at sites that had not yet implemented EMR at the time of treatment, information on whether a repeat dose of misoprostol was given is not available. For the first 3 years of the study period, the upper gestational age limit for this regimen was 56 days. In February 2009, based on newly published data, the upper limit was increased to 63 days [8]. All patients were scheduled to return in 7 to 14 days for a postabortion evaluation. Beginning in 2007, all patients also received routine antibiotic coverage beginning on the day of the mifepristone administration. The standard antibiotic regimen was a 7-day course of doxycycline (100 mg twice a day), with an alternative regimen of one dose of azithromycin (1 g) for cases in which doxycycline was contraindicated.

Our EPM database contains information on all patients undergoing medical abortion, including patient demographics and the ultrasound-determined gestational age. We also maintain a separate electronic database of adverse events including ongoing pregnancy, aspiration for symptoms and/or retained products of conception, infection requiring hospitalization, and hemorrhage requiring transfusion.

2.2. Statistical methods

Bivariate and multivariate logistic regression were used to assess predictors of successful medical abortion. Covariates available in our data set were poverty level, race/ethnicity, gestational age, and patient age; other patient-level data were not available. Results were considered statistically significant at $p < .05$. Statistical analysis was performed using Stata/SE 11.2 (College Station, TX).

The primary outcome of interest was successful abortion. A successful abortion was defined as expulsion of the pregnancy without the need for aspiration. Patients who required aspiration for an ongoing pregnancy or symptoms such as pain or bleeding were considered to have had unsuccessful medical abortions. We queried our adverse events database to identify continuing pregnancies (those pregnancies with documented fetal growth or cardiac activity seen at the follow-up), all cases of aspiration, and hospitalization for either infection or transfusion. We cross-checked this against the list of postprocedure visits in our EPM system in order to ensure that all cases had been identified.

Institutional review board (IRB) approval was obtained from the Ethical and Independent Review Service of Independence, MO, and an exemption for analysis of the existing data was granted by the Princeton University IRB.

3. Results

3.1. Sample description

For this descriptive study, we queried our EPM database and identified 15,890 patients who had a medical abortion between April 1, 2006, and May 31, 2011. During the period under review, medical abortions were provided at 14 different clinic sites belonging to our network in one urban area, all using the same evidence-based protocol. There were 2470 (15.5%) patients who failed to return for a follow-up visit and were excluded from analysis. An additional 20 patients were excluded from the analysis due to missing data on gestational age, and a further 27 patients were excluded because they did not complete the medical abortion (these patients either changed their mind and chose a surgical abortion, were ineligible for a medical abortion because they were beyond the 63-day gestational limit, or began the regimen but did not take all of the medications). This left 13,373 patients for analysis.

Demographic characteristics of the 13,373 women who had a medical abortion between April 1, 2006, and May 31, 2011, and who returned for follow-up are shown in Table 1. Half of the women were between the ages of 18 and 24, and small proportions were under the age of 18 (4.5%) or 40 or

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Table 1
Demographic characteristics of women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (*N*=13,373)

	n	%
Gestational age (days)		
22–28	554	4.1
29–35	1080	8.1
36–42	2495	18.7
43–49	4816	36.0
50–56	3142	23.5
57–63	1286	9.6
Poverty level (% FPL)		
0–100	9679	72.4
>100	3694	27.6
Race/ethnicity		
Hispanic/Latino	6215	46.5
White	3235	24.2
African American	1263	9.5
Asian	1172	8.8
Other/declined	1487	11.1
Patient age (years)		
<18	605	4.5
18–24	6684	50.0
25–29	3317	24.8
30–34	1613	12.1
35–39	855	6.4
40+	299	2.2

older (2.2%). Nearly half of women identified as Hispanic or Latino, and 72% reported an income at or below the poverty line. The most frequent gestational age in our data set was 43 to 49 days (36.0%), and the least frequent was 22 to 28 days (4.1%).

3.2. Frequency and predictors of successful abortion

Termination of pregnancy with 200 mg of oral mifepristone followed by 800 mcg of buccal misoprostol 24–48 h later was successful among 97.7% of women who completed follow-up. Only 307 (2.3%) of the 13,373 women included in this study underwent aspiration for any reason. Specifically, 70 (0.5%) women had a continuing pregnancy, and 237 (1.8%) women required aspiration for reasons other than continuing pregnancy, most commonly due to reported symptoms of pain and/or bleeding. Data on the need for a repeat dose of misoprostol were available from a subset of women from clinics in which the EMR system was used, which included 7335 women (54.8% of the total sample). Of these 7335 women, 87 (1.2%) received a repeat dose of misoprostol.

Table 2 shows the proportion of patients requiring aspiration for ongoing pregnancy or for symptoms, such as heavy bleeding, by gestational age. The proportion with ongoing pregnancy ranged from 0.15% for those at 36 to 42 days of gestation to 1.63% at 57 to 63 days of gestation. Compared with the reference category (43 to 49 days), odds of ongoing pregnancy were greater for those at the highest gestational age. The proportion of women treated with aspiration for symptoms, not ongoing pregnancy, ranged from 0.65 to 2.49%. The incidence of hospitalization for infection or hemorrhage requiring transfusion was very low (Table 3). In total, six women required hospitalization for any reason (two women were hospitalized for infection, and four were hospitalized for transfusion), and incidence was at or below 0.1% among all gestational ages.

In a multivariate logistic regression model (Table 4), poverty level and race/ethnicity were not significant predictors of successful abortion. Certain categories of gestational age were significantly associated with success; compared with the reference category (43 to 49 days), those at 36 to 42 days of gestation had greater odds of success, whereas those at 50 to 56 days and 57 to 63 days had lower odds of success. Compared with the reference category (18 to 24), those in the middle three age groups had significantly lower odds of success, but differences for those in the youngest (17 and under) and highest (40 and older) age groups were not significant.

3.3. Loss to follow-up

A comparison of patients who completed follow-up and those who were lost to follow-up is presented in Table 5. Compared with patients at 43 to 49 days of gestation, patients at higher gestational ages were more likely to be lost to follow-up. For patients with incomes at or below the Federal Poverty Level (FPL), the odds of being lost to follow-up were greater than those above FPL. Odds of being lost to follow-up were greater for those younger than 18 (compared with those 18 to 24) and lower for those aged 40 and older.

4. Discussion

4.1. General implications

This study demonstrates that the evidence-based regimen for medical abortion (mifepristone 200 mg orally followed by home use of misoprostol 800 mcg buccally 24–48 h later) is highly effective through 63 days estimated gestational age, with an overall success rate of 97.7%. This is higher than the efficacy rates reported in two pivotal trials used in submission for FDA approval of mifepristone,[1,2] yet utilizes one-third the dose of mifepristone (200 mg rather than 600 mg) and buccal administration and home use of misoprostol rather than oral administration in the clinic. Repeat dosing of misoprostol was administered in only 1.2% of patients for whom this information is available, and given the way in which the EMR system was implemented across study sites, we can assume that this rate would be representative of the entire sample. Although efficacy is lower at later gestational ages, even in the 57- to 63-day range, this evidence-based regimen was still more effective than rates reported in the FDA-approved regimen, which sets the upper gestational age limit at 49 days. Furthermore, the rates of unsuccessful abortion in this study are lower than the rates reported in the two trials that were initially submitted to the FDA for approval of mifepristone.

Table 2
Aspiration for ongoing pregnancy, symptoms or any indication among those who completed follow-up, by gestational age.

Gestational age	Aspiration for ongoing pregnancy n (%)	OR	95% CI	Aspiration for symptoms n (%)	OR	95% CI	Aspiration for any reason * n (%)	OR	95% CI
22–28 days	4 (0.72)	2.69	0.87–8.27	11 (1.99)	1.39	0.73–2.65	15 (2.71)	1.39	0.80–2.43
29–35 days	5 (0.46)	1.72	0.61–4.83	7 (0.65)	0.45	0.21–0.98	13 (1.20)	0.61	0.34–1.10
36–42 days	4 (0.16)	0.59	0.19–1.82	25 (1.00)	0.70	0.44–1.10	30 (1.20)	0.61	0.40–0.92
43–49 days	13 (0.27)	ref		69 (1.43)	ref		94 (1.95)	ref	
50–56 days	23 (0.73)	2.72	1.38–5.39	64 (2.04)	1.43	1.01–2.02	97 (3.09)	1.60	1.20–2.13
57–63 days	21 (1.63)	6.13	3.06–12.28	32 (2.49)	1.76	1.15–2.80	58 (4.51)	2.37	1.70–3.31
Totals	70 (0.5)			237 (1.8)			307 (2.3)		

OR: odds ratio; CI: confidence interval
* This column includes 29 cases wherein reason for aspiration is unknown.

This study adds to the growing literature supporting provision of medical abortion using evidence-based regimens, and supports the conclusion that legislative efforts to restrict medical abortion to the FDA regimen are based on political goals to restrict abortion services, not efficacy or patient safety.

4.2. Limitations

Our study has some limitations. It is retrospective in nature and relies on the accuracy of our EPM database. However, review of our EPM system has shown a high degree of accuracy when compared with patient records [13]. In addition, we are not a closed system, and it is possible and even likely that some patients who experienced complications did not return to us for care. However, since many patients need to pay for aftercare obtained outside our system, but not within our system, it is more likely than not that the patients who did not return for follow-up did so because they did not feel that they needed follow-up, rather than that they were experiencing a complication. In that case, excluding them from our analysis would have tended to overestimate, rather than underestimate, the need for aspiration in our population. We based our analysis of efficacy only on those patients who did return for a follow-up visit, so we cannot exclude the possibility of additional visits or treatment elsewhere.

Loss to follow-up is common in studies of medical abortion, as many patients may determine on their own that their abortion is complete and that follow-up is not needed. The rate of loss to follow-up in this study (15.5%) is lower than loss to follow-up found in other clinical medical abortion studies, which report loss of follow-up of 18 to 45% [14–17]. We found that loss to follow-up was significantly more common among those at higher gestational ages; given that odds of success are lower among those with more advanced pregnancies, it is possible that this study underestimates the true odds of unsuccessful abortion. Loss to follow-up was significantly higher among the youngest age group and lower among the oldest age group, but as these age categories were unrelated to whether the abortion was successful, we do not believe that these differences would systematically bias our results.

Table 3
Hospitalizations for infection or transfusion in women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (*N*=13,373)

Gestational age	Patients *n*	Infections *n* (%)	Transfusions *n* (%)
22–28 days	554	0 (0.00)	1 (0.18)
29–35 days	1080	1 (0.09)	0 (0.00)
36–42 days	2495	0 (0.00)	0 (0.00)
43–49 days	4816	1 (0.02)	0 (0.00)
50–56 days	3142	0 (0.00)	3 (0.10)
57–63 days	1286	0 (0.00)	0 (0.00)
Total	13,373	2 (0.01)	4 (0.03)

4.3. Conclusion

In summary, an evidence-based regimen of mifepristone 200 mg orally followed by misoprostol 800 mcg buccally

Table 4
Factors associated with successful medical abortion in women using mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Successful *n* (%)	Unsuccessful *n* (%)	OR	95% CI
Gestational age (days)				
22–28	539 (97.3)	15 (2.7)	0.72	0.41–1.25
29–35	1067 (98.8)	13 (1.2)	1.68	0.94–3.01
36–42	2465 (98.8)	30 (1.2)	1.65	1.09–2.50
43–49	4722 (98.1)	94 (2.0)	Ref	
50–56	3045 (96.9)	97 (3.1)	0.62	0.47–0.83
57–63	1228 (95.5)	58 (4.5)	0.42	0.30–0.58
Total patients	13,066 (97.7)	307 (2.3)		
Poverty level (% FPL)				
0–100	9466 (97.8)	213 (2.2)	0.95	0.74–1.23
>100	3600 (97.5)	94 (2.5)	Ref	
Race/ethnicity				
Hispanic/Latino	6074 (97.7)	141 (2.3)	Ref	
White	3163 (97.8)	72 (2.2)	1.02	0.76–1.37
African American	1228 (97.2)	35 (2.8)	0.90	0.62–1.31
Asian	1146 (97.8)	26 (2.2)	1.02	0.67–1.57
Other/declined	1454 (97.8)	33 (2.2)	1.08	0.74–1.59
Patient age (years)				
<18	597 (98.7)	8 (1.3)	1.44	0.70–2.98
18–24	6560 (98.1)	124 (1.9)	Ref	
25–29	3233 (97.5)	84 (2.5)	0.72	0.54–0.96
30–34	1556 (96.5)	57 (3.5)	0.51	0.37–0.70
35–39	829 (97.0)	26 (3.0)	0.58	0.37–0.89
40+	291 (97.3)	8 (2.7)	0.68	0.33–1.40

OR, odds ratio; CI, confidence interval.

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Table 5
Loss to follow-up analysis among women having a medical abortion with mifepristone 200 mg and misoprostol 800 mcg buccally (N=13,373)

	Completed follow-up *n* (%)	Lost to follow-up *n* (%)	OR[a]	95% CI
Gestational age (days)				
22–28	554 (85.1)	97 (14.9)	1.00	0.79–1.25
29–35	1080 (86.3)	172 (13.7)	0.91	0.76–1.08
36–42	2495 (85.6)	419 (14.4)	0.96	0.84–1.09
43–49	4816 (85.1)	845 (14.9)	Ref	
50–56	3142 (83.0)	645 (17.0)	1.17	1.05–1.31
57–63	1286 (81.7)	288 (18.3)	1.28	1.10–.48
Poverty level (% FPL)				
0–100	9679 (83.7)	1887 (16.3)	1.24	1.12–1.38
>100	3694 (86.5)	579 (13.6)		
Race/ethnicity				
Hispanic/Latino	6215 (84.1)	1173 (15.9)		
White	3235 (83.4)	643 (16.6)	1.05	0.95–1.17
African American	1263 (82.8)	262 (17.2)	1.10	0.95–1.27
Asian	1172 (91.1)	115 (8.9)	0.52	0.43–0.64
Other/declined	1487 (84.5)	273 (15.5)	0.97	0.84–1.12
Patient age (years)				
<18	605 (80.0)	152 (20.0)	1.42	1.17–1.71
18–24	6684 (84.9)	1186 (15.1)		
25–29	3317 (83.7)	646 (16.3)	1.10	0.99–1.22
30–34	1613 (84.8)	289 (15.2)	1.01	0.88–1.16
35–39	855 (84.6)	156 (15.4)	1.03	0.86–1.23
40+	299 (89.0)	37 (11.0)	0.70	0.49–0.99

OR, odds ratio; CI, confidence interval.
[a] OR represents odds of being lost to follow-up.

48–72 h later is safe and effective through 63 days estimated gestational age. Further, need for aspiration for any reason was low, the chance of needing aspiration increased with gestational age at the time of medical abortion, and the frequency of hospitalization was rare. This study reinforces the safety and efficacy of the evidence-based regimen for medical abortion, and contributes to the evidence against restrictions that require use of the FDA-approved regimen.

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Exhibit 35

2019 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to FDA (Mar. 29, 2019)

Citizen Petition

March 29, 2019

The undersigned submit this petition to request the Commissioner of Food and Drugs to: (I) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (II) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS), and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

A. Action Requested

I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.

Current language and requested language for the Mifeprex Label and the Mifeprex *Risk Evaluation and Mitigation Strategy* (REMS) are included in Exhibit A.[1] Requests include:

A. Indications and Usage. Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

C. Contraindications. Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

D. Adverse Event Reporting. Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

[1] Other documents will require corresponding modifications, including the Mifeprex Medication Guide, Prescriber Agreement Form, and Patient Agreement Form.

E. Additional studies. The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

A. Retain the Mifeprex REMS.

B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

   a. The "TelAbortion" Direct-to-Consumer Mifeprex Study

   b. The Mifeprex through Pharmacy Dispensing Study

   c. Beyond the Current Studies

2. Mifeprex Prescribers Should be Certified.

B. Statement of Grounds

I. RESTORE AND STRENGTHEN ELEMENTS OF THE MIFEPREX REGIMEN AND PRESCRIBER REQUIREMENTS APPROVED IN 2000.[2]

A. Indications and Usage. Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days' gestation.

In 2016, FDA increased the maximum gestational age for Mifeprex use for abortion from 49 days (7 weeks) to 70 days (10 weeks), and changed the method of administration of misoprostol from oral to buccal (*i.e.*, in the cheek pouch). However drug-induced abortion[3] regimens demonstrate an increase in complications and failures after 49 days' gestation.

In a 2011 study of thousands of patients, the majority of whom had a drug-induced abortion using what is now the Mifeprex regimen, the rate of infection and the rate of failure requiring surgical intervention increased with gestational age.[4] The American College of Obstetricians and Gynecologists (ACOG) has stated: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[5]

Further, a 2015 meta-analysis examined all the existing publications on buccal administration of misoprostol, 20 studies in all, from November 2005 through January 2015. The failure rate of the buccal misoprostol regimen increased as the gestational age

[2] The FDA approved Mifeprex for use in the United States on September 28, 2000, with safeguards considered necessary to ensure patient safety. The drug's initial approval was for termination of pregnancy, in a regimen with misoprostol, through 49 days of pregnancy. FDA significantly modified the drug's label at the application of the manufacturer, Danco Laboratories, in 2016, extending approved use to 70 days of pregnancy. Additional changes included: a new dosage of both Mifeprex and misoprostol; permitting home administration of Mifeprex and misoprostol; a new route of administration for the misoprostol (buccal, in the cheek pouch); permitting non-physicians to become certified prescribers; a decrease from 3 to 1 mandatory office visits by the patient; and reduced reporting requirements. U.S. Gov't Accountability Office, GAO-18-292, Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf; Mifeprex Medication Guide, https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.

[3] The terms "Medication abortion," "medical abortion," "chemical abortion," and "drug-induced abortion" [or termination of pregnancy] share the same meaning and refer to the use of abortion-inducing drugs, rather than surgery, to induce abortion. The current FDA-approved regimen uses two drugs, mifepristone (a.k.a. Mifeprex or RU-486) and misoprostol.

[4] Mentula MJ, Niinimaki M, Suhonen S, Hemminki E, Gissler M, and Heinkinheimo O, *Immediate Adverse Events after Second Trimester Medical Termination of Pregnancy: Results of a Nationwide Registry Study,* Human Reproduction 26(4), 927-932 (2011).

[5] ACOG Practice Bulletin 143: *Medical Management of First-Trimester Abortion*, p. 5 (Mar. 2014, reaffirmed 2016).

increased, especially at gestational ages greater than 49 days.[6] The current FDA label also acknowledges this fact.[7]

Given the serious risks of failure, hemorrhage, infection, and ongoing pregnancy that increase as pregnancy advances, the gestational limit for the Mifeprex regimen should have never been increased.

B. Dosage and Administration.

1. Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

The 2000 Mifeprex regimen required Mifeprex to be "provided by or under the supervision of a *physician*" who meets qualifications discussed in this section below.[8] However, the 2016 regimen replaced "physician" with "healthcare provider," thus permitting non-physicians to apply to be certified prescribers.[9] Given the regimen's serious risks, the FDA should limit the ability to prescribe and dispense Mifeprex to qualified, licensed physicians. Physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age.

The current Mifeprex Risk Evaluation and Mitigation Strategy (REMS), discussed in Section II below, continues to provide that "Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, *by or under the supervision of a certified prescriber*."[10] Yet, abortion providers today are promoting and performing "telemedicine abortions," where the certified prescriber's "supervision" of the dispensing of Mifeprex is limited to a videoconference.[11] This practice demonstrates a flagrant disregard for FDA safeguards.

To ensure true supervision, the FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex. This requirement would be consistent with other requirements in the Mifeprex Label and REMS.

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[6] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21.
[7] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[8] Mifeprex 2000 label, Dosage and Administration, emphasis added.
[9] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[10] Mifeprex 2016 REMS, emphasis added, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.
[11] *See* Planned Parenthood Releases New Educational Video on Telemedicine Abortion (Feb. 6, 2018), https://www.plannedparenthood.org/about-us/newsroom/press-releases/planned-parenthood-releases-new-educational-video-on-telemedicine-abortion.

In the Mifeprex Label, the FDA emphasizes that "Mifeprex is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)" because of the drug's "risks of serious complications." In a bold-print box, the FDA states that before prescribing Mifeprex, a provider must inform a patient: about the risks of serious events; whom to call and what to do if certain symptoms occur; and to take the Medication Guide with her if she visits an emergency room or healthcare provider who did not prescribe Mifeprex, so that she receives appropriate, informed care.[12]

Further, a provider must sign a Provider Agreement Form, attesting that he or she can:

- **Assess the duration of pregnancy accurately.**[13] Failures and complications of Mifeprex abortion increase with increasing gestational age. Mifeprex use is approved through 70 days' gestation.[14] FDA should strengthen this requirement by mandating that gestational age be accurately assessed by ultrasound in order to both ensure compliance with FDA restrictions and adequately inform the patient of gestational age-specific risks, which rise with increasing gestational age.

- **Diagnose ectopic pregnancies**[15] (*i.e.,* extrauterine pregnancy; pregnancy outside the uterus), which Mifeprex cannot end. When an ectopic pregnancy progresses, it can rupture the fallopian tube, causing bleeding, severe pain, or death. If a woman with an extrauterine pregnancy is given Mifeprex, she may believe the symptoms for ectopic pregnancy are simply the side effects of drug-induced abortion, which are similar. As of December 31, 2017, at least 97 women with ectopic pregnancies in the United States had been given Mifeprex.[16] Of these women, at least two bled to death from an undiagnosed ectopic pregnancy.[17] They likely did not recognize that their cramps, abdominal pain, and perhaps vaginal bleeding were dangerous—not side effects expected in a Mifeprex abortion.[18]

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[12] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[13] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.
[14] *See* Section I.A, *supra.*
[15] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.
[16] Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2017, RCM # 2007-525, NDA 20-687, https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM603000.pdf).
[17] *Id.*
[18] Donna Harrison, M.D. & Michael J. Norton Testimony before the Iowa Board of Medicine, p. 3 (Aug. 21, 2013), *citing* Postmarket Drug Safety Information for Patients and Providers, Questions and Answers on Mifeprex,

- **Provide surgical intervention if needed, or has made plans to provide such care through others.**[19] He or she must assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[20]

Clearly, a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional contraindications (*i.e.*, circumstances that make a treatment or medication *unadvisable*) to Mifeprex use. These physical contraindications include pelvic infections, ovarian masses, cardiac arrhythmias, and liver abnormalities.[21] A physician bears responsibility to diagnose and rule out contraindications prior to Mifeprex use. It is inadequate to entrust this critical care to another healthcare provider who is not trained in diagnosis. Further, a healthcare provider who is not physically accessible to a patient cannot provide adequate follow-up care to patients, as required by the FDA Mifeprex regimen.

Thirty-four states permit only physicians to prescribe Mifeprex,[22] with nineteen states requiring the provider to be physically present with the patient.[23] For example, the law in Alabama states that the physical presence and care of a physician are necessary because "the failure and complications from medical abortion increase with advancing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because abortion-inducing drugs do not treat ectopic pregnancies but rather are contraindicated in ectopic pregnancies."[24]

Lawmakers in these states recognize that abortion providers cannot diagnose contraindications and cannot adequately care for their patients through a videoconference. Fundamentally, telemedicine "may be legitimate when it comes to discrete, document-based tasks such as reading X-rays," but it "is not the standard of care when it comes to abortion or the management of miscarriage."[25]

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https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm492705.htm.

[19] Mifeprex Prescriber Agreement Form, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_Prescriber_Agreement_Form.pdf.

[20] *Id.*

[21] Harrison & Norton Testimony, p. 3.

[22] Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, Vol. 21, p. 44 (2018).

[23] *Id*.

[24] Ala. Code § 26-23E-7.

[25] Harrison & Morton Testimony, p. 19.

2. The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

The 2016 regimen significantly diminished doctor-patient interaction. While the 2000 Mifeprex label required three patient visits with the abortion provider, women may now obtain Mifeprex at a clinic and self-administer it at home. They are no longer required to return to the clinic for the administration of misoprostol, which prevents abortion providers from ensuring that they take the drugs at the correct times. Further, providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit,[26] increasing the threat that Rh-negative patients will not receive administration of Rhogam, which is necessary to prevent serious risks in subsequent pregnancies.

The 2016 regimen directs that patients be given or prescribed misoprostol to take 24 to 48 hours after taking Mifeprex. However, without monitoring, a patient may take misoprostol before 24 hours have passed since she consumed Mifeprex, rendering the regimen ineffective and increasing the likelihood that she will experience a failed drug-induced abortion and require surgery.

Using buccal misoprostol sooner than 24 hours after administering mifepristone leads to a significantly increased failure rate. In one study investigating the timing of buccal misoprostol after mifepristone, nearly one out of every three to four women who took buccal misoprostol shortly after mifepristone failed to abort.[27] The failure rate ranged from 27% to 31%, depending on the pregnancy gestation.[28] Given these results, the authors of this study strongly recommended that buccal misoprostol not be taken immediately after mifepristone because of the very high abortion failure rate.[29] However, with home administration of misoprostol, healthcare providers have no control over when their patients consume the drug.

A woman may also choose to swallow misoprostol rather than keep the pill between her cheek and gum for 30 minutes, converting a "buccal" administration into an "oral" administration. An oral administration of misoprostol following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy.

Further, waiting until 24 hours after Mifeprex to administer misoprostol does not guarantee success, and the failure rate of buccal misoprostol is higher than that under the 2000 regimen. A comprehensive systematic review and meta-analysis of the existing

[26] *See* Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[27] Lohr PA, Reeves MF, Hayes JL, Harwood B, Creinin MD, *Oral Mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study*, Contraception 76 (2007) 215-220.
[28] *Id.*
[29] *Id.*

studies of the 2016 regimen found that women who take misoprostol earlier than 48 hours after mifepristone are more likely to fail the regimen.[30]

Under the 2000 regimen, doctors were also able to provide care to patients during the most challenging and painful time in the drug-induced abortion. According to the World Health Organization, up to 90% of women will abort within 4-6 hours after taking misoprostol.[31] The 2000 regimen permitted a patient to be in a clinic for this period of time, during which she would be under the observation and care of medical personnel. This observation period is for "both patient safety and compassion. . . . This is the time when women should be in a place where their bleeding can be monitored, their vital signs can be observed by trained medical personnel, and they can receive sufficient pain medication during the most difficult part of the expulsion."[32]

Abortion complications are also more frequent when women abort at home, without the oversight of a healthcare provider. A 2018 combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden determined that "[t]he complication frequency [of drug-induced abortion] was significantly higher among women <7 gestational weeks who had their abortions *at home*."[33]

In-person contact with a healthcare provider is critical to post-abortion care as well. Abortion providers should perform a "follow-up [physical exam] after the use of mifepristone in order to confirm abortion and rule out life-threatening infection."[34] Before FDA approved the 2016 regimen, the follow-up visit was considered "very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred."[35] In fact, the 2000 label provided that "[e]ach patient must understand the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex."[36] ACOG's current policy explains that:

> Women are not good candidates for medical abortion if they … desire quick completion of the abortion process [or] are not available for follow-up contact or evaluation….[37]

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[30] Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet.Gynecol 126 (1) July 2015 12-21.
[31] World Health Organization, *Safe Abortion: Technical and Policy Guidance for Health Systems* 45.
[32] Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015) ¶ 136.
[33] Carlsson I, Breding K, and Larsson PG, *Complications Related to Induced Abortion: a Combined Retrospective and Longitudinal Follow-up Study*, BMC Women's Health (2018) 18:158, p. 4 (emphasis added).
[34] Harrison & Norton Testimony, p. 18.
[35] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[36] Mifeprex 2000 label, Information for Patients.
[37] ACOG Practice Bulletin 143, p. 6.

In addition to ensuring for all drug-induced abortion patients that the uterus has been emptied of retained tissue and that they are not suffering from infection, the follow-up examination is particularly critical for Rh-negative patients. These patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without follow-up, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.[38]

Nonetheless, abortion advocates strongly supported the reduction in required visits, and continue to advocate for the elimination of direct provider-patient contact. Gynuity Health Projects (an organization that "has been at the forefront of efforts to increase women's access to medical abortion in settings throughout the world")[39] has conducted at least three domestic and five international studies[40] on eliminating pelvic ultrasound or exam after drug-induced abortion. Following one study, researchers determined that "[s]emi-quantitative pregnancy tests … could be used in lieu of transvaginal ultrasound and/or serum hCG at clinic-based follow-up or by women themselves for home-based follow-up."[41]

In a more recent study, researchers asserted that the "common practice of scheduling a clinical contact after every medical abortion may not be necessary to ensure safety; enabling patients to determine for themselves whether or not a contact is needed can be a

[38] ACOG Practice Bulletin 181*: Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).

[39] *See* Gynuity Health Projects, Medical Abortion, https://gynuity.org/programs/medical-abortion. Founded by Beverly Winikoff, M.D, M.P.H., in 2003, Gynuity outlines on its "Medical Abortion" page the organization's research projects, including efforts to: "Develop innovative service delivery systems through telemedicine; Simplify and de-medicalize medical abortion services; Expand access to medical abortion in the 1st and 2nd trimesters of pregnancy; Conduct clinical research to develop new abortion medications; Develop a 'missed menses pill'/menstrual regulation method; Develop additional clinical indications for mifepristone." Gynuity has launched a "coalition to expand access to mifepristone in the United States," co-created a "medical abortion commodities database," "introduce[d] medical abortion in new settings," "incorporate[ed] new clinical evidence into service guidelines," and "expanded medical abortion access through education and local champions."

[40] *See*, *e.g., Self-Assessment of Medical Abortion Outcome Using Serial Multi-level Pregnancy Tests* [NCT02570204] (Sept. 2015 – Dec. 2016), https://www.clinicaltrials.gov/ct2/show/NCT02570204?term=Self-Assessment+of+Medical+Abortion+Outcome+Using+Serial+Multi-level+Pregnancy&rank=1; *Exploring the Role of At-home Semi-Quantitative Pregnancy Tests for Medical Abortion Follow-up* [NCT01150279] (Aug. 2009 – May 2014), https://www.clinicaltrials.gov/ct2/show/NCT01150279?term=Exploring+the+Role+of+At-home+Semi-Quantitative+Pregnancy+Tests+for+Medical+Abortion+Follow-up&rank=1; *De-Medicalizing Mifepristone Medical Abortion* [NCT00120224] (May 2005 – Apr. 2007), https://www.clinicaltrials.gov/ct2/show/NCT00120224?term=De-Medicalizing+Mifepristone+Medical+Abortion&rank=1.

[41] Lynd K, et al., *Simplified Medical Abortion Using a Semi-Quantitative Pregnancy Test for Home-Based Follow-up,* Int J Gynaecol Obstet. 2013 May;121(2):144-8.

reasonable approach."[42] They reached this conclusion even with 26% of participants failing to provide sufficient follow-up information.[43]

Gynuity researchers also conducted a recent systematic review of existing studies on "the accuracy and acceptability of a strategy for identifying ongoing pregnancy after medical abortion treatment using a low-sensitivity pregnancy test (LSPT)." While the researchers acknowledged that "the LSPT strategy had *moderate* sensitivity for identifying ongoing pregnancy" and "the LSPT itself had a limited role in the detection of treatment failures [*i.e.*, ongoing pregnancy] in the studies," they stated that the "LSPT strategy shows promise for reducing the need for in-person follow-up after medical abortion. A range of home-based options should be validated to meet the varied needs of women and abortion providers in diverse settings."[44]

In reality, a de-emphasis on follow-up care increases risks of post-abortion complications. As discussed above, the 2000 regimen's requirement that women return approximately 14 days after ingesting mifepristone was considered necessary to ensure that all pregnancy tissue had been passed.[45] This determination is crucial, because retained pregnancy tissue can lead to continued bleeding and serious intrauterine infections. The return visit permits healthcare providers to ensure that a patient is not experiencing these or other complications from the abortion procedure, and that Rh negative patients are administered Rhogam to protect future pregnancies.

Abortion advocates argue that three clinic visits make accessing abortion-inducing drugs more difficult for patients with transportation challenges; however, as noted above, ACOG acknowledges that drug-induced abortion is *contraindicated* for patients who "are not available for follow-up contact or evaluation."[46] Surgical abortion is a better choice for these patients, because it "[d]oes not require follow-up in most cases."[47]

Drug-induced abortion is a longer process that requires more attention and care from healthcare providers. Three visits to a physician in the interest of patient safety should not be sacrificed for the convenience of healthcare providers or even their patients.

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[42] Raymond EG, et al., *Self-assessment of Medical Abortion Outcome Using Symptoms and Home Pregnancy Tests*, Contraception 97 (2018) 324-28.
[43] *Id.*
[44] Raymond EG, et al., *Low-sensitivity Urine Pregnancy Testing to Assess Medical Abortion Outcome: A Systematic Review*, Contraception (2018), https://doi.org/10.1016/j.contraception.2018.03.013 (emphasis added).
[45] Mifeprex 2000 label, Day 14: Post-Treatment Examination.
[46] ACOG Practice Bulletin 143, p. 6.
[47] *Id*.

C. Contraindications. Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

The 2000 Mifeprex Label stated:

> Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.[48]

This critical language was excluded from the 2016 Mifeprex Label. Yet, studies comparing the outcome of surgical versus drug-induced abortion "have clearly demonstrated that Mifeprex abortions have a greater risk of hemorrhage, infection, continued pregnancies, retained tissue and need for emergency reoperation than surgical abortions."[49] ACOG acknowledges that "[c]ompared with surgical abortion, medical abortion takes longer to complete, requires more active patient participation, and is associated with higher reported rates of bleeding and cramping," and has lower success rates.[50]

Drug-induced abortion is optional. If a woman does not meet the criteria necessary to use abortion-inducing drugs, then surgical abortion is still an option. For women with transportation difficulties, an abortion provider can complete surgical abortion "in a predictable period of time," and the procedure "[d]oes not require follow-up in most cases."[51]

Efforts to promote abortion-inducing drugs to women in rural areas where access to emergency medical care is scarce are detrimental to women's health. It is better for a patient in a remote region to have a surgical abortion, "which requires a single visit, and is less likely to result in serious or life-threatening complications."[52]

[48] Mifeprex 2000 label, Contraindications.
[49] Harrison Aff. ¶ 115.
[50] ACOG Practice Bulletin 143, p. 3 & Box 1.
[51] *Id.*
[52] Harrison & Norton p. 9.

D. Adverse Event Reporting. Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

The 2016 regimen dramatically reduced accountability for Mifeprex providers by limiting adverse event reporting (AER) requirements, a critical safety mechanism.[53] While prescribers were required to report any serious adverse event associated with Mifeprex under the 2000 label, they are now required to report only deaths associated with Mifeprex.

Even with the 2000 regimen requirements, collecting accurate and complete adverse event information was highly difficult. Adverse events were often not reported or were interpreted by emergency health care providers as the results of spontaneous abortion.[54] The Mifeprex label instructs prescribers to "[a]dvise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe Mifeprex, so that the provider knows that she is undergoing a medical abortion."[55] Yet, many Mifeprex prescribers violate FDA protocol, instructing their patients to lie to emergency medical personnel. The organization Aid Access instructs patients that if they need to go to an emergency room:

> You do not have to tell the medical staff that you tried to induce an abortion; you can tell them that you had a spontaneous miscarriage. Doctors have the obligation to help in all cases and know how to handle a miscarriage. The symptoms of a miscarriage and an abortion with pills are exactly the same and the doctor will not be able to see or test for any evidence of an abortion, as long as the pills have completely dissolved.[56]

Such deception prevents emergency healthcare providers from appropriately caring for their patients, and further decreases the likelihood that adverse events will be reported.

With reduced AER reporting requirements under the 2016 label, what was previously difficult is now virtually impossible. The FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events. AERs are the only objective means by which FDA has any data whatsoever on the effects of the

[53] Mifeprex 2016 label.
[54] *See* GAO-18-292, pp 24-25.
[55] Mifeprex 2016 label, https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[56] Aid Access, *How do you know if you have complications, and what should you do?*, https://aidaccess.org/en/page/459/how-do-you-know-if-you-have-complications-and-what-should-you-do.

Mifeprex regimen on women, and the voluntary and minimal nature of the current AERs means that FDA has no accurate information about the actual number of women injured by drug-induced abortion, or the nature of complications caused by this drug.

After prescribing Mifeprex and misoprostol, certified prescribers should at minimum be required to report the following directly to the FDA Medwatch reporting system, copying Danco Laboratories: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications. Detailed information must also be included, such as pulse, blood pressure, temperature, pre- and post-transfusion hemoglobin/hematocrit, white blood count, number of units of blood transfused, surgeries, and any other pertinent laboratory or hospital course information, as well as emergency room and hospital discharge diagnoses.

Further, FDA should provide guidance to emergency healthcare providers and physicians responsible for treating complications so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage. The guidance should also instruct these providers on how to report adverse events.[57]

The abysmal quality of the current AERs received from Danco Laboratories shows the lack of concern that Danco has demonstrated for the safety of the women who have undergone drug-induced abortion. Responsible reporting is a fundamental safety mechanism that should not be sacrificed in the interest of convenience for abortion providers.

E. Additional Studies. The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

Mifeprex was approved for use in the pediatric population in 2000 after the FDA waived, without explanation, the requirement for studies in the pediatric population. The developmental stage of puberty involves a complex interplay of both progesterone and estrogen effects on the developing female reproductive system. The use, and especially the potential multiple use, of Mifeprex, which is a powerful progesterone blocker, is

[57] The Self-Induced Abortion Legal Team has created a document titled "Self-Induced Abortion and the Law: What Emergency Room Staff Need to Know." This document heavily emphasizes patient privacy requirements, including the penalties that healthcare providers may face if they disclose patient information. While these concerns are valid, emergency healthcare providers should also have training on public health reporting requirements and how such reporting does not violate HIPAA or other laws regarding patient privacy. *See,* https://www.sialegalteam.org.

likely to significantly impact the developing reproductive system of the adolescent female.[58] It is irresponsible to allow the continued uninvestigated use of Mifeprex in the pediatric female population[59] without requiring long-term studies on the impact of Mifeprex use on pubertal development.

More than one out of every three abortions in the U.S. is a repeat abortion.[60] The repeat use of Mifeprex has been associated in some studies with adverse reproductive health outcomes in future wanted pregnancies.[61] This concern requires further study.

The adverse events of hemorrhage, retained tissue, and infection are common after Mifeprex use. The hemorrhage is often significant enough to warrant transfusion. When patients lack access to emergency medical facilities, such complications could easily translate to deaths. Thus a study of deaths and of severe hemorrhages requiring transfusion should be done to compare outcomes in women with and without access to emergency medical facilities.

II. RETAIN THE MIFEPREX RISK EVALUATION AND MITIGATION STRATEGY (REMS), AND CONTINUE LIMITING THE DISPENSING OF MIFEPREX TO PATIENTS IN CLINICS, MEDICAL OFFICES, AND HOSPITALS, BY OR UNDER THE SUPERVISION OF A CERTIFIED PRESCRIBER.

A. Retain the Mifeprex REMS.

Mifeprex, when used for abortion, is subject to a Food and Drug Administration (FDA) *Risk Evaluation and Mitigation Strategy* (REMS) with *elements to assure safe use* (ETASU). FDA determined that the Mifeprex REMS is necessary to ensure the safety and efficacy of the drug, because it carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The approved Mifeprex regimen includes the use of another potent drug, misoprostol, which carries its own risks.

Under the Mifeprex REMS with ETASU, a healthcare provider must be certified to prescribe Mifeprex by reviewing the prescribing information and completing a

[58] Arain M, et al., *Maturation of the adolescent brain*, Neuropsychiatric Disease and Treatment, 2013:9 449-461.
[59] Because of their immaturity, minors are also less likely to understand the importance of following prescriber instruction or of recognizing when they need to seek emergency medical treatment.
[60] Jones R, et al., *Which Abortion Patients Have Had a Prior Abortion? Findings from the 2014 U.S. Abortion Patient Survey*, Journal of Women's Health, DOI: 10.1089/jwh.2017.6410 (2014).
[61] Fang L, et al., *Repeated Abortion Affects Subsequent Pregnancy Outcomes in BALB/c Mice*, PLoS ONE 7(10): e48384. doi:10.1371/journal.pone.0048384 (2012).

"Prescriber Agreement Form," attesting that they can: assess the duration of pregnancy accurately; diagnose ectopic pregnancies; and provide surgical intervention in cases of incomplete abortion or severe bleeding, or designate someone else to provide that care. Further, they must agree to follow the guidelines for use of Mifeprex.

The REMS also requires Mifeprex to "be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber." Mifeprex may not be distributed or dispensed through retail pharmacies. Also, a patient must sign a "Patient Agreement Form" and be fully informed of the risks by a certified prescriber. She must receive the Mifeprex Medication Guide, informing her that she needs a "follow-up assessment" 7 to 14 days after she has taken Mifeprex to ensure that she is well and has terminated her pregnancy.[62]

The REMS remains the lone safeguard to monitor and mitigate the risks of death and adverse events from the Mifeprex regimen. Gynuity Health Projects and researchers from the University of California, San Francisco (UCSF) obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They intend to use the results of these studies to press for the elimination of the Mifeprex REMS.[63] [See Section II.B, below.]

The Mifeprex Medication Guide acknowledges that serious risks accompany FDA's approved regimen for drug-induced abortion, which includes the use of Mifeprex and another potent drug, misoprostol. The document improperly downplays the risks, however, stating that "*rarely*, serious and potentially life-threatening bleeding, infections, or other problems can occur following . . . medical abortion." Specifically, "in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure."[64]

In fact, the internationally used criteria for reporting complications from drugs demonstrate that complications from drug-induced abortions are common, not rare. The Council for International Organizations of Medical Sciences (CIOMS)[65] defines the word

[62] GAO-18-292, pp 4-7 (2018); Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf; 21 U.S.C. § 355-1; Mifeprex Medication Guide, https://www.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.
[63] *See* Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (July 17, 2018) p. 14.
[64] Mifeprex Medication Guide, https://ww.w.fda.gov/downloads/Drugs/DrugSafety/ucm088643.pdf.
[65] The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, nonprofit organization established jointly by WHO and UNESCO in 1949. Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. In 2013, the membership of CIOMS included 49 international, national, and associate member organizations, representing many of the biomedical disciplines, national academies of sciences, and medical research councils.

"rare" in adverse event reporting as an event that happens in between "1 out of 1,000" to "1 out of 10,000" uses. "Common" is the uniform term used for events that happen in between "1 out of 10" to "1 out of 100" uses.[66] Given that "about 1 out of 100 women" using Mifeprex/misoprostol require surgery, serious complications are common, not rare.[67]

Also, as discussed in Section I.C above, Mifeprex abortions carry greater risks than surgical abortions.[68] A study of over 42,000 women in Finland who had abortions from 2000 to 2006 found that "overall, medical abortion had roughly four times the rate of adverse events than surgical abortion, and hemorrhaging was experienced by 16 percent of medical abortion patients compared with 2 percent of surgical abortion patients."[69]

A combined retrospective and longitudinal follow-up study of complications related to induced abortion in Sweden published in 2018 determined that the share of complications related to drug-induced abortions at less than 12 weeks *increased* significantly during 2008-2015 without an evident cause. The increase was from 4.2% in 2008 to 8.2% in 2015, with incomplete abortion as the most common complication related to drug-induced abortions at less than 12 weeks.[70]

Abortion advocates are also attacking the REMS by advocating for mifepristone use in spontaneous miscarriage management. In a small recent study, researchers compared the efficacy and safety of using mifepristone with misoprostol for the management of early miscarriages to using misoprostol alone.[71] Notably, 6-10% of study participants had a gestational age of "4-5 weeks gestation."[72] It is not clear from the authors how participants of that gestational age could meet the published guidelines for diagnosis of non-viable pregnancy recently published by the Society of Radiologists in Ultrasound multispecialty consensus panel.[73] The panel requires the crown-rump length cutoff to 7 mm for embryos without a heartbeat and the mean sac diameter cutoff to 25 mm for

[66] CIOMS training manual on medicine safety, http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf.
[67] *See* Mifeprex Medication Guide; CIOMS training manual on medicine safety, *supra.*
[68] *See* Harrison Aff. ¶ 115; ACOG Practice Bulletin 143, p. 3 & Box 1.
[69] GAO-18-292, p. 25, *discussing* Niinimaki M, et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy,* Obstetrics & Gynecology, vol. 114, no. 4 (October 2009): 795-804.
[70] Carlsson I, Breding K, and Larsson PG, *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study*, BMC Women's Health (2018) 18:158.
[71] Schreiber CA, et al, *Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss*, N Engl J Med 2018; 378:2161-70.
[72] *Id.* Table 1.
[73] Doubilet PM, Benson CB, Bourne T, et al., *Diagnostic criteria for nonviable pregnancy early in the first trimester*, N Engl J Med 2013; 369:1443–1451.

"empty" sacs, in order to minimize interventions that "interrupt a pregnancy that otherwise would have had a normal outcome."[74]

The authors admit that the study "was not powered to show differences between groups in the proportions of serious adverse events,"[75] an important consideration prior to recommending a change in spontaneous abortion management protocols. Yet, the authors incorrectly stated "such events were rare."[76] Table 3 gives a total number of serious adverse events as 3.4% for the mifepristone pretreatment group, and 2.0% for the misoprostol alone group.[77] Under the CIOMS criteria for reporting complications from drugs, discussed above, the rate of 2%-3.4% of adverse events in each study arm demonstrates clearly that adverse events are common, not rare, in both misoprostol alone and mifepristone + misoprostol miscarriage management.

Further, the Mifeprex + misoprostol arm raises a concern about the need for further study of adverse events, especially hemorrhage. Mifepristone is known to inhibit endometrial hemostasis (*i.e.*, arrest of bleeding),[78] as demonstrated by many reports of hemorrhage with transfusions reported to the FDA after use of mifepristone and misoprostol for elective abortions.[79]

Of additional concern is the vaginal route of administration of misoprostol. After reports of overwhelming sepsis following vaginal administration of misoprostol, Planned Parenthood changed the route of administration of misoprostol from vaginal to buccal,[80] with subsequent decrease in reported infections. Animal studies have demonstrated that both mifepristone[81] and misoprostol[82] can profoundly suppress innate immunity and the ability to fight infections.

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[74] Hu M, Poder L, Filly R, *Impact of New Society of Radiologists in Ultrasound Early First-Trimester Diagnostic Criteria for Nonviable Pregnancy*, J Ultrasound Med 2014; 33:1585–1588.
[75] Schreiber, *supra* p. 2168.
[76] *Id.*
[77] *Id.* p. 2169.
[78] Miech RP, *Pathopharmacology of excessive hemorrhage in mifepristone abortions*, Ann Pharmacother 2007 Dec; 41(12):2002-7.
[79] Gary MM, Harrison DJ. "Analysis of severe adverse events related to the use of mifepristone as an abortifacient." Ann Pharmacother. 2006 Feb;40(2):191-7; Food and Drug Administration "Mifepristone U.S. Postmarketing Adverse Events Summary" 2011, https://www.minnpost.com/sites/default/files/attachments/Mifeprex_April2011_AEs.pdf.
[80] Fjerstad M, Trussell J, Sivin I, Lichtenberg ES, Cullins V, *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, N Engl J Med 2009; 361:145-51.
[81] Sternberg EM, Hill JM, Chrousos GP, Kamilaris T, Listwak SJ, Gold PW, Wilder RL, *Inflammatory mediator-induced hypothalamic-pituitary-adrenal axis activation is defective in streptococcal cell wall arthritis-susceptible Lewis rats*, Proc Natl Acad Sci U S A. 1989 Apr;86(7):2374-8; Miech RP, *Pathophysiology of mifepristone-induced septic shock due to Clostridium sordellii*, Ann Pharmacother. 2005 Sep;39(9):1483-8. Epub 2005 Jul 26.
[82] Aronoff DM et al., *Misoprostol impairs female reproductive tract innate immunity against clostridium sordellii*, 180 J. Immunol. 8222-8230 (2008).

Despite the clear methodological errors, including a failure to accurately diagnose fetal death according to accepted criteria as well as lack of adherence to the stated inclusion criteria, and despite the absence of power to evaluate safety, abortion advocates are calling for the routine use of mifepristone to manage spontaneous miscarriages.[83] Any change in spontaneous miscarriage management with mifepristone should require an FDA New Drug Application (NDA) with two randomized controlled trials (RCTs) comparing the arms of mifepristone and misoprostol, misoprostol alone, surgical management, and expectant management. Without blinded RCTs to evaluate not only efficacy but also safety, it is premature to remove the REMS for Mifeprex to facilitate mifepristone access for spontaneous miscarriage management.

Despite the presence of serious risks and contraindications to the Mifeprex regimen, Gynuity, the University of California, San Francisco (UCSF), and other abortion advocates want the FDA to eliminate the remaining safeguards that were enacted to ensure the safety and efficacy of Mifeprex. They are pursuing their goals through publication, advocacy, litigation,[84] and/or controversial research enabled by FDA.[85]

Further, as Section II.B below explains, lifting the REMS is only the starting point for abortion advocates.

B. Continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

1. Mifeprex should be dispensed only in clinics, medical offices, and hospitals.

The Mifeprex REMS requires that Mifeprex "be dispensed to patients only in clinics, medical offices and hospitals, by or under the supervision of a certified prescriber." That prescriber must be capable of assessing the duration of a pregnancy accurately, diagnosing ectopic pregnancies, and providing or referring for surgical intervention in cases of incomplete abortion or hemorrhaging.[86]

Abortion advocates, however, want the FDA to permit healthcare providers to prescribe Mifeprex to pregnant patients over the Internet or phone, with the drug available at pharmacies or through the mail, and through advance provision (*i.e.*, before a patient is pregnant). Eliminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls. Healthcare providers

[83] Molly Walker, *Mifepristone: Better for Managing Early Miscarriage*, Medpage Today, (June 6, 2018), https://www.medpagetoday.com/obgyn/pregnancy/73336.
[84] *Chelius v. Azar*. CIV. NO. 1:17-cv-00493-DKW-KSC (Dist. Ct. HI 2018).
[85] See Section II.B, below.
[86] Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.

prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs.[87] Further, as discussed above, Rh-negative patients must be administered Rhogam in order to prevent Rh isoimmunization in subsequent pregnancies. Without direct patient contact, women will not receive the Rhogam after the abortion, greatly increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies.[88] [See Section I.B.2, *supra*.]

Telemedicine abortion further distances women from the practitioners responsible for caring for them, and approval by FDA would further absolve abortion providers of responsibility for the well-being of their patients. Promoting telemedicine abortion to women and adolescent girls in rural areas with limited access to healthcare is extremely dangerous—they will have little recourse if they face known and predictable emergency complications such as severe hemorrhage.[89]

Nonetheless, Gynuity Health Projects and researchers from UCSF obtained approval from FDA through Investigational New Drug Applications (INDs) to conduct studies that *do not* comply with the Mifeprex REMS. They will use the results of these studies to press for the elimination of the Mifeprex REMS.

a. The "TelAbortion" Direct-to-Consumer Mifeprex Study

Gynuity Health Projects is the sponsor of the study "Feasibility of Medical Abortion by Direct-to-Consumer Telemedicine."[90] Gynuity filed an IND with the FDA.[91] The status is listed as "recruiting," with age eligibility that includes 11-year-old children and an estimated enrollment of 1,000 participants at five locations.[92] The start date is listed as March 22, 2016, and the estimated completion date was extended from June 2018 to June 2019.

The study's brief summary states: "This pilot study is designed to obtain preliminary data on the safety, acceptability, and feasibility of direct-to-consumer telemedicine

[87] Harrison & Norton Testimony, p. 2.
[88] ACOG Practice Bulletin 181*: Prevention of Rh D Alloimmunization* (Aug. 2017); and SOGC Clinical Practice Guidelines: *Prevention of Rh Alloimmunization* (No. 133, Sept. 2003).
[89] Harrison & Norton Testimony, p. 9.
[90] (NCT02513043), https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1.
[91] Raymond EG, Chong E, & Hyland P, *Increasing Access to Abortion with Telemedicine*, JAMA Internal Medicine Vol. 176, N. 5 (May 2016).
[92] Hawaii – University of Hawaii Women's Options Center; Maine – Maine Family Planning; New York – Choices Women's Medical Center (active, but not recruiting according to ClinicalTrials.gov, and not listed on TelAbortion.org); Oregon and Washington – Planned Parenthood Columbia Willamette; Oregon Health and Sciences University Women's Health Research Unit. Washington State patients may also participate because an Oregon abortion provider is also licensed in Washington State. Claire Lampen, *Webcam Abortion Services Offer Crucial Access—So What's Stopping them?* Gizmodo (Apr. 17, 2018).

abortion."[93] The study's website states that "[a] TelAbortion involves all the same steps and procedures as a regular medical abortion, but you do them without going into an abortion clinic."[94]

Women who participate in the study have a video "evaluation" with the study abortion provider over the Internet, during which they can ask questions, provide medical history, and learn about the pre-abortion tests that they need. They also electronically sign consent forms for the study. Afterwards, they are required to obtain the tests and direct the reports to be sent to the study provider.

Once a patient is determined eligible, the study provider will send her a package containing Mifeprex and misoprostol, with instructions that she must follow on her own. She is also instructed to have additional tests to verify that the abortion is complete, and later have another consultation with the study provider to review the results.[95]

Obviously, a woman may *not* take the abortion drugs in the manner prescribed, nor obtain the follow-up care that is recommended. With a doctor-patient relationship limited to online chats, she has virtually no accountability or support as she navigates a complicated procedure. The responsibility of the provider of the drugs to follow up with the patient is obviated as well.

b. The Mifeprex through Pharmacy Dispensing Study

The University of California, San Francisco (UCSF) is the sponsor of the "Alternative Provision of Medication Abortion via Pharmacy Dispensing" study.[96] Daniel Grossman, M.D., with UCSF is listed as the study's "responsible party."[97] Like Gynuity, UCSF filed an IND with the FDA to obtain authorization for this study.[98] The status is listed as "recruiting," with July 2019 as the estimated completion date. The sponsors plan to recruit 300 patients at four study clinic sites and survey 50 pharmacists at associated study pharmacy sites.[99]

[93] NCT02513043, https://www.clinicaltrials.gov/ct2/show/NCT02513043?term=NCT02513043&rank=1.
[94] TelAbortion: The Telemedicine Abortion Study: FAQs, http://telabortion.org/faq/.
[95] *Id.*
[96] NCT03320057, https://www.clinicaltrials.gov/ct2/show/NCT03320057?term=NCT03320057&rank=1; Daniel Grossman, MD, Research Protocol: *Alternative Provision of Medication Abortion via Pharmacy Dispensing*, Version #:1.3 (JUL. 17, 2018) p. 5.
[97] *Id.*
[98] In a May 2018 phone conversation with a contact for the UCSF study, she stated that the study was approved through an IND application with FDA.
[99] Grossman, pp. 5-7; 16-17.

The stated aim of the study is to "investigate the feasibility, acceptability, and effectiveness of pharmacy dispensing of Mifeprex; safety data will also be collected. . . . *The results of this study eventually could lead to changes in the Mifeprex REMS. . . .*"[100]

The sponsors intend to measure "pharmacist satisfaction with dispensing Mifeprex and the proportion of pharmacists who refuse to dispense the medication to patients." They secondarily intend to assess patient satisfaction, describe clinical outcomes, including effectiveness and adverse events, and compare pharmacists' knowledge about medication abortion before and after.[101]

Patients enroll at one of the study clinic sites on Day 1, where they choose medication abortion, have an ultrasound if one has not been done, and obtain pre-abortion counseling. They then are prescribed Mifeprex, misoprostol, and anything else necessary to be filled at the associated study pharmacy site.[102] Some patients have serum hCG measured on the day of Mifeprex administration and again around eight days later "to assess for completion of the abortion."[103] The "follow-up" for patients "may include a follow-up visit or a phone call from clinic staff approximately 7-14 days after the initial visit."[104] However, as discussed extensively above, a clinician needs to perform an exam to rule out retained tissue—even if the patient has a negative serum hCG. A phone call that "may" be placed, or fail to connect, is not enough.

Notably, "[a]ll except one of [the participating] pharmacies is [sic] located within the same building as the clinic…."[105] While UCSF is using a community pharmacy not affiliated with the University, the other three study clinic sites are using affiliated pharmacies.[106]

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[100] Grossman, p.14 (emphasis added). The sponsors dubiously assert that "pharmacy dispensing could [] help increase the number of clinicians willing and able to provide medication abortion by enabling them to avoid the associated costs and logistical challenges of stocking and dispensing the medication at their facilities." They reference a survey of Fellows of the American College of Obstetricians and Gynecologists that sought to determine if doctors not presently practicing abortion would prescribe Mifeprex if their patients could obtain the drug at a pharmacy. Fifty-four percent responded to the survey. Seventy-seven percent of respondents *do not* perform abortions and nine percent perform surgical abortions only—of those, 19% said they would prescribe Mifeprex if it could be obtained at a pharmacy, and an additional 18% said they were unsure. Based on this, the sponsors claim "the proportion of obstetrician-gynecologists providing [Mifeprex] would at least double (from 14% to 29%) "if the dispensing restriction in the REMS were removed and physicians could write a prescription for Mifeprex that could be dispensed at a pharmacy." The fact that 46 percent of the fellows surveyed did not take the time to respond, however, places this conclusion in doubt. *See* Grossman, pp. 12-14.
[101] Grossman, pp. 15-16.
[102] Grossman, p. 23.
[103] Grossman, p. 23.
[104] Grossman, p. 24.
[105] Grossman, p. 20.
[106] Grossman, pp 16-17.

While the rationale for the study states that pharmacy dispensing of Mifeprex could "help facilitate provision of medication abortion through telemedicine,"[107] the sponsors emphasize that the only difference between this study and FDA protocol "is that the patient would obtain the mifepristone directly from the pharmacist, rather than in a clinic facility."[108] In fact, the schedules for the participating pharmacists are "mapped" to "ensure that trained pharmacists are available to dispense to study participants during business hours."[109]

The following demonstrates the extensive assistance that the sponsors offer patients in obtaining the drugs from the participating pharmacies:

> [The patient] will be told that only a limited number of pharmacies are able to dispense Mifeprex and given information about how to get to the participating pharmacy (as well as the hours during which a participating pharmacist will be working, if needed). If there are any gaps in staffing at the pharmacy, the patient will be notified of the timing of those gaps in coverage before leaving the clinic via the pharmacy directions/handout. If this will be an issue for the patient, a solution will be found at the clinic before the patient leaves or she will not be enrolled in the study. Patients will be told that if they have any problems accessing the medications at the clinic, they should come back to the clinic [where they can obtain Mifeprex].[110]

While this assistance may ensure that the study does not deviate dramatically from FDA protocol, the study *certainly* does not model the experience a patient would have outside of this controlled environment—particularly a patient who obtains Mifeprex through telemedicine and has no physical contact with her prescriber.

The physical proximity of the study pharmacy sites to the study clinic sites, the probable professional associations between participating doctors and pharmacists, and the extensive assistance offered by the clinics to ensure that patients access abortion-inducing drugs at participating pharmacies, raise questions as to whether the study is fundamentally biased and will inaccurately forecast widespread behavior and experiences if the REMS is removed. Therefore, any results of the study cannot provide a justification for permitting pharmacy distribution of Mifeprex, much less abortion through telemedicine.

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[107] Grossman, p. 6.
[108] Grossman, p. 6.
[109] Grossman, p. 18.
[110] Grossman, pp. 19-20.

Further, as discussed below, eliminating the REMS to enable pharmacy dispensing of Mifeprex is only the beginning of a long-term strategy to achieve over-the-counter status for Mifeprex, further diminishing patient care and abortion provider accountability.

c. Beyond the Current Studies

A recent article by Dr. Grossman and colleagues reveals that they want Mifeprex access extended even beyond the parameters contained in their Pharmacy Dispensing study. They used an online survey to gauge women's "personal interest in and general support for three alternative methods for accessing abortion pills: (1) in advance from a doctor for future use, (2) over-the-counter (OTC) from a drugstore and (3) online without a prescription."[111]

None of the options in the survey require a healthcare provider to provide patient care comparable to even the *inadequate* care provided in the two studies discussed above. Only the first option requires a prescription from a doctor; however, the doctor would not know in advance when his patient actually becomes pregnant and chooses to use the drugs. The survey disingenuously stated that "[m]edication abortion, or the abortion pill, is a safe and effective way to terminate a pregnancy up to 10 weeks," without informing participants of a single risk associated with the regimen.[112]

Further, in a November, 21, 2018 op-ed, Dr. Grossman advocated for providing abortion pills before women are pregnant. He stated:

> The idea is simple: Give women abortion pills *before* they need them – "advance provision," as it's known – so that they can take them as soon as they discover a pregnancy. Women could get the pills from their gynecologist at the time of their annual exam, say, or the pills could be made available online.[113]

Incredibly, Dr. Grossman stated that he has "few medical concerns about handing out abortion pills in advance."[114] He asserts that evidence from advance provision research "could strengthen the case for making [abortion-inducing drugs] available without a prescription."[115]

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[111] Biggs MA, et al, *Support for and interest in alternative models of medication abortion provision among a national probability sample of U.S. women,* Contraception (2018), https://doi.org/10.1016/j.contraception.2018.10.007.
[112] *See id.*
[113] Daniel Grossman, *American women should have access to abortion pills before they need them*, Los Angeles Times (Nov. 21, 2018).
[114] *Id.*
[115] *Id.*

In addition to his failure to address all of the dangers posed by abortion-inducing drugs, Dr. Grossman does not acknowledge the risk that women will share their abortion-inducing pills with other women. While an abortion provider may screen his patient for contraindications to Mifeprex, nothing will stop his patient from giving her stored Mifeprex to a friend who is unaware that she is Rh negative, for instance, which poses health risks for future pregnancies (See section I.B.2, *supra*).

In fact, Dr. Grossman's research program has listed a study titled "Alternative Provision of Medication Abortion Via Advance Provision" on ClinicalTrials.gov, with May 2019 listed as the estimated study start date.[116] In the study, patients who are "at risk of unintended pregnancy and with a desire to avoid pregnancy will be assessed by a clinician and provided counseling on pregnancy recognition and testing, as well as how to administer [drug-induced abortion] at home." They will then receive Mifeprex and misoprostol while *not* pregnant. If/when the patient becomes pregnant and wants to take the drugs, she is instructed to contact a study clinician for an "over-the-phone assessment of eligibility" for drug-induced abortion, "including evaluation of contraindications and gestational age" before taking the drugs, and "then attend a follow-up visit with the clinician."[117] However, it is impossible for the study sponsors to truly assess the patient for contraindications, verify gestational age, prevent patients from sharing the drugs with others, or ensure that patients attend a follow-up visit.

In a 2018 Policy Review, the Guttmacher Institute also advocated for lifting the Mifeprex REMS. However, the article did not stop there. The author argues:

> [w]hile lifting the REMS on mifepristone would open new possibilities for medication abortion access, stopping there would fall short of realizing the full potential of this method, particularly when it comes to self-managed abortion care. In a self-management model, anyone who needs to terminate a pregnancy would be able to legally access mifepristone and misoprostol without a requirement to see a health care provider or pharmacist first. . . . To fully integrate self-managed medication abortion with existing abortion practices in the United States, misoprostol and mifepristone must first become available without a prescription.[118]

These recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex. In spite of the serious risks and contraindications to the Mifeprex regimen, abortion advocates will not rest until Mifeprex is available to all, without a prescription

[116] NCT03829696, https://clinicaltrials.gov/ct2/show/NCT03829696?term=NCT03829696&rank=1.
[117] *Id.*
[118] Donovan MK, *Self-Managed Medication Abortion: Expanding the Available Options for U.S. Abortion Care*, Guttmacher Policy Review, vol. 21 (2018).

or mandatory medical management of any kind. The FDA's vigilance in protecting women from such negligence is critically important.

2. Mifeprex Prescribers Should be Certified.

The 2016 regimen requires Mifeprex prescribers to be certified as qualified. This is simply common sense—only healthcare providers qualified to prescribe an abortion-inducing drug should do so. The prescriber form attests that the healthcare provider must be able to assess pregnancy duration, diagnose ectopic pregnancy, and provide or refer for surgical intervention if necessary.

Given that drug-induced abortion is contraindicated beyond 10 weeks' gestation and when the pregnancy is not in the uterus, and that *at least* 1 out of 100 women using Mifeprex need surgery,[119] these qualifications are entirely logical. Yet, abortion advocates, ignoring the best interests of their patients, claim such restrictions are onerous.[120]

CONCLUSION

The Mifeprex REMS with ETASU remains critical for patient safety. Mifeprex carries risks of life-threatening hemorrhage, infection, continued pregnancy, retained tissue, need for emergency surgery, and death. The 2000 regimen provided significantly more protections for patients than the 2016 regimen. FDA should restore and strengthen elements of the Mifeprex regimen and provider requirements, including: limiting Mifeprex use to 49 days' gestation; requiring that Mifeprex be administered only by or under the supervision of a physically present physician; requiring three office visits by a patient who has been prescribed Mifeprex; clarifying that Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care; expanding mandatory adverse event reporting; and requiring additional studies of Mifeprex use in at-risk populations.

At the very least, FDA should not further erode patient protections. The agency should retain the Mifeprex REMS, and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

[119] Mifeprex Risk Evaluation and Mitigation Strategy (REMS), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2016-03-29_REMS_full.pdf.
[120] Mifeprex REMS Study Group, *Sixteen Years of Overregulation: Time to Unburden Mifeprex*, N Engl. J. Med. 376;8 (Feb. 23, 2017).

C. Environmental Impact

This petition is categorically excluded under 21 C.F.R. § 25.30.

D. Economic Impact

Available upon Commissioner's request, pursuant to 21 C.F.R. §10.30(3).

E. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners, which are unfavorable to the petition.

Signature: /s/ Donna J. Harrison M.D., Executive Director

Name of petitioner: American Association of Pro-Life Obstetricians and Gynecologists

Mailing address: PO Box 395, Eau Claire, MI 49111-0395

Telephone number: (202) 230-0997

Signature: /s/ Quentin L. Van Meter, M.D., FCP, President

Name of petitioner: American College of Pediatricians

Mailing address: PO Box 357190, Gainesville, FL 32635-7190

Telephone number: (352) 376-1877

Exhibit 36

2019 FDA Abbreviated New Drug Application (ANDA) Approval Letter to GenBioPro, Inc. (Apr. 11, 2019)

ANDA 091178

ANDA APPROVAL

(b) (6), (b) (4)
GenBioPro, Inc.
(b) (6), (b) (4)
Attention: (b) (6), (b) (4)

Dear Sir:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 3, 2009, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Mifepristone Tablets, 200 mg.

Reference is also made to the complete response letter issued by this office on February 23, 2018, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is **approved**, effective on the date of this letter. The (b) (6) has determined your Mifepristone Tablets, 200 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Mifeprex Tablets, 200 mg, of Danco Laboratories, LLC.

Under section 506A of the FD&C Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FD&C Act authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. In accordance with section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA under section 505(j) is subject to certain elements of the REMS required for the applicable listed drug.

The details of the REMS requirements were outlined in our letter dated June 15, 2011. In that letter, you were also notified that pursuant to section 505-1(i) of the FD&C Act, a drug that is the subject of an ANDA and the listed drug it references must use a single, shared system for elements to assure safe use (ETASU), unless FDA waives that requirement.

Your REMS, known as the Mifepristone REMS Program, submitted on May 30, 2017; is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems

The REMS consists of ETASU and an implementation system.

Your REMS must be fully operational before you introduce Mifepristone Tablets, 200 mg, into interstate commerce.

The Mifepristone REMS uses a single, shared system for the ETASU. This single, shared system REMS Program currently includes the products listed on the FDA REMS website, available at http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

We remind you that you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FD&C Act.

We also remind you that section 505-1(f)(8) of the FD&C Act prohibits holders of an approved covered application from using any element to assure safe use to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing a REMS assessment or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

ANDA 091178 REMS ASSESSMENT

NEW SUPPLEMENT FOR ANDA 091178/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR ANDA 091178/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES
SUBMITTED IN SUPPLEMENT XXX

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR ANDA 091178

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS submission.

For more information on submitting REMS in SPL format, please email REMSWebsite@fda.hhs.gov

REPORTING REQUIREMENTS

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts.

All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

(b) (6)

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Date: 4/11/2019 02:22:21PM
GUID: 54078879000a1b9e15dd31ed6f0343ca

Exhibit 37

2019 FDA Supplemental Approval Letter to Danco Laboratories, LLC (Apr. 11, 2019)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-022

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated November 4, 2015, received November 5, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Prior Approval supplemental new drug application proposes modifications to the approved risk evaluation and mitigation strategy (REMS) for Mifeprex to establish a single, shared system (SSS) REMS for mifepristone products for the medical termination of intrauterine pregnancy and updates to the approved Prescribing Information, Medication Guide, and REMS materials including the Prescriber Agreement and Patient Agreement Forms to incorporate language reflecting the proposed SSS REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at:

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The most recent modification was approved on March 29, 2016. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS establish a SSS REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Mifeprex and ANDAs referencing Mifeprex, called the Mifepristone REMS Program.

Your proposed modified REMS, submitted on January 25, 2018, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the initial approval of the SSS REMS (04/11/19) and every three years thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Both cumulative data from the date of the initial approval of the SSS REMS (04/11/19) and data from the reporting period (i.e., from the preceding Mifeprex REMS assessment cut-off date to the cut-off date for the Mifepristone REMS Program.)

REMS Assessment Plan

Provide each metric for the current reporting period and cumulative for the RLD and ANDA(s):

1. Number of prescribers enrolled
2. Number of prescribers ordering mifepristone
3. Number of healthcare providers who attempted to order mifepristone who were not enrolled; describe actions taken
4. Number of women exposed to mifepristone
5. Summary and analysis of any program deviations and corrective action taken
6. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

Reference ID: 4418041

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) If the new indication for use introduces unexpected risks: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use: Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous

Reference ID: 4418041

REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING NUMBER
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

Or

NEW SUPPLEMENT FOR NDA 020687/S-000/ SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

Or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page

Reference ID: 4418041

of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email REMS_Website@fda.hhs.gov.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

04/11/2019 02:13:59 PM

Exhibit 38

2020 Letter from Am. Coll. of Obstetricians & Gynecologists and Soc'y for Maternal-Fetal Med., to FDA about Mifepristone REMS (Apr. 20, 2020)

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal•Fetal Medicine
High-risk pregnancy experts

April 20, 2020

Stephen M. Hahn, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue NW
Silver Spring, MD 20993

Re: Docket Number: FDA-2020-D-1106; Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency Guidance for Industry and Health Care Professionals

Dear Commissioner Hahn:

On behalf of more than 60,000 of the nation's primary care obstetrician-gynecologists and subspecialty and high-risk obstetric practitioners dedicated to advancing women's health, thank you for your recent action to suspend enforcement of Risk Evaluation and Mitigation Strategy (REMS) requirements for certain drugs with laboratory testing or imaging requirements for the duration of the COVID-19 public health emergency. The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine urge the U.S. Food and Drug Administration (FDA) to immediately expand this policy to REMS and Elements to Assure Safe Use (ETASU) requirements for certain prescription drugs requiring in-person health care professional administration, where treatment could safely occur through telehealth or self-administration. In addition, physicians who provide such services in accordance with current clinical guidelines during this pandemic should not be held liable.

Obstetrician-gynecologists are serving on the front lines responding to the COVID-19 crisis. In order to provide the safest care for their patients and themselves, in-person visits are limited to emergency and essential physically necessary visits. We support the FDA's acknowledgment that REMS-required health care professional in-person dispensation is difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. Under these circumstances, undergoing in-person clinic administration in order to obtain a drug subject to a REMS can put patients and others, including health care professionals and their families, at risk for COVID-19 transmission. As referenced in ACOG Committee Opinion #798, *Implementing Telehealth in Practice*, evidence suggests that telehealth provides comparable health outcomes when compared with traditional methods of health care delivery without compromising the patient–physician relationship.[1] Telehealth has quickly become integrated into nearly every aspect of obstetrics and gynecology. During this pandemic, it is essential to use telehealth services to limit COVID-19 transmission.

It is critical that the FDA promptly expand its recent policy to apply to the REMS and ETASU requirements for certain drugs requiring in-person dispensation, especially mifepristone. The current REMS and ETASU requirements for mifepristone are outdated and serve as a barrier to accessing this safe, effective medication. Further, they cause unnecessary delays in obtaining time-sensitive health care, without supporting improvements to patient safety or outcomes. During this federally declared public health emergency, these antiquated and superfluous requirements put patients and their physicians at risk, with no demonstrated benefit. As noted in the ACOG Position Statement, *Improving Access to*

Mifepristone for Reproductive Health Indications, mifepristone has been used by over 3 million women in the United States since FDA approval in 2000 and strong evidence exists regarding the safety of mifepristone for medication-induced abortion and medical management of early pregnancy loss.[2,3,4,5]

Restricting access to mifepristone interferes with the ability of obstetrician–gynecologists and other women's health clinicians to deliver the highest quality care for their patients, especially during the COVID-19 pandemic. Abortion is an essential component of comprehensive health care and is a time-sensitive service for which a delay of several weeks, or in some cases days, may increase the risks or potentially make it completely inaccessible.[6] Temporarily waiving REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals is particularly important for patients who suffer from other medical conditions and are at higher risk of serious complications from COVID-19, as well as those in rural areas for whom hours of travel for in-person administration would disallow social distancing recommendations and travel advisories.

In addition, we urge you to consider waiving the requirement for health care professional administration of subcutaneous depot medroxyprogesterone acetate (DMPA). Several studies have shown patient interest in self-administration and increased continuation of DMPA via subcutaneous at-home delivery.[7,8,9] In a period when limiting patient interactions with the health care system is essential to prevent COVID-19 transmission, it is in our patients' best interest to have unencumbered access to the contraceptive method of their choice, including DMPA.

Ensuring the safety of patients and physicians during the COVID-19 pandemic requires policy changes such as those already enacted by FDA to waive the REMS requirements for certain drugs with laboratory testing or imaging requirements. We strongly urge FDA to further protect patients and their health care professionals from the risk of transmission by promptly expanding the existing policy to waive REMS and ETASU requirements that certain drugs be dispensed in-person by certain medical professionals. Thank you for your consideration. We are available to answer any questions you may have regarding these issues.

Sincerely,

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists

Judette Louis, MD, MPH
President
Society for Maternal-Fetal Medicine

Matt J. Granato, LL.M., MBA
Chief Executive Officer
Society for Maternal-Fetal Medicine

[1] Implementing telehealth in practice. ACOG Committee Opinion No. 798. American College of Obstetricians and Gynecologists. Obstet Gynecol 2020;135:e73–9.
[2] Improving Access to Mifepristone for Reproductive Health Indications. Position Statement. American College of Obstetricians and Gynecologists. June 2018. Available at https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications.
[3] Cleland K, Smith N. Aligning mifepristone regulation with evidence: Driving policy change using 15 years of excellent safety data. *Contraception*. 2015;92(3):179-181. doi:10.1016/j.contraception.2015.06.016.
[4] Sixteen Years of Overregulation: Time to Unburden Mifeprex. *N Engl J Med*. 2017;376(8):790-794.
[5] Song LP, Tang SY, Li CL, Zhou LJGYK, Mo XT. Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol. *J Obstet Gynaecol Res*. 2018;44(9):1705-1711. doi:10.1111/jog.13716.
[6] Joint Statement on Abortion Access During the COVID-19 Outbreak. March 18, 2020. Available at https://www.acog.org/news/news-releases/2020/03/joint-statement-on-abortion-access-during-the-covid-19-outbreak.
[7] Upadhyay UD, Zlidar VM, Foster DG. Interest in self-administration of subcutaneous depot medroxyprogesterone acetate in the United States. *Contraception*. 2016;94(4):303-313. doi:10.1016/j.contraception.2016.06.006.
[8] Kohn JE, Simons HR, Della Badia L, et al. Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. *Contraception*. 2018;97(3):198-204. doi:10.1016/j.contraception.2017.11.009.
[9] Burke HM, Chen M, Buluzi M, et al. Effect of self-administration versus provider-administered injection of subcutaneous depot medroxyprogesterone acetate on continuation rates in Malawi: a randomised controlled trial. *Lancet Glob Heal*. 2018;6(5):e568-e578. doi:10.1016/S2214-109X(18)30061-5.

Exhibit 39

2021 FDA Letter to Am. Coll. of Obstetricians & Gynecologists and Soc'y for Maternal-Fetal Med. about Mifepristone REMS (Apr. 12, 2021)

U.S. FOOD & DRUG ADMINISTRATION

April 12, 2021

Maureen G. Phipps, MD, MPH, FACOG
Chief Executive Officer
American College of Obstetricians and Gynecologists
c/o Rachel Tetlow, Federal Affairs Director
rtetlow@acog.org

Skye Perryman, General Counsel
sperryman@acog.org

William Grobman, MD, MBA
President
Society for Maternal-Fetal Medicine
w-grobman@northwestern.edu

Dear Drs. Phipps and Grobman,

In your letter of April 20, 2020, to former Commissioner Stephen Hahn, you expressed concerns about the in-person dispensing requirements for certain prescription drugs during the current public health emergency. In my letter to you of March 19, 2021, I indicated that staff in the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) were evaluating the issues you raised.

Following up on my March 19, 2021, letter I am writing to report the results of CDER's review and analysis.

CDER conducted a literature search for studies pertinent to the in-person dispensing requirement in the Mifepristone REMS Program during the COVID-19 pandemic. Based on this literature search, CDER identified four publications that included relevant clinical outcome data.[1] CDER

[1] Chong E, et al. Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic. Contraception 2021 (accepted manuscript). https://www.sciencedirect.com/science/article/pii/S0010782421000913; Kerestes C, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 (accepted manuscript). https://doi.org/10.1016/j.contraception.2021.03.025; Aiken A et al. Effectiveness, Safety and Acceptability of No-test Medical Abortion Provided Via Telemedicine: a National Cohort Study. British J Obstet Gynecol 2021. https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668; Reynolds-Wright JJ et al. Telemedicine medical abortion at home under 12 weeks' gestation: a prospective observational cohort study during the COVID-19 pandemic. BMJ Sex Reprod Health 2021. https://srh.bmj.com/content/early/2021/02/04/bmjsrh-2020-200976

found that although there are limitations to the study designs, the overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic.

CDER also reviewed postmarketing adverse events that reportedly occurred from January 27, 2020 - January 12, 2021, with mifepristone use for medical termination of early pregnancy, along with available information about deviations or noncompliance events associated with the Mifepristone REMS Program.[2] CDER found that the small number of adverse events reported to FDA during the COVID-19 public health emergency (PHE) provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to the reported adverse events.

In summary, provided the other requirements of the Mifepristone REMS Program are met, and given that the in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare personnel because it may involve a clinic visit solely for this purpose, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form. Further, to the extent all of the other requirements of the Mifepristone REMS Program are met, CDER intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

CDER is communicating this decision to the approved application holders subject to the Mifepristone REMS Program.

Sincerely yours,

Janet Woodcock, M.D.
Acting Commissioner of Food and Drugs

[2] See Mifepristone REMS Program at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. CDER's analysis covers both products that are subject to the Mifepristone REMS Program (Mifeprex and the approved generic, Mifepristone Tablets, 200 mg).

Exhibit 40

2021 FDA Supplemental Approval Letter to Danco Laboratories, LLC (May 14, 2021)

NDA 020687/S-024

SUPPLEMENT APPROVAL

Danco Laboratories LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your supplemental new drug application (sNDA) dated and received March 15, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

This Changes Being Effected sNDA provides for changes to the single, shared system risk evaluation and mitigation strategy (REMS) for mifepristone products for the medical termination of intrauterine pregnancy, known as the Mifepristone REMS Program, to include gender neutral language in the Patient Agreement Form. This sNDA also provides for minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Mifeprex was originally approved on August 7, 2012, and the most recent REMS modification, establishing the Mifepristone REMS Program, was approved on April 11, 2019. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the Mifepristone REMS Program consists of a

revised Patient Agreement Form to include gender neutral language and minor revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form.

The timetable for submission of assessments of the REMS remains the same as that approved on April 11, 2019.

There are no changes to the REMS assessment plan described in our April 11, 2019 letter.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved Mifepristone REMS Program, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the Mifepristone REMS Program, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the

health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g., ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000/
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call [redacted].

Sincerely,

{See appended electronic signature page}

[redacted]

Center for Drug Evaluation and Research

ENCLOSURE:

- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

05/14/2021 02:14:29 PM

Exhibit 41

2021 Updated REMS Mifepristone Tablets,
200 mg (May 14, 2021)

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 05/2021

Mifepristone Tablets, 200 mg

Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
         2) They will follow the guidelines for use of mifepristone (see b.i-v below).
   b. As a condition of certification, healthcare providers must follow the guidelines for use of mifepristone described below:
      i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.

Reference ID: 4799010

ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*

iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Place the signed *Patient Agreement Form* in the patient's medical record.

v. Record the serial number from each package of mifepristone in each patient's record.

vi. Report any deaths to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non- identifiable reference and the serial number from each package of mifepristone.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements

ii. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

2. Mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Mifepristone Sponsors must:

i. Ensure that their mifepristone is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that their mifepristone is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the prescriber regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors. The distributors must:

Reference ID: 4799010

i. Put processes and procedures in place to:

a. Complete the healthcare provider certification process upon receipt of a Prescriber Agreement Form.

b. Notify healthcare providers when they have been certified by the Mifepristone REMS Program.

c. Ship mifepristone only to clinics, medical offices, and hospitals identified by certified prescribers in their signed *Prescriber Agreement Form*.

d. Not ship mifepristone to prescribers who become de-certified from the Mifepristone REMS Program.

e. Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors, FDA or a third party acting on behalf of Mifepristone Sponsors or FDA to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the REMS Program.

3. Mifepristone Sponsors must audit their new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

4. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

5. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicants other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (04/11/2019) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

Reference ID: 4799010

Exhibit 42

2021 FDA Center for Drug Evaluation and Research Director Patrizia Cavazzoni Letter to Dr. Graham Chelius (Dec. 16, 2021)

December 16, 2021

Graham Chelius, M.D.
The Society of Family Planning
The California Academy of Family Physicians

Dear Dr. Chelius:

This letter is to inform you that FDA has completed its review of the Mifepristone Risk Evaluation and Mitigation System (REMS) Program.[1] The agency has determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks. However, we have determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. See 21 USC 355-1(g)(4)(B). The modifications to the REMS will consist of: (1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement"); and (2) adding a requirement that pharmacies that dispense the drug be specially certified.

A REMS Modification Notification letter has been sent to both Applicants subject to the Mifepristone REMS Program. The letter describes the modifications and directs the Applicants to submit prior approval supplements within 120 days. We have also answered a related citizen petition from the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians. That response will be posted in the public docket (Docket No. FDA-2019-P-1534; available at www.regulations.gov).

Sincerely,

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[1] We also note your letter of September 29, 2021 to us on this subject.

Exhibit 43

2021 FDA Letter to Am. Ass'n of Pro-Life Obstetricians & Gynecologists and Am. Coll. of Pediatricians denying in part and granting in part 2019 Citizen Petition, Docket No. FDA-2019-P-1534 (Dec. 16, 2021) (2019 Petition Denial)

Donna J. Harrison, M.D.
Executive Director
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Quentin L. Van Meter, M.D., FCP
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P.O. Box 357190
Gainesville, FL 32635-7190

December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[2] 73 FR 16313 (Mar. 27, 2008).

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:[3]

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.

- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.

- Reduced the number of office visits by the patient under the approved regimen from three to one.

- Replaced the term "physician" with the term "healthcare provider."

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:[4]

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.

- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

[3] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[4] See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[5]

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.[6]

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

[5] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[6] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

FDA has recognized that during the COVID-19[7] public health emergency (PHE),[8] certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement").

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[9]

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA's intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

[7] The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

[8] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[9] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns "she" and "her" in the Patient Agreement Form were replaced with "the patient." The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.[10] In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.[11] Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

[10] We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

[11] Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprex Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion[12] regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.[13] Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.[14] The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.[15]

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.[16] As discussed

[12] In this response, the terms "medical abortion" and "medication abortion" both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.
[13] See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.
[14] See 1999 Medical Officer's Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.
[15] See 2016 Clinical Review, supra n. 13, at 28-31.
[16] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,[17] a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.[18] However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data[19] and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[20] This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.[21] The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.[22]

You also state that the failure rate of the approved regimen (which you refer to as the "buccal misoprostol regimen") increases as the gestational age increases, especially at

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[17] Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, Human Reproduction. 2011;26(4):927-932.
[18] Id. at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.
[19] See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).
[20] Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.
[21] Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United Sates, NEJM. 1998;338 (18):1241-1247.
[22] See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

gestational ages greater than 49 days, relying on a 2015 meta-analysis,[23] and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the "ability" to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen's serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[24]

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.[25] Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

[23] Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21).
[24] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf; see also https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[25] See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);[26,27] one trial studied a regimen using vaginal misoprostol (Warringer);[28] a fourth study did not specify the route of misoprostol administered (Puri).[29] Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the "standard care" group.[30] Our 2016 review also included a systematic review of six controlled clinical studies by Renner;[31] the authors concluded that the evidence "indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services." Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.[32] The authors concluded, based in part on two of the studies that we had reviewed in 2016,[33] that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:[34]

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

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[26] Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. Bull World Health Organ. 2015;93:249-258.

[27] Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. BJOG. 2015; 122: 510-517.

[28] Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet. 2011; 377: 1155-61.

[29] Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters. 2015; 22(44) 94-103.

[30] 2016 Clinical Review, supra n. 13, at 43.

[31] Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG 2013 Jan;120(1):23-31.

[32] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.

[33] Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include avurvedic physicians and nurses. International Perspectives on Sexual and Reproductive Health 2012;38(3)133-42)

[34] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."[35] Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.[36] In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."[37]

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

[35] ACOG Practice Bulletin No. 225, supra n. 22.
[36] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70.
[37] FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See https://www.regulations.gov/document/FDA-2002-P-0364-0002.

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[38] Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form[39] with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."[40]

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

[38] Id.
[39] See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[40] ACOG Practice Bulletin Number 225 supra n. 22.

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).

- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:

    - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).

    - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).

- Because providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.[41]

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.[42] Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, "[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[43] The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.[44] As reflected in ACOG's guidance, appropriate follow-

[41] See 2016 Clinical Review, supra n. 13, at 44 and 64-67.
[42] ACOG Practice Bulletin Number 225, supra n. 22.
[43] Id.
[44] Id.

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.[45] We note that this is consistent with current ACOG recommendations, which state that "follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[46]

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)'s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document[47] appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[48] In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.[49] For the years 2008 to 2010, data were collected retrospectively; for the years

[45] Baiju, N, Acharya, G, D'Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.
[46] ACOG Practice Bulletin Number 225, supra n. 22.
[47] World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.
[48] Id. at Section 2.3 Post-abortion care and follow-up, at 52.
[49] Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women's Health 18:158.

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between "at home" abortions (managed as an outpatient) and "at the hospital" abortions, in 2015 and found no statistically significant difference (8.2 percent "at home" versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.[50]

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,[51] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan." Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[52] We note that these findings are also consistent with ACOG guidelines, which state that "[r]outine in-person follow-up is not necessary after uncomplicated medication abortion" and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.[53] Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

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[50] 2016 Clinical Review, supra n. 13, at 51-57.
[51] See ACOG Practice Bulletin Number 225, supra note 22.
[52] 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.
[53] ACOG Practice Bulletin Number 225, supra note 22.

iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.[54] Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.[55]

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.[56] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[57] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).[58] The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

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[54] See 2016 Clinical Review, supra n. 13, at 41 and 48.
[55] Id. at 38.
[56] Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, Contraception, 76:215-220).
[57] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447–50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333–6.
[58] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.[59] It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.[60] As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a "minimum 24-hour interval between" mifepristone and misoprostol (emphasis included in the labeling).[61] The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen" (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that "based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent)."[62] The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

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[59] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[60] 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.)
[61] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[62] See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.[63] Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home, Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[64] However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[65] This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

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[63] Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, Obstet Gynecol 112(6):1303-1310.

[64] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

[65] See https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers.

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study[66] and ACOG statements as evidence that medical abortions have greater risks and more need for emergency "operation" than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.[67] For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.[68] In addition, one of the required qualifications listed in the Prescriber Agreement Form is the "[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[69] Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

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[66] See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimaki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, Obstet. Gynecol. 114:795 (Oct. 2009)).

[67] See Mifeprex labeling, approved 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[68] Id.

[69] Mifepristone REMS Program, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. Emphasis added.

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.[71] Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers "violate FDA protocol," instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access[72] to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing "many Mifeprex prescribers violate FDA protocol, instructing their patients to lie," or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA's determination as to whether a REMS is necessary

[71] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."

[72] We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019.

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.[73] In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[74]

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,[75] as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

[73] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).
[74] Id.
[75] See supra n. 10.

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[76]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

[76] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.

c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS[77] assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

[77] This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,[78] through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.[79] To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.[80] Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies[81]

[79] See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

[80] In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

[81] Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

and dispensing mifepristone from pharmacies by mail.[82] Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,[83] and (2) prescribers using couriered delivery of medications.[84] Different studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization."[85]

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. PLoS ONE 13(1): e0191174. https://doi.org/10.1371/journal.pone.019117; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. Contracept X. 2020; 2: 100023.

[82] Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2021, ISSN 0010-7824, https://doi.org/10.1016/j.contraception.2021.09.008, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. JAMA Network Open. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. Aust N Z J Obstet Gynaecol 2018;58: 335-340.

[83] See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. Contraception 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. Contraception 2019; 100:173-177. See also Chong et al., infra n. 103 Kerestes et al., infra n. 105, and Aiken et al., infra n. 106.

[84] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.

[85] Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. BJOG 2019;126;609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.16765; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. BMJ 2017;357:j2011 http://dx.doi.org/10.1136/bmj.j2011.

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,[86] Rocca,[87] Wiebe[88]). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca[89] conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[90] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

[86] Grossman et al., supra n. 81.
[87] Rocca et al., supra n. 81.
[88] Wiebe et al., supra n. 81.
[89] Rocca et al., supra n. 81.
[90] Wiebe et al., supra n. 81.

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)[91], in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),[92] timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)[93] evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,[94] Upadhyay,[95] Hyland[96]). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay[97] reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

[91] Grossman et al., supra n. 81.
[92] Wiebe et al., supra n. 81.
[93] Rocca et al., supra n. 81.
[94] Grossman et al, supra n. 82.
[95] Upadhyay et al., supra n. 82.
[96] Hyland et al., supra n. 82.
[97] Upadhyay et al., supra n. 82.

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[98] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up." The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study[99] the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland[100] study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay[101] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

[98] Hyland et al., supra n. 82.
[99] Grossman et al., supra n. 82.
[100] Upadhyay et al., supra n. 82.
[101] Hyland et al., supra n. 82.

2018),[102] Chong (outcomes from May 2016 to September 2020)[103] and Anger (outcomes from March 2020 to September 2020).[104] A fourth study, Kerestes,[105] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)[106] reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,[107] complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).[108] Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,[109] approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,[110] which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")[111]

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[102] Raymond et al., supra n. 83.
[103] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.
[104] Anger et al., supra n. 83.
[105] Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.
[106] Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. BJOG 2021;128:1464–1474.
[107] Raymond, supra n. 83.
[108] The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.
[109] Chong et al., supra n. 103.
[110] Anger et al., supra n. 83.
[111] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. Contraception 2020;101:361-366)

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.[112] There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the "test" group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was "hospitalized and/or blood transfusion" and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the "no-test" group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were "hospitalized and/or blood transfusion" and 12.5 percent had an unplanned clinical encounter.

Kerestes[113] included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity's TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)[114] reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators' analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger's comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

[112] We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.
[113] Kerestes et al., supra n. 105.
[114] Aiken et al., supra n. 106.

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright[115] reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))[116] reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail though a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

[115] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.
[116] Endler et al., Norten et al., and Aiken et al., supra n. 85.

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that "[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls" and that "health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs" (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the "physician serves a patient's medical needs;"[117] in the context of medical abortion, this

[117] See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.[118]

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).[119] Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).[120] The rate of infections requiring hospitalization or

[118] See https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine.
[119] Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf. Accessed December 13, 2021 (CIOMS).
[120] Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),[121] and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).[122] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.[123] study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.[124] reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

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[121] Id. at 36 (defining the "rare" standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).
[122] Id. at 36 (defining the "uncommon" standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.
[123] Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. Obstet Gynecol. 2009;114(4):795-804.
[124] Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the Frist Trimester. Obstetrics & Gynecology 126;22-28.

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an "at home" and "at the hospital" abortion.[125]

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman's unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency's conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),[126] certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

[125] Carlsson et al., supra n. 49.
[126] Section 505B of the FD&C Act (21 U.S.C. 355c).

subpopulations, unless that requirement is waived or deferred.[127] In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.[128] Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented. [129] This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses," and in the Medication Guide, which states "You can become pregnant again right after your pregnancy ends." Although you state that more than one out of every three abortions in the United Sates is a repeat abortion (Petition at 14),[130] we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).[131] Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.[132]

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

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[127] Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).
[128] 2016 Clinical Review, supra n. 13, at 74-76.
[129] Id. at 47.
[130] In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. J Womens Health.
[131] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.
[132] 2016 Clinical Review, supra n. 13, at 47.

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.[133]
We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[133] You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

Exhibit 44

Questions and Answers on FDA's Adverse Event Reporting System (FAERS), https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers

Questions and Answers on FDA's Adverse Event Reporting System (FAERS)

What is FAERS?

The FDA Adverse Event Reporting System (FAERS) is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation (ICH E2B (/drugs/guidances-drugs/international-council-harmonisation-efficacy)). Adverse events and medication errors are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddra.org/) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) terminology.

How does FDA use the information in FAERS?

FAERS is a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product, evaluating a manufacturer's compliance to reporting regulations and responding to outside requests for information. The reports in FAERS are evaluated by clinical reviewers, in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), to monitor the safety of products after they are approved by FDA.

If a potential safety concern is identified in FAERS, further evaluation is performed. Further evaluation might include conducting studies using other large databases, such as those available in the Sentinel System. (/sentinel-initiative-transforming-how-we-monitor-product-safety) Based on an evaluation of the potential safety concern, FDA may take regulatory action(s) to improve product safety and protect the public health, such as updating a product's labeling information, restricting the use of the drug, communicating new safety information to the public, or, in rare cases, removing a product from the market.

Who sends reports to FAERS?

Healthcare professionals, consumers, and manufacturers submit reports to FAERS. FDA receives voluntary reports directly from healthcare professionals (such as physicians, pharmacists, nurses and others) and consumers (such as patients, family members, lawyers and others). Healthcare professionals and consumers may also report to the products' manufacturers. If a manufacturer receives a report from a healthcare professional or consumer, it is required to send the report to FDA as specified by regulations.

How can I report an adverse event or medication error to FDA?

The MedWatch (https://www.fda.gov/Safety/MedWatch/default.htm) website provides information about voluntary and mandatory reporting (https://www.fda.gov/Safety/MedWatch/HowToReport/default.htm).

Can mandatory reporters submit adverse events electronically?

Yes, the FDA Adverse Events Reporting System (FAERS) Electronic Submissions (/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions) website provides drug and therapeutic biological product manufacturers, distributors, packers, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit post-marketing individual case safety reports (ICSRs), with and without attachments.

Does FAERS data have limitations?

Yes, FAERS data does have limitations. First, there is no certainty that the reported event (adverse event or medication error) was due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Furthermore, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population. For more information, please refer to the question " What points should I consider while viewing the dashboard content? (https://fis.fda.gov/extensions/fpdwidgets/2e01da82-13fe-40e0-8c38-4da505737e36.html#_Toc493751926)"

Is FAERS data available to the public?

FAERS data is available to the public in the following ways:

- FAERS dashboard (/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard): a highly interactive web-based tool that allows for the querying of FAERS data in a user friendly fashion.
- FAERS data files (/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files): provides raw data consisting of individual case safety reports extracted from the FAERS database. A simple search of FAERS data cannot be performed with these files by persons who are not familiar with the creation of relational databases.
- Individual case safety reports from the FAERS database can also be obtained by sending a Freedom of Information (FOI) request to FDA (/how-make-foia-request).

How do I find or confirm my report is in FAERS?

To confirm that your report is in FAERS, please send a Freedom of Information (FOI) request to FDA (/how-make-foia-request).

What are the benefits of the FAERS public dashboard?

This tool makes the data easier to query and produces user-friendly information and charts. For example, users can view a summary of adverse event reports received from 1968 to the present or for a specific timeframe. In addition, users can search on a product of interest within a specific timeframe.

Will there be a tutorial so I can learn how to use this database?

Yes, a recorded webinar (/about-fda/pharmacy-student-experiential-program/fda-drug-topics-fda-adverse-events-reporting-system-faers-public-dashboard-january-30-2018) is available which reviews the capabilities, and limitations, of the FAERS public dashboard.

Is the FAERS public dashboard accessible on an Android™ or iPhone®?

Yes, but the user interface layout may not be very user friendly. FDA will continue to work on the dashboard to make the user interface Android and iPhone friendly.

Can I download my search results from the dashboard?

Yes, you will be able to export a limited set of search data to an Excel® spreadsheet and then download it. FDA will still continue to provide the FAERS Latest Quarterly Data Files (/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-latest-quarterly-data-files) online.

Note: The data fields listed on the FAERS Dashboard currently is a subset of the data fields available in the FAERS Quarterly Data files. Future release of the FAERS Dashboard plans to make the other data fields available. Also the data displayed in the FAERS Dashboard may not be identical to the data in the FAERS Quarterly Data files due to different data extraction dates.

Where else can I find safety information?

- Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS): quarterly reports on potential serious side effects identified by FAERS. (/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system)
- Post-marketing Drug and Biologic Safety Evaluations (/drugs/surveillance/postmarket-drug-and-biologic-safety-evaluations): provides summary information about ongoing and completed post-marketing safety evaluations of adverse experience reports made to FDA for New Drug Applications (NDAs) and Biologic License Applications (BLAs) approved since September 27, 2007.
- Center for Drug Evaluation and Research (CDER): Drug Safety and Availability (https://www.fda.gov/Drugs/DrugSafety/default.htm)
- Post-market Drug Safety Information for Patients and Providers (https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm)
- MedWatch: The FDA Safety Information and Adverse Event Reporting Program (https://www.fda.gov/Safety/MedWatch/default.htm)

How are versions of a case in FAERS handled?

Each unique submission of a case received is assigned a version number (for example, Case #1234567, version 1). The initial version received will be version 1. If a follow up is received on a previously submitted case, then that version of the case will be version 2, and so on. The latest version of a case represents the most current information about that case.

The data is updated quarterly.

What points should I consider while viewing the dashboard content?

When you view the website output of reported reactions (side effects or adverse drug reactions) for a drug product, it is important to consider the following points:

- **Data Quality:** There are many instances of duplicative reports and some reports do not contain all the necessary information. Duplicate reporting occurs when the same report is submitted by the consumer and the sponsor. The information in FAERS evolves daily and the number of individual cases may increase or decrease. It is therefore possible that the information on this website may change over time.
- **Existence of a report does not establish causation:** For any given report, there is no certainty that a suspected drug caused the reaction. While consumers and healthcare professionals are encouraged to report adverse events, the reaction may have been related to the underlying disease being treated, or caused by some other drug being taken concurrently, or occurred for other reasons. The information in these reports reflects only the reporter's observations and opinions.

- **Information in reports has not been verified:** Submission of a report does not mean that the information included in it has been medically confirmed nor it is an admission from the reporter that the drug caused or contributed the event.
- **Rates of occurrence cannot be established with reports:** The number of suspected reactions in FAERS should not be used to determine the likelihood of a side effect occurring. The FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, information in these reports cannot be used to estimate the incidence (occurrence rates) of the reactions reported.
- **Patients should talk to their doctor** before stopping or changing how they take their medications.
- **Patient Outcomes received in FAERS**: These data describe the outcome of the patient as defined in U.S. reporting regulations (21 CFR 310.305, 314.80, 314.98, 600.80). Serious means that one or more of the following outcomes were documented in the report: death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome. Documenting one or more of these outcomes in a report does not necessarily mean that the suspect product(s) named in the report was the cause of the outcomes.

Importantly, the FAERS data by themselves are not an indicator of the safety profile of the drug.

Exhibit 45

Kathi A. Aultman, et al., *Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019*, 26 Law & Medicine 3 (2021).

Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019

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ABSTRACT: *Objectives:* Primary: Analyze the Adverse Events (AEs) reported to the Food and Drug Administration (FDA) after use of mifepristone as an abortifacient. Secondary: Analyze maternal intent after ongoing pregnancy and investigate hemorrhage after mifepristone alone.

***Methods*: Adverse Event Reports (AERs) for mifepristone used as an abortifacient, submitted to the FDA from September 2000 to February 2019, were analyzed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3).**

***Results*: The FDA provided 6158 pages of AERs. Duplicates, non-US, or AERs previously published (Gary, 2006) were excluded. Of the remaining, there were 3197 unique, US-only AERs of which there were 537 (16.80%) with insufficient information to determine clinical severity, leaving 2660 (83.20%) Codable US AERs (Figure 1). Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.**

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The deaths included: 9 (45.00%) sepsis, 4 (20.00%) drug toxicity/ overdose, 1 (5.00%) ruptured ectopic pregnancy, 1 (5.00%) hemorrhage, 3 (15.00%) possible homicides, 1 (5.00%) suicide, 1 (5.00%) unknown (Table 1).

Retained products of conception and hemorrhage caused most morbidity. There were 75 ectopic pregnancies, including 26 ruptured ectopics (includes one death).

There were 2243 surgeries including 2146 (95.68%) D&Cs of which only 853 (39.75%) were performed by abortion providers.

Of 452 patients with ongoing pregnancies, 102 (22.57%) chose to keep their baby, 148 (32.74%) had terminations, 1 (0.22%) miscarried, and 201 (44.47%) had unknown outcomes.

Hemorrhage occurred more often in those who took mifepristone and misoprostol (51.44%) than in those who took mifepristone alone (22.41%).

***Conclusions*: Significant morbidity and mortality have occurred following the use of mifepristone as an abortifacient. A pre-abortion ultrasound should be required to rule out ectopic pregnancy and confirm gestational age. The FDA AER system is inadequate and significantly underestimates the adverse events from mifepristone.**

A mandatory registry of ongoing pregnancies is essential considering the number of ongoing pregnancies especially considering the known teratogenicity of misoprostol.

At the very least, the FDA should reinstate the original 2011 REMS and strengthen the reporting requirements.

***Conflict of Interest Statement*: The authors did not report any potential conflicts of interest. Authors note that although Dr. Harrison is an associate editor for Issues in Law and Medicine, she recused herself from any involvement in the peer review process for this manuscript.**

***Keywords*: Mifepristone, Mifeprex, RU-486, Misoprostol, Abortifacient, Medical Abortion, Abortion Pill, Medical Abortion Complications, No touch abortion, DIY Abortion, Self-Administered Abortion, Adverse Events, Adverse Event Reports, Post-marketing Surveillance, FAERS, Drug Safety, Emergency Medicine, FDA, REMS, Risk Evaluation Mitigation Strategy.**

Introduction

The application for mifepristone (RU-486, RU-38486, Mifeprex) as an abortifacient was submitted to the Food and Drug Administration (FDA) in 1996 by the Population Council, which was given the manufacturing and distribution rights from Roussel Uclaf. [1] The Population Council partnered with Danco Laboratories, newly created in 1995, and gave them the manufacturing, marketing, and distribution rights. The FDA approved mifepristone in September 2000 under restricted distribution regulations (Subpart H) due to the FDA's conclusion that restrictions "on the distribution and use of mifepristone are needed to ensure safe use of this product."[2]

Included in these restrictions was the requirement that all serious Adverse Events (AEs), after the use of mifepristone as an abortifacient, be reported to the FDA by Danco as part of post-marketing surveillance. According to the FDA,[3] the purpose of such post-marketing surveillance includes identification of potential risks recognized after the time of approval, identification of unexpected deaths, causal attribution of AEs based on the product's known pharmacological action, and AEs for which a Risk Evaluation Mitigation Strategy (REMS) is intended to mitigate the risk.

In 2006, in response to the deaths of 4 women from a rare bacterial sepsis from *Clostridium sordellii (C. sordellii)*, the FDA and CDC convened a workshop, during which mifepristone alteration of the immune system was detailed, and they concluded that such alteration could lead to impaired ability to respond to *C. sordellii* toxin.[4]

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[1] Citizen petition re: Request for Stay and Repeal of the Approval of Mifeprex (mifepristone) for the Medical Termination of Intrauterine Pregnancy through 49 Day's Gestation Final. Before the Department of Health and Human Services: Food and Drug Administration. AAPLOG. 2002. 7-10. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Documents/2002%20Aug%2020%20Citizen%20Petition_Mifeprex.pdf

[2] Center for Drug Evaluation and Research. Approval Letter for Mifeprex NDA 20-687. February 18, 2000. Food and Drug Administration. p 5. Accessed November 16, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687approvable00.pdf

[3] US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Best Practices in Drug and Biological Product Postmarket Safety Surveillance for FDA Staff. November 2019. p 7-8. Accessed Jan 16 2021. https://www.fda.gov/media/130216/download p7-8

[4] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109,110. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

There is evidence that both mifepristone[5,6,7] and misoprostol[8] can suppress immune response to *C. sordellii* in animal models.

In response to the septic deaths, Planned Parenthood changed their off-label protocol from vaginal administration of misoprostol to buccal in 2006.[9,10] Yet, as we found in our analysis, sepsis deaths from *C. sordellii* and other bacteria continued to occur after 2007. All sepsis deaths occurred with either vaginal or buccal misoprostol, which were both off label routes of administration until the buccal route was authorized in 2016.[11]

In 2011, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for Mifepristone incorporating the original restrictions.[12] In May 2015, Mifepristone's sponsor submitted a supplemental new drug application to the FDA to obtain approval to revise the drug's labeling, which the FDA approved in 2016.[13,14] The 2016 changes in the Regimen and Prescriber Agreement extended the original gestational age limit from 49 days to 70 days, changed the mifepristone dose from 600 mg to 200 mg orally, changed the misoprostol dose from 400 mcg orally on Day 3 to 800 mcg buccally on Day 2 or 3, allowed non-physicians to become prescribers, reduced the number of required office visits from 3 to just one initial office visit, and allowed a repeat dose of misoprostol if complete expulsion did not occur.[15] The prescriber agreement was changed so

[5] Emerging Clostridial Disease Workshop: May 11, 2006, Atlanta, GA. Department of Health and Human Services, Centers for Disease Control and Prevention, Food and Drug Administration, National Institutes of Health. 2006. p. 109, 110 Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2006%20CDC%20FDA%20Clostridial%20Disease%20Transcript.pdf

[6] Webster JI, Sternberg EM. Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. J Endocrinol. 2004;181(2):212, 213, 216, 217. doi.org/10.1677/joe.0.1810207

[7] Hawes AS, Rock CS, Keogh CV, Lowry SF, Calvano SE. In vivo effects of the antiglucocorticoid RU 486 on glucocorticoid and cytokine responses to Escherichia coli endotoxin. Infect Immun. 1992;60(7):2645, 2646. doi:10.1128/IAI.60.7.2641-2647.1992

[8] Aronoff DM, Hao Y, Chung J, et al. Misoprostol impairs female reproductive tract innate immunity against Clostridium sordellii. J Immunol. 2008;180(12):8227-8229. https://doi.org/10.4049/jimmunol.180.12.8222

[9] Trussell, J, Nucatola, D, Fjerstad, M, Lichtenberg, ES. Reduction in infection-related mortality since modifications in the regimen of medical abortion. Contraception, 2014;89(3):193-196. https://doi.org/10.1016/j.contraception.2013.11.020

[10] Fjerstad M, Trussell, J, Sivin, I, Lichtenberg, ES, Rates of Serious Infection after Changes in Regimens for Medical Abortion. N Engl J Med. 2009 July 9;361(2):148-149. July 9, 2009 N Engl J Med 2009; 361:145-151. doi:10.1056/NEJMoa0809146

[11] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[12] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. 1-11. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[13] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 1. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[14] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. 1-8. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[15] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p.7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

that instead of being required to "report any hospitalization, transfusion or other serious event to Danco Laboratories,"[16] providers were only required to report deaths.[17] The requirement to report ongoing pregnancies that are not terminated was also eliminated. "The FDA approved GenBioPro, Inc.'s abbreviated new drug application (ANDA) for generic Mifeprex on April 11, 2019" and "established a single, shared system REMS for mifepristone products" without substantially changing the REMS.[18]

During the COVID-19 pandemic the Maryland District Court issued a preliminary injunction prohibiting the FDA from enforcing the in-person dispensing and signature requirements contained in the mifepristone REMS.[19] This decision eliminated the need for an initial office visit for dispensing the medication and opened the door for dispensing of the drug via telehealth with no actual clinician contact. On January 12, 2021, the Supreme Court enabled the FDA to enforce the mifepristone REMS.[20] These requirements are essential for the safety of women and must be kept in place.

The first systematic analysis of these Adverse Event Reports (AERs) obtained by the Freedom of Information Act (FOIA), was published by Gary and Harrison in 2006.[21] This paper extends that analysis to AERs not previously published and augments the scant published literature on mifepristone safety.

Objectives

Primary: To analyze and codify the significant adverse events and their treatment after the use of mifepristone as an abortifacient, extending the previously published analysis by Gary in 2006.[22] Secondary: To examine maternal decisions in the case of ongoing pregnancy after attempted mifepristone termination, and to determine if failing to take misoprostol after mifepristone increased the risk of hemorrhage.

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[16] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2011. p. 7. Reference ID: 2957855. Published June 8, 2011. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifeprex_2011-06-08_Full.pdf

[17] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[18] Questions and Answers on Mifeprex. Food and Drug Administration. March 28, 2018. Updated 4-12-2019. Accessed November 13, 2020. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/questions-and-answers-mifeprex

[19] American College of Obstetricians and Gynecologists, et al., v. Food and Drug Administration, et al., No. 20-1320, 2020 WL 3960625 (D. Md. July 13, 2020). Accessed November 16th, 2020. https://www.courthousenews.com/wp-content/uploads/2020/07/093111166803.pdf

[20] FDA v ACOG. SCOTUS. 20a34_3f14. Accessed January 20, 2021. https://www.supremecourt.gov/opinions/20pdf/20a34_3f14.pdf

[21] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[22] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Materials and Methods

FDA AERs related to the use of mifepristone from September 2000 to February 2019 were obtained through the Freedom of Information Act (FOIA) from the FDA, and a comparison was made with FDA reports available online on the FDA Adverse Events Reporting System (FAERS) Dashboard.[23] Duplicate AERs were identified by comparing FDA case identification numbers, manufacturer identification numbers, dates of treatment, patient age, and descriptions of case scenarios to ensure that each case was included only once in this analysis. The authors excluded duplicates, cases originating outside of the United States, and cases previously published in the Gary analysis[24] (Figure 1).

One of the concerns in looking at AEs is the risk of falsely assigning causality. The FDA does not give guidance for determining causality for AEs in the AERs but does give guidance for selecting AEs for inclusion in the Adverse Reaction section of the Drug Label.[25] They recommend that, "Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as" the "frequency of reporting," "the extent to which the adverse event is consistent with the pharmacology of the drug," "the timing of the event relative to the time of drug exposure," and other factors. Although a causal relationship cannot be attributed with certainty to all reported AEs for a drug, a causal relationship seems probable for each of the categories of AEs we chose to analyze based on these factors, except for ectopic pregnancies and some of the deaths. Ectopic pregnancies were included in our analysis not because there is a causal relationship, but because ectopic pregnancy is a contraindication to the use of mifepristone and the diagnosis was missed, putting women's lives at risk. The deaths must be evaluated individually to determine causality.

Because reporting is often voluntary and sporadic, there is no denominator for how many mifepristone abortions are performed in the U.S. It was therefore impossible to calculate complication rates for mifepristone and misoprostol abortions based on AER data. For clarity, we specified the denominator used in each case. Coding for severity was done using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAEv3),[26] since this was

[23] FDA Adverse Events Reporting System (FAERS) Public Dashboard. Food and Drug Administration. Accessed November 13, 2020. https://fis.fda.gov/sense/app/d10be6bb-494e-4cd2-82e4-0135608ddc13/sheet/33a0f68e-845c-48e2-bc81-8141c6aaf772/state/analysis

[24] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[25] Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); January 2006. P. 8. Accessed January 8, 2021. https://www.fda.gov/media/72139/download

[26] Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Cancer Center Therapy Evaluation Program (CTEP); 2003. 1-77. Published December 12, 2003. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/CTCAEv3.pdf

the methodology used in the original analysis of the first 607 Adverse Events.[27] The five levels of coding are: Mild, Moderate, Severe, Life-threatening, and Death.

Overall severity (Figure 1) for each unique AER was determined independently by two board-certified physicians (Obstetrics and Gynecology or Family Medicine). Since within each AER, a patient may have experienced several Adverse Events (AEs), the overall severity of the AER was based on the highest severity of its AEs. For the diagnoses we analyzed (Table 1), each AE was coded in the same manner and stratified according to type, severity, and treatment. Disagreements were resolved by discussion or review by a third board-certified Obstetrician-Gynecologist who also reviewed coding for uniformity. Surgeries, transfusions, providers, and location of treatment were analyzed and tabulated.

Ruptured ectopic pregnancies were coded as Life-threatening and unruptured ectopic pregnancies as Severe.

Infections were coded as Life-threatening when evidence of sepsis was present, or ICU-level treatment was required. They were coded as Severe if parenteral/IV antibiotics were given and Moderate if oral antibiotics were prescribed.

Life-threatening hemorrhage was defined, as in the previous analysis, to be transfusion of two or more units of packed red blood cells (PRBCs), hemoglobin less than 7, or documented large volume, rapid blood loss with clinical symptomatology of acute blood loss anemia (e.g., syncope, tachycardia, hypotension). Severe hemorrhage was defined as requiring surgical intervention and/or less than 2 U PRBCs. Moderate hemorrhage was defined as management with fluids/medication alone.

Retained Products of Conception (RPOC) was coded as Severe if a dilatation and curettage/evacuation (D&C) was performed. Ongoing viable intrauterine pregnancy was considered equivalent in severity to RPOC requiring curettage and thus Severe. When the ultimate outcome was unknown, the pregnancy was considered ongoing if "ongoing pregnancy" was noted or ultrasound showed cardiac motion or significant growth.

AEs which did not contain sufficient information to assign an accurate severity code were deemed "Uncodable." AERs lacking any codable information were deemed overall Uncodable.

The percent of women with significant hemorrhage after mifepristone alone was compared to those who took both mifepristone and misoprostol, to investigate the validity of the assertion that lack of subsequent misoprostol administration was a causative factor in hemorrhage after mifepristone use.[28]

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[27] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[28] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progester-one to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

Results

Adverse Event Report Overall Severity

Figure 1 summarizes the handling of the AERs provided by the FDA and their severity coding. The FDA provided 6158 pages of AERs. Of these, any duplicates, non-US, or AERs previously published in the Gary paper were excluded from the analysis. There were 3197 unique, US-only AERs of which 537 had insufficient information to determine clinical severity, leaving 2660 Codable US-only AERs. Of these, 20 were Deaths, 529 were Life-threatening, 1957 were Severe, 151 were Moderate, and 3 were Mild.

Deaths (Table 1)

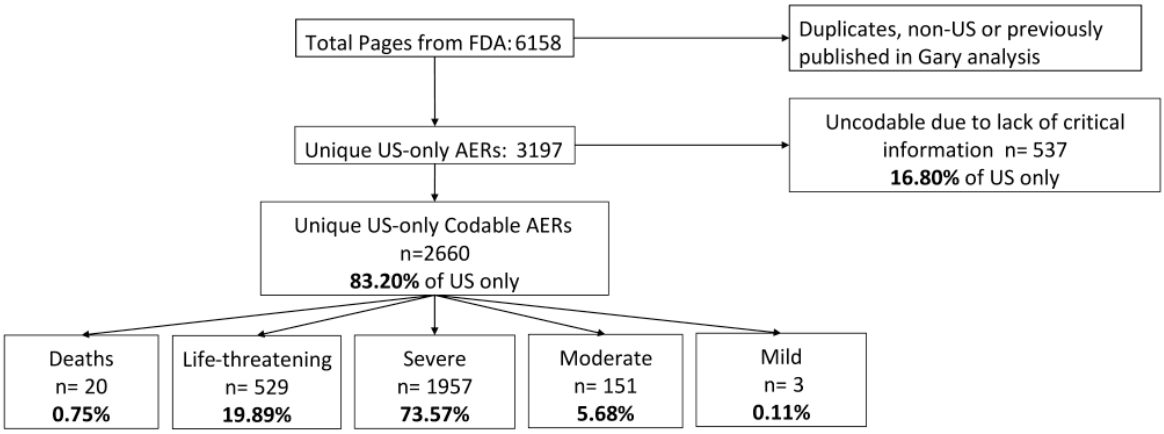
Our analysis identified 23 of the 24 deaths reported by the FDA as of 2018.[29] Three of those deaths were previously published in the Gary paper[30] leaving 20 deaths (Table 1). Our analysis yielded a total of 7 sepsis deaths. These included five cases of *C. sordellii* and one case of *Clostridium perfringens*, all consistent with those reported by the FDA. There was an additional death which we categorized as a sepsis death whereas the FDA labeled this case as "delayed onset toxic shock-like syndrome" but did not include it as a sepsis death. The patient had an exploratory laparotomy revealing green pus, which was culture positive for *prevotella* and *peptostreptococcus,* and she died intraoperatively.[31]

[29] RCM # 2007-525 NDA 20-687 Mifepristone U.S. Post-Marketing Adverse Events Summary through 12/31/2018. FDA. 1-2. Reference ID: 4401215. Accessed November 13, 2020. https://www.fda.gov/media/112118/download

[30] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

[31] Individual Case Safety Report number 4734082-4-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received August 4, 2005. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/Peptostreptococcus%20death%209.10277-8.pdf

Figure 1. AER Distribution



Note: From 2000 to 2016 FDA only required the manufacturer to report AEs which were severe, life-threatening or had fatal outcomes. Since 2016, FDA only requires the manufacturer to report fatal outcomes.

We categorized two deaths as suspicious for infectious death. One case was labeled by the FDA as "undetermined natural causes," however, the AER reported the cause of death as "acute visceral and pulmonary (1420 grams) congestion and edema," [32] which is consistent with the clinical findings for sepsis/Acute Respiratory Distress Syndrome (ARDS). This patient had autopsy-proven retained products of conception and blood cultures which grew *Strep viridans* isolated at less than 24 hours incubation. One additional case which the FDA labeled "methadone overdose"[33,34] we considered suspicious for sepsis. Prior to her death, this patient had fever and chills and was treated by an outside physician with cephalexin, which would have been ineffective against infections from *C. sordellii* or anaerobic gram-negative bacilli. There was no autopsy report or toxicology report in the AER.

Non-infectious deaths include one death that the FDA listed as "natural," caused by "pulmonary emphysema."[35] This patient was a 40-year-old chronic smoker who died within hours of misoprostol ingestion and had a contusion on her head consistent with a fall, a scenario possibly related to a cardiac event or acute respiratory reaction to misoprostol. She had an intact fetus at the time of

[32] Individual Case Safety Report number 9587011-03-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received May 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%20Visc%20pul%20cong.pdf

[33] Individual Case Safety Report number 4970303-0-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received April 21, 2014. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/death%2023%20yo%20meth%20overdose%20fever%20and%20chills.pdf

[34] Individual Case Safety Report number 5063156-8-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received July 27, 2006. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/methadone%20AER%20(1).pdf

[35] Individual Case Safety Report number 11283049-02-00-01. Danco Laboratories, LLC. Office of Post-marketing Drug Risk Assessment, Food and Drug Administration. Received December 8, 2015. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/emphysema.pdf

autopsy. Other non-infectious deaths included one death from a ruptured ectopic pregnancy, one from hemorrhage, 3 possible homicides, one suicide, and 4 deaths from drug toxicity/overdose. It is unknown whether the 8 women who died by homicide, suicide, or drug toxicity/overdose were screened for domestic violence, drug addiction, or depression prior to the abortion.

Infection (Table 1)

Infection was the leading cause of mortality. There were 502 cases of infection, which included 9 Deaths, 39 had Life-threatening sepsis, 249 were Severe infections, 132 Moderate infections, and 73 infections which were Uncodable.

Ectopic Pregnancy (Table 1)

There were 75 ectopic pregnancies. Of these, 26 were ruptured, including 1 death. Twenty-four were unruptured, and there were 25 for which the rupture status was not given. Fifty-six ectopic pregnancies were treated surgically and 11 were treated with methotrexate. The management was not documented in 7 cases. The patient who died received no treatment as she died on the way to the hospital.

Retained Products of Conception (RPOC) (Tables 1 and 2)

RPOC was the leading cause of morbidity. There were 977 confirmed cases of RPOC, including 2 molar pregnancies, and 1506 likely cases of RPOC (documentation was inadequate for confirmation). Of the 2146 total D&Cs, most were for RPOC, including 897 for confirmed RPOC, 1058 for bleeding or presumed RPOC, but no pathology was provided, and 2 for molar pregnancy. A small percentage of RPOC had medical treatment or no treatment.

Hemorrhage/Bleeding (Table 1)

There were 1639 bleeding events including one death. These included 466 Life-threatening and 642 Severe events. There were also 106 events coded as Moderate, while 424 reports of bleeding were Uncodable given the information in the database.

Ongoing Pregnancy (Table 1)

There were 452 ongoing pregnancies. Of these 102 chose to keep their baby, 148 chose termination, 1 miscarried, and 201 had an unknown outcome. Of those with an unknown outcome, there were 44 patients referred or scheduled for termination, who did not follow through (39 no-showed, 3 canceled, 2 did not schedule).

Surgeries (Table 2)

There were 2243 surgeries including 2146 D&Cs, 76 laparoscopies/laparotomies without hysterectomy, 7 hysterectomies, and 14 other surgeries. Of the hysterectomies, 3 were performed for sepsis, 2 for hemorrhage, 1 for a cervical ectopic, and 1 for placenta accreta. There were 1291 surgeries performed in the hospital or ER and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were performed in the hospital or ER, and 952 in an outpatient setting. Of the 2146 D&Cs, 1194 were provided by the Hospital or ER, 853 by the abortion provider, and 99 by another outpatient provider.

Transfusions (Table 2)

Four hundred and eighty-one patients required blood transfusion following medical abortions. Of these, 365 received 1 to 10 units packed red blood cells (PRBCs) alone, 1 received fresh frozen plasma (FFP) alone, 8 received a combination of PRBCs and FFP, and 107 received an unknown amount of blood product.

Relationship of Misoprostol Use to Hemorrhage (Table 3)

The use of mifepristone with misoprostol was associated with a higher incidence of hemorrhage than the use of mifepristone alone. Of the 3056 women who took both mifepristone and misoprostol, 1572 (51.44%) hemorrhaged, whereas, among the 58 women who did not take misoprostol, only 13 (22.41%) hemorrhaged. It was unclear whether 84 patients took misoprostol or not. Fifty-four (64.29%) of them hemorrhaged. The hemorrhage rate was higher for the mifepristone with misoprostol group as compared to the mifepristone alone group even if all the unknowns were assigned to the mifepristone alone group or vice versa.

Table 1 - Diagnoses[a]

Deaths	Deaths (n)	Deaths (%)	Deaths: % of (3197) Unique US AERs (%)	Organism (%)
Sepsis	9	45.00%	0.28%	
Sepsis confirmed	7	35.00%	0.22%	100%
Clostridium sordellii	*5*	*25.00%*	*0.16%*	*71.43%*
Clostridium perfringens / Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Peptostreptococcus	*1*	*5.00%*	*0.03%*	*14.29%*
Sepsis Likely, Unknown Organism	2	10.00%	0.06%	
Visceral and Pulmonary Congestion consistent with ARDS / sepsis	1	5.00%	0.03%	
Fever / chills treated with cephalexin, found dead[b]	1	5.00%	0.03%	
Ruptured Ectopic Pregnancy	1	5.00%	0.03%	
Hemorrhage	1	5.00%	0.03%	
Possible Homicide	3	15.00%	0.09%	
Suicide	1	5.00%	0.03%	
Drug Toxicity/Overdose	4	20.00%	0.13%	
Unknown[c]	1	5.00%	0.03%	
Total Deaths	**20**	**100%**	**0.63%**	
Infections, Level of Severity	**Infections (n)**	**Infections (%)**	**Infections: % of (3197) Unique US AERs (%)**	
Death	9	1.79%	0.28%	
Life threatening infection/sepsis	39	7.77%	1.22%	
Severe infection (IV anitbiotics)	249	49.60%	7.79%	
Moderate infection (oral antibiotics)	132	26.29%	4.13%	
Uncodable[d]	73	14.54%	2.28%	
Total Infections	**502**	**100%**	**15.70%**	

Table 1 – Diagnoses (Continued)

Ectopic Pregnancies, Rupture Status	Ectopic Pregnancies (n)	Ectopic Pregnancies (%)	Ectopic Pregnancies: % of (3197) Unique US AERs (%)
Ruptured[e]	26	34.67%	0.81%
Unruptured[f]	24	32.00%	0.75%
Surgical Treatment	13	17.33%	0.41%
Methotrexate Treatment	11	14.67%	0.34%
Unknown Rupture Status[g]	25	33.33%	0.78%
Surgical Treatment	18	24.00%	0.56%
Unknown Treatment	7	9.33%	0.22%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**
Ectopic Pregnancies, Level of Severity	**Ectopic Pregnancies (n)**	**Ectopic Pregnancies (%)**	**Ectopic Pregnancies: % of (3197) Unique US AERs**
Death	1	1.33%	0.03%
Life Threatening (Ruptured, survived)	25	33.33%	0.78%
Severe (Not Ruptured)	24	32.00%	0.75%
Uncodable	25	33.33%	0.78%
Total Ectopic Pregnancies	**75**	**100%**	**2.35%**

Table 1 – Diagnoses (Continued)

Retained Products of Conception (RPOC)	RPOC (n)	RPOC (%)	RPOC: % of (3197) Unique US AERs (%)
RPOC confirmed	977	39.35%	30.56%
RPOC confirmed (by pathology or ultrasound); Had D&C	891	35.88%	27.87%
RPOC confirmed by U/S but D&C not documented	29	1.17%	0.91%
RPOC treated medically	27	1.09%	0.84%
Tissue at os (no D&C)[h]	27	1.09%	0.84%
Molar Pregnancy	2	0.08%	0.06%
No Treatment, RPOC on autopsy	1	0.04%	0.03%
RPOC Likely	1506	60.65%	47.11%
Had D&C, no pathology provided	1056	42.53%	33.03%
Unknown[i]	450	18.12%	14.08%
Total RPOCs	**2483**	**100%**	**77.67%**
Bleeding Events, Level of Severity	**Bleeding Events (n)**	**Bleeding Events (%)**	**Bleeding Events: % of (3197) Unique US AERs**
Death	1	0.06%	0.03%
Life threatening or Disabling: 2U or more transfusion or Hgb<7 or witnessed massive blood loss	466	28.43%	14.58%
Severe: surgical intervention and/or 1 U transfusion	642	39.17%	20.08%
Moderate: medical intervention	106	6.47%	3.32%
Uncodable[j]	424	25.87%	13.26%
Total Bleeding Events	**1639**	**100%**	**51.27%**

Table 1 – Diagnoses (Continued)

Ongoing Pregnancies, Outcome	Ongoing Pregnancies (n)	Ongoing Pregnancies	Ongoing Pregnancies: % of (3197) Unique US AERs (%)	Ongoing Pregnancies with Unknown Outcome (%)
Desired to Keep Pregnancy	102	22.57%	3.19%	
Kept Pregnancy	101	22.35%	3.16%	
Kept Pregnancy but baby died in-utero	1	0.22%	0.03%	
Terminated Pregnancy	148	32.74%	4.63%	
Surgical Termination[k]	139	30.75%	4.35%	
Medical Termination	9	1.99%	0.28%	
Unknown Intent, miscarried[l]	1	0.22%	0.03%	
Unknown Outcome	201	44.47%	6.29%	100%
Referred D&C but did not show	39	8.63%	1.22%	19.40%
Referred D&C but cancelled	3	0.66%	0.09%	1.49%
Told to schedule/referred D&C did not go	2	0.44%	0.06%	1.00%
Unknown outcome, no other information[m]	157	34.73%	4.91%	78.11%
Total	**452**	**100%**	**14.14%**	

[a] Because of rounding, percentages may not appear to add up exactly.
[b] FDA attributed to methadone overdose.
[c] 40 year old smoker died within hours of misoprostol ingestion. Per FDA, "natural causes due to severe pulmonary emphysema."
[d] Patients with documented infection but inadequate information to determine severity.
[e] One of the ruptured ectopics died on the way to the hospital. The other 25 were treated surgically.
[f] The unruptured ectopics include two cornual ectopics, one treated surgically and one treated medically.
[g] Includes two cervical ectopics, one treated with D&C/Hysterectomy/massive transfusion and one with unknown treatment.
[h] Either with path provided, or described as RPOC, placental fragments, fetus, or tissue.
[i] Suspected RPOC indicating D&C needed, but not documented as being done.
[j] Patients with documented bleeding but inadequate information to determine severity.
[k] Includes one hysterotomy for pregnancy in non-communicating horn.
[l] After no show for surgical termination.
[m] Includes 10 with known gestational age 20-29 weeks.

Table 2 – Treatment[a]

Type of Surgery	Type of surgery (n)	Type of surgery (%)	Surgery: % of (3197) Unique US AERs (%)
D&C[b]	**2146**	**95.68%**	**67.13%**
Hysterectomy	**7**	**0.31%**	**0.22%**
Sepsis (includes 2 deaths)	3	0.13%	0.09%
Hemorrhage after uterine perforation	2	0.09%	0.06%
Hemorrhage - Cervical Ectopic	1	0.04%	0.03%
Placenta accreta	1	0.04%	0.03%
Laparoscopy/Laparotomy without hysterectomy	**76**	**3.39%**	**2.38%**
Ectopic (Actual or Suspected)	66	2.94%	2.06%
Infection	7	0.31%	0.22%
Uterine Perforation	1	0.04%	0.03%
Salpingo oophorectomy for Torsion	1	0.04%	0.03%
Hysterotomy for pregnancy in non-communicating horn	1	0.04%	0.03%
Other Surgeries	**14**	**0.62%**	**0.44%**
Uterine Artery Embolization	1	0.04%	0.03%
Vaginal sutures (after 15 week surgical termination for ongoing pregnancy)	1	0.04%	0.03%
Paracenteses (multiple, same patient, death)	1	0.04%	0.03%
Necrotozing fasciitis debridement and below knee amputation	1	0.04%	0.03%
Upper and lower endoscopy for bright red bleeding	1	0.04%	0.03%
Unknown surgery for deep venous thrombosis	1	0.04%	0.03%
Angioplasty	1	0.04%	0.03%
Cholecystectomy	2	0.09%	0.06%
Appendectomy	1	0.04%	0.03%
Laceration repair (scalp, chin)	2	0.09%	0.06%
Unknown Surgery	2	0.09%	0.06%
Total	**2243**	**100%**	**70.16%**

Table 2 – Treatment (Continued)

Location of Surgery	Location of Surgery (n)	Location of Surgery (%)
All Surgeries	**2243**	**100.00%**
Hospital or ER	1291	57.56%
Outpatient	952	42.44%
D&C	**2146**	**100.00%**
Hospital or ER	1194	55.64%
Outpatient	952	44.36%
Surgical Provider for D&C	**Surgical Provider (n)**	**Surgical Provider (%)**
Hospital/ER	1194	55.64%
Abortion Provider	853	39.75%
Other Provider	99	4.61%
Total	**2146**	**100%**
Indication for D&Cs	**Indication for D&C (n)**	**Indication for D&C (%)**
Confirmed D&C[c]	**2146**	**100%**
RPOC (confirmed by pathology or ultrasound)	897	41.80%
RPOC/Bleeding (no pathology provided)	1058	49.30%
Ongoing pregnancy, surgical termination by D&C	139	6.48%
RPOC ruled out	34	1.58%
Ectopic evaluation	12	0.56%
Molar pregnancy	2	0.09%
Not able to take misoprostol	4	0.19%
Possible D&C	**680**	
Possible RPOC, unknown treatment, possible D&C	450	
RPOC confirmed by U/S but D&C not documented	29	
Ongoing pregnancy Unknown outcome, possible D&C	201	
TOTAL (Confirmed and Possible)	**2826**	

Table 2 – Treatment (Continued)

Transfusions	Transfusions (n)	Transfusions (%)	Transfusion: % of (3197) Unique US AERs (%)
PRBC alone	**365**	**75.88%**	**11.42%**
1U	32	6.65%	1.00%
1-2U	1	0.21%	0.03%
2U	246	51.14%	7.69%
2.5U	1	0.21%	0.03%
3U	45	9.36%	1.41%
4U	27	5.61%	0.84%
5U	5	1.04%	0.16%
6U	5	1.04%	0.16%
7U	2	0.42%	0.06%
10U	1	0.21%	0.03%
Other Blood products	**9**	**1.87%**	**0.28%**
1 U FFP	1	0.21%	0.03%
2 U PRBC/1 U FFP	1	0.21%	0.03%
2 U PRBC/ 4 U FFP	1	0.21%	0.03%
3 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 1 U FFP	1	0.21%	0.03%
4 U PRBC/ 2 U FFP	1	0.21%	0.03%
5 U PRBC/ 4 U FFP	1	0.21%	0.03%
6 U PRBC/ 2 U FFP	1	0.21%	0.03%
7 U PRBC/ FFP and Platelets unknown amount	1	0.21%	0.03%
Unknown amount (documented as given, units not recorded)	**107**	**22.25%**	**3.35%**
Total[d]	**481**	**100%**	**15.05%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] With or without suction, one with hysteroscopy.
[c] There were 8 patients who had 2 D&Cs and one who required uterine artery embolization. There were 4 perforations: two had resultant hysterectomies, one had a laparoscopy, and one received 2 U PRBCs but no documented surgery.
[d] Additionally there were 7 patients who likely received transfusion, but was not recorded, 3 patients who refused transfusion, and 1 patient for whom transfusion was considered but not given.

Table 3 – Relationship of Misoprostol to Hemorrhage[a]

	Mifepristone + Misoprostol		Mifepristone alone		Unknown		Mifepristone + Misoprostol + unknown [b]		Mifepristone alone + unknown [c]	
	n	%	n	%	n	%	n	%	n	%
No Hemorrhage	**1484**	**48.56%**	**45**	**77.59%**	**30**	**35.71%**	**1514**	**48.23%**	**75**	**52.82%**
Hemorrhage	**1572**	**51.44%**	**13**	**22.41%**	**54**	**64.29%**	**1625**	**51.77%**	**67**	**47.18%**
Death	1	0.03%	0	0.00%	0	0.00%	1	0.03%	0	0.00%
Life threatening	441	14.43%	5	8.62%	20	23.81%	461	14.69%	25	17.61%
Severe	633	20.71%	3	5.17%	6	7.14%	639	20.36%	9	6.34%
Moderate	101	3.30%	1	1.72%	4	4.76%	105	3.35%	5	3.52%
Uncodable	396	12.96%	4	6.90%	24	28.57%	420	13.38%	28	19.72%
Total US AERs	**3056**	**100%**	**58**	**100%**	**84**	**100%**	**3139**	**100%**	**142**	**100%**

[a] Because of rounding, percentages may not appear to add up exactly.
[b] Assumes all unknowns took both mifepristone and misoprostol.
[c] Assumes all unknowns took mifepristone, but not misoprostol.

Discussion

This article is critically important considering the paucity of published literature on mifepristone safety and the minimal analysis done on the AERs by the FDA.

Ectopic Pregnancies

Although reported as AEs, ectopic pregnancies are not a direct adverse event from the medication, but rather a contraindication to its administration. They were reported as adverse events because the ectopic pregnancies were missed.

The American College of Obstetricians and Gynecologists (ACOG) notes that "According to the Centers for Disease Control and Prevention, ectopic pregnancy accounts for approximately 2% of all reported pregnancies. However, the true current incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting where events are not tracked, and national surveillance data on ectopic pregnancy have not been updated since 1992. Despite improvements in diagnosis and management, ruptured ectopic pregnancy continues to be a significant cause of pregnancy-related mortality and morbidity. In 2011–2013, ruptured ectopic pregnancy accounted for 2.7% of all pregnancy-related deaths and was the leading cause of hemorrhage-related mortality."[36]

[36] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi:10.1097/AOG.0000000000002560

Confirmed/suspected ectopic pregnancy and undiagnosed adnexal mass are contraindications to mifepristone use under current prescribing requirements. The label warnings state: "Ectopic pregnancy: exclude before treatment." [37] Unfortunately, it is difficult to rule out ectopic pregnancy by history alone because, "half of all women who receive a diagnosis of an ectopic pregnancy do not have any known risk factors."[38] According to ACOG Practice Bulletin No. 193, "The minimum diagnostic evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy." Of the 75 reported ectopic pregnancies in the FDA AERs we analyzed, over a third were known to be ruptured including one death. Clearly, an ultrasound should be required prior to the administration of mifepristone to document that the pregnancy is located within the uterus. Although not 100% effective, this will screen for ectopic pregnancy, confirm gestational age, which can be inaccurate based on menstrual history alone,[39] and screen for adnexal masses, another contraindication to mifepristone use.[40]

Ongoing pregnancies

Of the women with an ongoing pregnancy, less than a third were known to have proceeded with termination of the pregnancy, and almost a quarter were known to have kept their pregnancy; in almost half, the outcome was unknown. The significant percentage of women with ongoing pregnancy who changed their mind and chose to keep their pregnancy, after initially choosing termination, raises concerns regarding the pre-abortion counseling and informed consent they received. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options.

Additionally, the high percentage of women with ongoing pregnancies for whom there is no follow up or known outcome is concerning. As health care providers we are to continue to care for our patients and manage any complications, yet in the AERs we reviewed this was not typically the case for the abortion provider. Furthermore, a federal registry of known outcomes and birth defects is imperative. One of the initial FDA post-marketing requirements for

[37] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. p. 1. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

[38] ACOG Practice Bulletin No. 193: Tubal Ectopic Pregnancy, Obstet Gynecol: March 2018; 131(3): e91-e103. doi: 10.1097/AOG.0000000000002560

[39] Shipp, Thomas D. 2020. Overview of ultrasound examination in obstetrics and gynecology. Lit Rev current through Dec 2020. UpToDate. Edited by Barss A Vanessa. Wolters Kluwer. June 10, 2020. Accessed January 11, 2021. https://www.uptodate.com/contents/ectopic-pregnancy-clinical-manifestations-and-diagnosis/print?source=history_widget.

[40] MIFEPREX. Package insert. Danco; 2016. Approved March 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf

Danco was a surveillance study of outcomes of ongoing pregnancies.[41] The FDA released them from this post-marketing commitment in January 2008 because Danco reported that only one or two ongoing pregnancies per year were followed for final outcomes in part because of consent requirements.[42] This is disturbing in light of the percentage of women in our analysis who kept their pregnancies, as well as those with ongoing pregnancy and unknown outcomes, all of whom could have been followed for final outcomes. The significant lack of follow-up of ongoing pregnancies (44.47% with unknown outcomes) and the very minimal information on those who chose to keep the pregnancy, highlights the need for a national registry especially considering the teratogenicity of misoprostol.[43]

Relationship of Misoprostol to Hemorrhage

The Creinin study of abortion pill reversal was stopped for safety concerns due to hemorrhage in 3 of the 12 study participants.[44] One of the conclusions of that study was that "Patients who use mifepristone for a medical abortion should be advised that not using misoprostol could result in severe hemorrhage, even with progesterone treatment."[45] The authors hypothesized that the absence of misoprostol caused these women to hemorrhage. The women who had documented use of misoprostol in our database hemorrhaged at a higher rate than those documented not to have taken misoprostol.

Reporting of Adverse Events

Although not the initial goal of this study, the analysis of the AERs revealed glaring deficiencies in the AE reporting system making it difficult to properly evaluate adverse events. When mifepristone was approved in 2000, FDA required that providers "must report any hospitalization, transfusion or other serious event to Danco Laboratories."[46] This created an inherent conflict of interest as it is not in the best interest of the entities or providers to report adverse events to those regulating them. Because only severe events were reportable, this requirement likely resulted in an underestimation of moderate and mild AEs. It

[41] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

[42] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[43] Cytotec (misoprostol tablets). Package insert. G.D. Searle; Revised November 2012. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/019268s047lbl.pdf

[44] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):158-165. doi:10.1097/AOG.0000000000003620

[45] Creinin MD, Hou MY, Dalton L, Steward R, Chen MJ. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion: A Randomized Controlled Trial. Obstet Gynecol. 2020;135(1):5. doi:10.1097/AOG.0000000000003620

[46] M I F E P R E X™(Mifepristone) Tablets, 200 mg Prescriber's agreement. Food and Drug Administration. September 28, 2000, 1-2. Accessed November 16, 2020. http://wayback.archive-it.org/7993/20170113112742/http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111364.pdf

is also likely that some of the AEs that we coded as Mild or Moderate were actually Severe but there was not enough information in the AER for us to justify coding them as Severe. In March 2016, the FDA substantially reduced the prescribing requirements and changed the drug protocol [47] and yet at the same time eliminated reporting requirements except for deaths.[48] With the relaxation of reporting requirements, the ability to perform any relevant post-marketing evaluation of mifepristone was lost. It is imperative for the safety of women that the FDA restore and strengthen the 2011 REMS requirements.

The information in the AERs is almost exclusively obtained from abortion providers, rather than the physician treating the complication, yet in this analysis, abortion providers managed only 39.75% of surgical complications (a number which is likely much lower since these are only the cases which are known to the abortion provider). Throughout the reports, there was also a lack of detail and many patients who were simply "lost to follow-up." This resulted in 16.80% of the AERs being Uncodable as to severity and likely under-coding of many AERs and AEs, as coding could only be assigned based on the scant information provided. Many of the AEs experienced by women were unknown to the abortion provider until the follow-up examination, which is troubling considering the poor follow-up rate and elimination of the requirement for an in-office follow up visit. Some of the patient deaths were not known to the abortion provider until they saw the death in an obituary or were contacted by an outside source. Because of this, in addition to abortion providers, hospitals, emergency departments, and private practitioners should be required to report AEs.

Complications occur in the best of hands in all areas of medicine, but as physicians, we are responsible to manage those complications and follow our patients through to resolution. The findings that: 1. the most common outcome of ongoing pregnancy was unknown outcome, 2. abortion providers performed less than half the D&Cs done for complications, and 3. a third of ectopic pregnancies (missed prior to administering the abortifacient) had unknown rupture status, leave us deeply concerned regarding the care these women received. A post-marketing requirement was that there be a "cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention."[49] The applicant was released from this requirement because they stated that because there were so few providers

[47] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[48] NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg: Risk Evaluation and Mitigation Strategy (REMS). Food and Drug Administration. 2016. p. 3, 6. Reference ID: 3909592. Published March 29, 2016. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf

[49] Center for Drug Evaluation and Research. NDA 20-687. Approval Letter for MIFEPREX (mifepristone) Tablets, 200 mg to Population Council. Food and Drug Administration. Written September 28, 2000. Accessed November 13, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.htm

without surgical intervention skills, no meaningful study could be done.[50] Yet, that same year the FDA changed the provider agreement to allow non-physicians to become prescribers.[51] These findings highlight the importance of follow-up and management of complications by the abortion provider. Allowing any further relaxation of mifepristone prescribing requirements will put women at an even higher risk of adverse events

Limitations and Strengths

It was not possible to calculate complication rates for mifepristone and misoprostol abortions based on AER data because there is no denominator for how many mifepristone abortions are performed in the U.S. since reporting is often voluntary and sporadic. For clarity, we specified the denominators we used.

Our analysis was limited by the fact that the number of AEs for which we received reports is likely a gross underestimation of the actual number of AEs that occurred. In our analysis, the surgical management of over half the complications was performed by someone other than the abortion provider, yet treating physicians are not required to report complications. Few reports were generated by those in Emergency Departments and hospitals who treated the complications.

Our analysis was also limited by the lack of information in the AERs, including redaction of critical dates, a paucity of diagnosis and treatment information, and lack of follow up.

Our study has several strengths. Our data comes from information provided to the FDA and is the largest analysis of AERs for mifepristone abortions. This data is publicly available under the Freedom of Information Act so that anyone can verify the data for themselves. This analysis reviews all AERs not reported in the first study by Gary.[52] Although heavily redacted, there was sufficient information in over 80% of the AERs to evaluate severity. An objective standardized system, CTCAEv3, was used to code for severity, and each AER was coded by at least two board-certified obstetrician-gynecologists or family medicine physicians.

Conclusions and Relevance

This article is important because it augments the scant published literature on mifepristone safety.

Due to the lack of adequate reporting of adverse events, especially by those treating them, these unique AERs represent a fraction of the actual adverse events occurring in American women.

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[50] 2016 03 20 FDA resp to Cit Pet.pdf. Docket No. FDA-2002-P-0364. FDA. March 29, 2016. p. 31. Accessed November 13, 2020. https://aaplog.wildapricot.org/resources/2016%2003%2020%20%20FDA%20resp%20to%20Cit%20Pet.pdf

[51] GAO-18-292 Revised Mifeprex Labeling: Food and Drug Administration Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts. Report to Congressional Requesters. Food and Drug Administration. 2018. p. 7. Published March 2018. Accessed November 13, 2020. https://www.gao.gov/assets/700/690914.pdf

[52] Gary M, Harrison D. Analysis of Severe Adverse Events Related to the Use of Mifepristone as an Abortifacient. Ann Pharmacother. 2006 Feb 40(2):191-7. https://doi.org/10.1345/aph.1G481

Significant morbidity and mortality have occurred with the use of mifepristone as an abortifacient, including at least 24 US deaths reported by the FDA from September 2000 to December 2018. Because of this and the significant morbidity associated with this drug, the FDA should consider at a minimum reinstating the original 2011 REMS and strengthening the reporting requirements. The reporting of transfusions, hospitalizations, and other serious adverse events are essential.

Given the morbidity and mortality of undiagnosed ectopic pregnancy, a clear contraindication to the use of mifepristone, an ultrasound to confirm pregnancy location is essential before mifepristone is dispensed.

Considering the significant percentage of women with ongoing pregnancies who chose to continue their pregnancy, there must be reasonable waiting periods, parental involvement, and adequate pre-abortion counseling on all pregnancy options. It is also critical that a pregnancy registry be established.

In our analysis, the patients who used mifepristone alone had a lower rate of hemorrhage than those using mifepristone followed by misoprostol.

The FDA Adverse Event Reporting System is woefully inadequate to determine the post-marketing safety of mifepristone due to its inability to adequately assess the frequency or severity of adverse events. The reliance solely on interested parties to report, the large percentage of uncodable events, the redaction of critical clinical information unrelated to personally identifiable information, and the inadequacy of the reports highlight the need to overhaul the current AER System.

This analysis evaluated 3197 adverse events resulting from the use of mifepristone as an abortifacient and brought to light serious concerns about the safety requirements and care of women undergoing mifepristone abortion. Although complications may occur in the best of hands, and no medical procedure is without risks, safety measures must be employed to minimize these adverse outcomes. Women undergoing abortion should receive the same quality of informed consent and pre-procedural counseling that is standard of care prior to other medical treatment or surgery. It is imperative that women considering abortion be provided adequate and complete information and counseling on risks, advantages, disadvantages, and alternative options. Although there may be disagreements about the ethics of abortion, there must be total agreement that our patients—whether undergoing a medical abortion or otherwise—deserve the highest standard of medical care.

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Exhibit 46

Christina A. Cirucci, et al., *Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act*, 8 Health Servs. Rsch. & Managerial Epidemiology 1 (2021)

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Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act

Christina A. Cirucci[1], Kathi A. Aultman[2], and Donna J. Harrison[3]

Abstract

Background: As part of the accelerated approval of mifepristone as an abortifacient in 2000, the Food and Drug Administration (FDA) required prescribers to report all serious adverse events (AEs) to the manufacturer who was required to report them to the FDA. This information is included in the FDA Adverse Event Reporting System (FAERS) and is available to the public online. The actual Adverse Event Reports (AERs) can be obtained through the Freedom of Information Act (FOIA).

Methods: We compared the number of specific AEs and total AERs for mifepristone abortions from January 1, 2009 to December 31, 2010 from 1. Planned Parenthood abortion data published by Cleland et al. 2. FAERS online dashboard, and 3. AERs provided through FOIA and analyzed by Aultman et al.

Results: Cleland identified 1530 Planned Parenthood mifepristone cases with specific AEs for 2009 and 2010. For this period, FAERS online dashboard includes a total (from all providers) of only 664, and the FDA released only 330 AERs through FOIA. Cleland identified 1158 ongoing pregnancies in 2009 and 2010. FAERs dashboard contains only 95, and only 39 were released via FOIA.

Conclusions: There are significant discrepancies in the total number of AERs and specific AEs for 2009 and 2010 mifepristone abortions reported in 1. Cleland's documentation of Planned Parenthood AEs, 2. FAERS dashboard, and 3. AERs provided through FOIA. These discrepancies render the FAERS inadequate to evaluate the safety of mifepristone abortions.

Keywords

mifepristone, misoprostol, adverse drug reaction reporting systems, drug-related side effects and adverse reactions, postmarketing product surveillance, induced abortion, steroidal abortifacient agents, United States food and drug administration

Introduction

The accelerated approval of mifepristone in the United States (US) in 2000 included post-marketing restrictions to monitor safety. Prescribers were required to report any ongoing pregnancies, hospitalizations, transfusions, and other serious events to the manufacturer, who was required to submit them to the Food and Drug Administration (FDA).[1] Adverse events (AEs) are documented in the FDA Adverse Event Reporting System (FAERS), available online.[2] Copies of the actual Adverse Event Reports (AERs) can be obtained via the Freedom of Information Act (FOIA).[3]

A paper published by Cleland et al. analyzed eight adverse events/outcomes (AEs) from mifepristone abortions at 63 days and less performed by Planned Parenthood in 2009 and 2010. They analyzed hospital admissions, blood transfusions, emergency department (ED) treatments, intravenous (IV)

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antibiotics, infections requiring IV antibiotics or hospitalization, deaths, ongoing pregnancies, and ectopic pregnancies. Cleland explained that Planned Parenthood reports all significant AEs to Danco Laboratories, which submits them to the FDA, per the mifepristone prescribing information. Their analysis for these specific AEs led them to conclude that, "Among the 233 805 medical abortions provided at Planned Parenthood health centers in 2009 and 2010, significant adverse events or outcomes were reported in 1530 (0.65%) cases."[4] Unless associated with another AE, they did not include data on incomplete abortion managed at Planned Parenthood or hemorrhage without transfusion, two of the most common AEs resulting from mifepristone abortion. They also admit that "we cannot exclude the possibility that some clinically significant adverse events or outcomes were not included. Some patients may have experienced a significant adverse event or outcome but did not follow up after their medical abortion."[4] Cleland did not provide the loss to follow-up rate.

In 2021, Aultman et al. published an analysis of the AERs for mifepristone abortion from September 2000 to February 2019 (excluding those published by Gary in 2006) utilizing AERs obtained through FOIA.[5,6]

The objective of this paper was to compare the total number of AERs/cases (which may include more than one AE) and the individual AEs identified by Cleland for 2009 and 2010 mifepristone abortions from three sources: those identified by Planned Parenthood as published by Cleland, those currently posted on the FAERS dashboard, and those provided by the FDA in response to FOIA and analyzed by Aultman.

Methods

We searched the FAERS dashboard for any US AERs related to mifepristone abortion occurring from January 1, 2009 through December 31, 2010 and tabulated the total number of AERs, hospital admissions, deaths, ongoing pregnancies, and ectopic pregnancies. The FAERS did not have enough information to evaluate for transfusion, ED visits, IV antibiotics, or infections requiring IV antibiotics or hospital admission. Since FAERS does not provide the "abortion date," we used the "event date"; in cases where there was no "event date," we used the "latest manufacturer received date." We evaluated Aultman's AERs for the events in Cleland and confirmed any missing reports by searching the 6158 pages of AERs related to mifepristone abortion obtained by FOIA. In analyzing FOIA data, Aultman accounted for duplicates. In the FAERS data, we accounted for duplicates for deaths and ectopic pregnancies, but FAERS did not provide sufficient detail to do so for hospital admissions and ongoing pregnancies. We then compared the total number of reports, as well as hospitalizations, ongoing pregnancies, ectopic pregnancies, and deaths from Cleland, FAERS, and FOIA AERs for 2009 and 2010. Adverse events not reported by Cleland were not evaluated. The FAERS and FOIA total AERs include reports from all sources, not just from Planned Parenthood, and include all reports for those years, not just those with the eight AEs evaluated by Cleland.

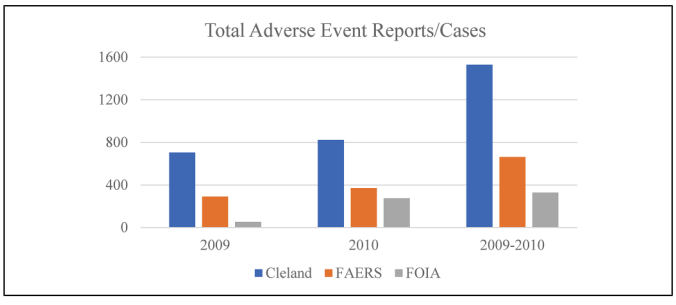

Figure 1. Comparison of total adverse event reports from three sources.

Results

Our analysis shows significant discrepancies between the number of AERs identified by Planned Parenthood as reported in Cleland, the number in the FAERS database, and the number received under FOIA. There are also discrepancies in the number of hospitalizations, ectopic pregnancies, and ongoing pregnancies.

Total Reports (Figure 1)

Cleland identified 1530 cases involving eight specific AEs after Planned Parenthood mifepristone abortion in 2009 and 2010. The FAERS dashboard contains only 664 AERs for this period, and only 330 were provided through FOIA. Both include AERS with other types of adverse events not included by Cleland and include reports from all sources, not just Planned Parenthood.

Specific Adverse Events/Outcomes (Table 1)

Cleland identified 548 ongoing pregnancies after mifepristone abortion in 2009, the FAERS dashboard includes just 56, and only seven were received via FOIA. For 2010, Cleland identified 610 ongoing pregnancies, FAERS contains just 39, and only 32 were obtained via FOIA. Cleland identified 70 hospital admissions in 2009 and 65 in 2010. FAERS includes 87 and 125, respectively, but the FDA only provided 14 and 94 via FOIA. Ectopic pregnancy, although not caused by mifepristone, is a contraindication to its use. Cleland reported eight ectopic pregnancies in 2009 and eight in 2010. FAERS includes eight for 2009 and nine for 2010. The FOIA AERs have only one ectopic for 2009 and eight for 2010. Cleland reported no deaths in 2009 and one in 2010. FAERS and FOIA were consistent with one death in 2009 and two in 2010.

Discussion

The total number of AEs published in Cleland is significantly higher than the number in the FAERs database, even though Cleland did not evaluate all AEs, including

Table 1. Comparison of Number of Specific Adverse Events[a] from Three Sources.

	2009			2010			Total 2009 to 2010		
	Cleland	FAERS[b]	FOIA	Cleland	FAERS[b]	FOIA	Cleland	FAERS[b]	FOIA
Hospital Admission	70	87	14	65	125	94	135	212	108
Transfusion	42		10	72		59	114		69
ED Treatment	87		27	151		105	238		132
IV Antibiotics	23		5	34		27	57		32
Infection requiring IV Antibiotics or Admission	14		4	23		21	37		25
Death	0	1	1	1	2	2	1	3	3
Ongoing Pregnancy	548	56	7	610	39	32	1158	95	39
Ectopic Pregnancy	8	8	1	8	9	8	16	17	9

[a]Events are not mutually exclusive.
[b]If blank, FAERS dashboard does not provide this detail.

failed abortions treated at Planned Parenthood.[4] The discrepancy is particularly concerning because the total number of AEs and AERs in the FAERS should be significantly higher than Cleland since Planned Parenthood performs only 37% of US abortions.[7] It is unclear why so many cases identified by Planned Parenthood in Cleland do not appear in FAERS. Cleland states, "In accordance with the mifepristone prescribing information, Planned Parenthood Federation of America reports all significant adverse events and outcomes to Danco Laboratories, the US distributor of mifepristone, which in turn reports them to the FDA."[4] If this claim is true, then either Danco did not report a significant number of adverse events to the FDA, or the FDA did not include them in FAERS. It also raises the question of whether FAERS includes all complications reported by the other 63% of abortion providers.

We are concerned that FDA and others will continue to rely on Cleland's statement, "significant adverse events or outcomes were reported in 1530 (0.65%) cases"[4] to claim that the complication rate for the abortion pill regimen is low. Although Cleland's paper is a study of over 200 000 abortions and is cited extensively in support of the safety of medical abortion[8–11] the analysis excludes the most common adverse events (retained products of conception and hemorrhage not requiring transfusion). Additionally, Cleland's reported complication rate of 0.65% is only a report of the complications known to Planned Parenthood. Cleland does not report the percent of patients lost to follow-up.[4]

There is also concern that the FDA will continue to rely on the FAERS to make decisions about removing mifepristone REMS, despite the findings herein that FAERS does not include all the events even known to the abortion provider. To compound this problem, in 2016, the FDA eliminated the requirement to report adverse events resulting from mifepristone other than death.[12] Nevertheless, in her April 12, 2021 letter to the American College of Obstetricians and Gynecologists, FDA Commissioner Janet Woodcock stated that, based on a review of post-marketing AEs from January 27, 2020, to January 12, 2021, the in-person dispensing requirements in the mifepristone REMS would not be enforced.[13] It is alarming that policy decisions that affect women's safety are based on a lack of information in the FAERS. Whether the inaccuracy of FAERS extends to required reporting for other medications is unknown to us, but the findings in this paper have significant implications for drug safety evaluation in general.

The ability of the FAERS to accurately identify complications from mifepristone abortion depends on 1. the abortion provider being aware of the adverse event, 2. the provider reporting the adverse event to the manufacturer, 3. the manufacturer reporting to the FDA, and 4. the FDA including the event in the FAERS. One problem inherent in this system is that adverse events unknown to the abortion provider or occurring in patients lost to follow-up will be missed. In addition, ED physicians or treating physicians other than the abortion provider were never obligated to report and may not even be aware of the system. For those events known to Planned Parenthood, it is unclear whether the error occurred in the abortion provider reporting to the manufacturer, the manufacturer reporting to the FDA, or the FDA uploading to the database.

FDA compliance in response to FOIA requests is required by law.[3] The number of AERs supplied under FOIA is much lower than the number in the FAERS database and known to the FDA at the time. Although there may be extenuating circumstances requiring that some information be withheld, withholding information, especially to this extent, interferes with independent, scientific analysis necessary to validate claims of safety and efficacy.

Strengths and Limitations

One of the limitations of this study is that Cleland only reported on a limited number of possible AEs. Because of the scant information included in the FAERS, we could not even compare all AEs reported by Cleland. Since we do not have

access to the Planned Parenthood records, reports cannot be evaluated on a patient-by-patient basis but only as a composite.

One of the strengths of this study is that it is the first known study comparing FAERS data with an outside report of mifepristone complications.

Conclusions

There are significant discrepancies in the number of AEs and total AERs reported for 2009 and 2010 mifepristone abortions identified by Planned Parenthood as reported by Cleland, those in FAERS, and those provided by FOIA, impugning the reliability of FAERS to evaluate the safety or efficacy of mifepristone abortions at a time when the FDA is under pressure to eliminate REMS on mifepristone.[14,15] The FDA used their review of post-marketing adverse events that occurred in 2020 and 2021 as a rationale for removing the in-person dispensing requirements for mifepristone during COVID, even though reporting requirements (other than death) were eliminated in 2016.[13] Whether Planned Parenthood did not submit all the AEs to Danco, Danco did not submit all to the FDA, or the FDA did not include all is unknown. By withholding a significant number of AERs, the FDA did not adequately comply with the FOIA request by the authors of the Aultman paper, hampering their ability to analyze the data. These discrepancies, and the fact that since 2016, reporting AEs other than deaths is no longer required,[12] demonstrate that the FAERS is inadequate to evaluate the safety of mifepristone.

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Author biographies

Christina A. Cirucci, MD received her Bachelor of Science in Mechanical Engineering from Virginia Tech in Blacksburg, VA and her MD from Thomas Jefferson University, Philadelphia, PA. She completed her residency in obstetrics and gynecology at the Medical College of Virginia in Richmond, VA. She is a diplomate of the American Board of Obstetrics and Gynecology and a life Fellow of the American College of Obstetricians and Gynecologists. She is a member of the Christian Medical and Dental Associations, the North American Menopause Society, the Pennsylvania Medical Society, and the Allegheny County Medical Society. She is a board member of the American Association of Pro-Life Obstetricians and Gynecologists. She worked in private practice for twenty years in Pittsburgh, PA.

Kathi A. Aultman, MD received her B.A. from Drew University in 1972, earned her MD at the University of Florida College of Medicine in 1977, and completed her OB/GYN Residency at the University of Florida affiliated Jacksonville Health Education Program in 1981. She is a diplomate of the American Board of Obstetrics and Gynecology and is currently an Associate Scholar with the Charlotte Lozier Institute. She is a member of the American Association of Prolife Obstetricians and Gynecologists, the Christian Medical and Dental Associations, the Florida Medical Association, and is a Life Fellow of the American College of Obstetricians and Gynecologists. She practiced medicine from 1981-2014 in Orange Park, Florida. Dr. Aultman was the co-founder and co-director of the first Rape Treatment Center in Jacksonville, Florida and performed sexual assault exams on women and children as a medical examiner for Duval and Clay Counties. She performed 1st trimester D&C with suction abortions and 2nd trimester D&Es. She also served as the Medical Director for Planned Parenthood of Northeast Florida, Inc. from 1981 to 1983.

Donna J. Harrison, MD received her MD from the University of Michigan and completed her OBGYN residency at a University of Michigan affiliate hospital (St. Joseph Mercy Hospital). She is a diplomate of the American Board of Obstetrics and Gynecology. She is currently CEO of the American Association of Pro-Life Obstetricians and Gynecologists.

Exhibit 47

FDA, *FDA Adverse Event Reporting System (FAERS) Electronic Submissions*

FDA Adverse Event Reporting System (FAERS) Electronic Submissions

Updates for Electronic Submission of Individual Case Safety Reports (ICSRs) to FAERS

FDA recently updated the following guidances for industry to incorporate technical updates: *E2B (R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide – Data Elements and Message Specification (/regulatory-information/search-fda-guidance-documents/e2br3-electronic-transmission-individual-case-safety-reports-implementation-guide-data-elements-and)* and *Appendix to the Implementation Guide — Backwards and Forwards Compatibility (/regulatory-information/search-fda-guidance-documents/e2br3-electronic-transmission-individual-case-safety-reports-implementation-guide-appendix)*.

Premarketing Safety Reporting

In preparation for the electronic transmission of premarketing safety reports in the International Council for Harmonisation (ICH) E2B(R3) format, FDA has posted the following documents regarding the electronic submission of ICSRs for certain investigational new drug application (IND) safety reports for drug and biological products and IND-exempt bioavailability/bioequivalence (BA/BE) safety reports to FAERS. These documents are posted to help sponsors prepare their systems for electronic submission of IND safety reports in the E2B(R3) format.

1. Providing Regulatory Submissions in Electronic Format: IND Safety Reports - Draft Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-regulatory-submissions-electronic-format-ind-safety-reports-guidance-industry) (October 2019)
2. Electronic Submission of IND Safety Reports - Technical Conformance Guide (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-submission-ind-safety-reports-technical-conformance-guide) (April 2022)
3. Technical Specifications Document - FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug) (August 2022)
4. Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies - Draft Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-

documents/electronic-submission-expedited-safety-reports-ind-exempt-babe-studies-guidance-industry) (August 2022)

5. FDA E2B(R3) Core and Regional Data Elements and Business Rules (/media/157982/download) (Excel file August 2022)
6. FDA ICSR XML Instances (/media/157983/download) (zip file August 2022)

Please note, FDA is not currently accepting the submission of premarket ICSRs in the E2B(R3) format. Please continue to submit IND safety reports using eCTD format and IND-exempt BA/BE safety reports on Form FDA 3500A. FDA will update this web page when final guidance for IND safety reporting is published, and when FDA will accept IND and IND-exempt BA/BE safety reports in E2B(R3) format on a voluntary basis. FDA will also update this web page to communicate when submission of safety reports in E2B(R3) format is required for certain INDs after the period of voluntary submission.

Postmarketing Safety Reporting

In preparation for the receipt of postmarketing safety reports in the E2B(R3) format, FDA has posted the following documents regarding the electronic submission of safety reports for drug and biological products to FAERS. These documents are posted to help prepare systems for electronic submissions of postmarketing safety reports.

1. Technical Specifications Document - FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-regional-implementation-guide-e2br3-electronic-transmission-individual-case-safety-reports-drug) (August 2022)
2. FDA E2B(R3) Core and Regional Data Elements and Business Rules (/media/157982/download) (Excel file August 2022)
3. FDA E2B(R3) Forward Compatible Rules (https://www.fda.gov/media/157993/download) (Excel file April 2022)
4. FDA ICSR XML Instances (/media/157983/download) (zip file August 2022)
5. Providing Submissions in Electronic Format – Postmarketing Safety Reports: Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-submissions-electronic-format-postmarketing-safety-reports) (April 2022)

Please note, FDA is not currently accepting the submission of postmarketing ICSRs in the E2B(R3) format. FDA will update this web page when postmarketing ICSRs will be accepted in the E2B(R3) format. In the meantime, please continue to submit postmarketing ICSRs in the E2B(R2) format.

For questions related to this update, please contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov (mailto:faersesub@fda.hhs.gov).

This page provides drug and nonvaccine biological product manufacturers, distributors, packers, outsourcing facilities, and other interested parties with information about FDA Adverse Event Reporting System (FAERS) electronic submissions and instructions on how to electronically submit postmarketing individual case safety reports (ICSRs) with and without attachments.

Since 2000, FDA has accepted electronic submissions of both expedited and non-expedited Individual Case Safety Reports (ICSRs) for human drug and nonvaccine biologic products. To date, FDA has only accepted electronic submissions of ISCRs in the XML format, prepared in accordance with International Conference on Harmonisation-E2B (ICH E2B) (/media/76278/download) (PDF - 266KB) to transmit information directly from database-to-database using standardized (ICH E2B(M)) data elements.

Starting June 10, 2015,* FDA is requiring that applicants electronically submit all ICSRs, ICSR attachments, and periodic safety reports. There are two options for submitting ICSRs electronically:

- Database-to-database transmission (“E2B”)
- The Safety Reporting Portal (SRP) by manually entering the data via our SRP portal.
- Attachments: for both methods, we will only accept attachments in the PDF format.

FDA issued a final rule on June 10, 2014, that requires industry to submit post-marketing safety reports in an electronic format. See the rule at: FDA issues final rule on postmarketing safety report in electronic format (http://wayback.archive-it.org/7993/20170111002213/http://www.fda.gov/Drugs/DrugSafety/ucm400526.htm) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) **(FDA Archive).*

Submitting Individual Case Safety Reports (ICSRs), ICSR Attachments, & Periodic Safety Reports (PSRs)

1. **Electronic submission of ICSRs**
   You have the 2 options for submitting ICSRs electronically.

   ICSR Option A: Database-to-Database Transmission (“E2B”)

   - ICSRs must be submitted in the XML format.
   - Attachments must be in the pdf format.
   - See document “Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (/media/132096/download)" (PDF - 204KB). XML files are submitted to the FDA via the Electronic Submissions Gateway (ESG).
   - For additional instruction on how to begin submitting ICSRs in the XML format, go to our document titled, "Steps to Submitting ICSRs Electronically in the XML

Format." (/drugs/fda-adverse-event-reporting-system-faers/steps-submitting-e2br2-icsrs-electronically-xml-format)

ICSR Option B: Safety Reporting Portal (SRP)

Applicants and non-applicants who do not have database-to-database capability may submit electronic ICSRs using the SRP. To submit via SRP, you must have an account to access the portal site. Those who are Gateway partners cannot use the SRP. Gateway partners are those companies that submit electronically via the Electronic Submission Gateway.

Steps for requesting an SRP account

- Contact FAERSESUB@fda.hhs.gov (mailto:FAERSESUB@fda.hhs.gov) to advise FDA of your intent to begin submitting via the SRP.

SRP account activation

- Your account will be activated in about 7 to 10 business days.
- You will be notified via email with the subject line “SRP Account Activation” that will include the web link to the SRP portal along with account information.
- After receiving this email, your account will be considered active and you may begin submitting reports.

2. **Submitting ICSR Attachments**
Attachments to ICSRs include supporting information for ICSRs such as relevant hospital discharge summaries and autopsy reports, death certificate, and published articles for ICSRs based on scientific literature.

   a. Database-to-Database Transmission (“E2B”).

      - Submit attachments to ICSRs through the electronic submission gateway (ESG). See page 32 of the document “Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (/media/132096/download)" (PDF - 204KB).

   b. Safety Reporting Portal (SRP).

      - To submit ICSR attachments via the SRP, use the features within the portal that allows you to browse, select, and attach documents to an ICSR.

3. **Submitting Periodic Safety Reports (PSR)**
Periodic safety reports are comprised of a descriptive portion and non-expedited ICSRs (21 CFR 314.80 and 600.80), regardless of the format.

   1. **Descriptive Portion:**

- Use Electronic Common Technical Document (eCTD) (/drugs/electronic-submissions-cder/electronic-common-technical-document-ectd) specifications to submit the descriptive portion electronically.
- Indicate in the descriptive portion that the ICSRs have been submitted electronically as XML files to the FDA Electronic Submissions Gateway (ESG) or via the Safety Reporting Portal (SRP).

2. **Non-expedited ICSRs:** must be submitted as described above and on or before the periodic safety report due date. Do NOT submit expedited ICSRs previously submitted.

Resources For You

- FAQ: Combination Products (/media/131508/download) (PDF - 92 KB)
- FAERS Submissions Frequently Asked Questions (/drugs/fda-adverse-event-reporting-system-faers/faers-submissions-frequently-asked-questions)
- Public Meeting: Electronic Submission of Adverse Event Reports to FDA Adverse Event Reporting System (FAERS) using International Council for Harmonisation (ICH) E2B(R3) Standards (/drugs/news-events-human-drugs/electronic-submission-adverse-event-reports-fda-adverse-event-reporting-system-faers-using)
- FAQs: Safety Reporting Portal (/drugs/fda-adverse-event-reporting-system-faers/faqs-safety-reporting-portal)

Exhibit 48

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments (April 2021)

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Technical Specifications Document

Associated Guidance Documents and Conformance Guide:

Draft Guidance for Industry: Providing Submissions in Electronic Format – Postmarketing Safety Reports (June 2014)

Guidance for Industry and FDA Staff: Postmarketing Safety Reporting for Combination Products (July 2019)

Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format: IND Safety Reports (October 2019)

Electronic Submissions of IND Safety Reports Technical Conformance Guide (October 2019)

For questions regarding this technical specifications document, contact the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, at FAERSESUB@fda.hhs.gov; or Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, at CBERICSRSubmissions@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2021

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

Revision History Table

Date	Version	Summary of Changes
2008-06-11	1.0	Initial Version
2008-08-06	1.1	Added Filename format information
2008-10-10	1.2	Updated UTF-8 to ISO-8859-1 encoding; indicated simultaneous acceptance of ICSR and ICSR attachments; provided another acceptable file extension for SGML files; and clarified use of abbreviations (NDA, ANDA, and STN)
2008-10-22	1.3	Provided clarification in Section II; updated footnote 3; and added new paragraph to Section V.C.
2013-07-05	1.4	Updated AERS to FAERS migration changes, removed references to SGML file formatting, incorporated updates from CBER
2018-02-06	1.5	Added a new section to highlight data fields for reporting ICSRs on Combination Products
2019-09-30	1.6	Added two new sections to provide regional data elements for electronic submissions of certain IND safety reports (section I) and IND-exempt Bioavailability (BA)/Bioequivalence (BE) studies (section J). Added an appendix (II) highlighting various case scenarios for electronic submissions of IND safety reports to FAERS.

2020-02-11	1.7	Added a new value to the data element B.4.k.1 for drug characterization to accommodate a similar device. Updated the data element B.4.k.18.2 to specify values. Updated the data element B.4.k.18.3 to use default value.
2020-12-18	1.8	Added a new regional data element A.1.FDA.16 (FDA Safety Report Type) in Table 2 Detailed Description of Administrative Tags Added section Submission Rules Added a new value to the data element B.4.k.1 and B.4.k.19 in section J. IND-exempt BA/BE Studies
2021-03-26	1.9	Updated section XML Header to include DTD 3.0 for premarketing reporting Updated the reference description to data element A.1.FDA.16 in Table 2 Detailed Description of Administrative Tags Updated section ICSR Message Header Information to include information in premarketing reporting Updated section AS2 Headers and Routing IDs for Premarketing Safety Report Submissions Updated section Submission Rules

Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

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Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments

This document provides current specifications for submitting individual case safety reports (ICSRs) and ICSR attachments in electronic form. The specifications apply to electronic submission of ICSRs for drug and biological products studied under an investigational new drug application (IND) (including bioequivalence studies conducted under IND), ICSRs from IND-exempt bioavailability (BA)/bioequivalence (BE) studies, and ICSRs for marketed drug and biological products and combination products to the FDA Adverse Event Reporting System (FAERS). The specifications do not apply to the following marketed biological products: prophylactic vaccines, whole blood or components of whole blood, human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated by FDA.

This document discusses the technical specifications for electronic submission of ICSRs and ICSR attachments through the FDA Electronic Submissions Gateway (ESG).[1] ICSRs (and any ICSR attachments) are to be prepared in accordance with the International Council for Harmonisation (ICH) E2B(R2) data elements in extensible markup language (XML) file format for compatibility with the FAERS database. ICSRs for marketed products should not be submitted to the electronic Common Technical Document (eCTD).[2]

If you have not previously submitted an ICSR in electronic format to FAERS, you should contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov and they will assist you with submission of a test file.

I. ELECTRONIC SUBMISSIONS OF ICSRS AND ICSR ATTACHMENTS

Each initial ICSR or follow-up ICSR may consist of structured information and non-structured information, such as ICSR attachments.

For the FDA to process, review, and archive the ICSRs, prepare your ICSRs for electronic submission by following these steps:

- Provide a unique filename for the submission; see section II of this document.
- Add a file header and file extension; see section IV of this document.
- Populate the elements of the ICSR file; see section V of this document.

---

[1] For information on providing submissions using the ESG, refer to https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm.

[2] See FAERS Electronic Submissions at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm.

- If applicable, add ICSR attachments to ICSRs; see section VI of this document.

II. SUBMISSION FILE NAME

Each electronic submission of ICSRs or attachments to ICSRs must have a unique filename (e.g., your named file + date and time stamp down to the second: filenameYYYYMMDDHHMMSS). You may choose your own format to maintain uniqueness.

III. ICSR ACKNOWLEDGEMENTS

A. ESG Acknowledgement

After submitting an ICSR or ICSR attachment, you should receive an ESG message delivery notice (MDN) notifying the sender of the receipt of their submission, but not acknowledging the acceptance of the submission. If the MDN is not received within 2 hours, go to the ESG System Status web page. If the ESG web page is non-operational, go to the ESG Home Page for further information.

B. FAERS Acknowledgment

The MDN is then followed by a FAERS acknowledgment within 2 hours of the ESG acknowledgement. The FAERS acknowledgement notifies the sender whether their submission has been processed. If you do not receive the FAERS acknowledgement, resubmit the ICSRs without changing the filename.

If you receive a report acknowledgement code 02, indicating that your submission did not process due to file error/s that are specified in the acknowledgment, then proceed as follows:

- For submission with a single ICSR, resubmit the corrected ICSR with a new unique filename.

- For a submission consisting of multiple ICSRs, if one or more ICSRs in the submission failed to process, separate those ICSRs from the processed ICSRs, correct them and resubmit only the corrected ICSRs as a new submission with a unique filename. For example, if there were 50 ICSRs in an original submission and 15 of them failed to process, then only those 15 ICSRs must be separated, corrected appropriately, and resubmitted with a new unique filename. The resubmission should not contain any of the previously processed ICSRs.

IV. ELECTRONIC TRANSPORT FORMAT: XML FILES

FDA accepts the data elements defined in the "Guidance for Industry E2BM Data Elements for

Transmission of Individual Case Safety Reports (April 2002)."[3] The ICH E2B(R2) guidance provides additional information and clarification of the previously issued guidances.[4]

The electronic transport format also known as the Document Type Definition (DTD) for XML files is described in the associated document "XML Formatted DTD" (DTD Version 2.1, DTD Version 2.2 and DTD Version 3.0) (see links to the documents below in section C).

A. AS2 Headers and Routing IDs for Postmarketing Safety Report Submissions

For postmarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for safety reports and attachments in one of the two ways listed below.

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS
  - PDF's: AERS_ATTACHMENTS

or

- Routing IDs
  - XML files: FDA_AERS
  - PDF's: FDA_AERS_ATTACHMENTS

B. AS2 Headers and Routing IDs for Premarketing[5] Safety Report Submissions

For premarketing safety report submissions, the sponsors should include the unique AS2 headers or routing IDs for premarketing safety reports and attachments, as listed below, to differentiate these reports between CDER and CBER, and from postmarketing ICSRs.

---

[3] For information on Guidance for Industry on E2BM Data Elements for Transmission of Individual Case Safety Reports, please refer to the following:

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073092.pdf.

[4] See the guidance for industry entitled *E2B Data Elements for Transmission of Individual Case Safety Reports* (January 1998) (E2B). FDA currently supports use of E2B data elements in addition to the E2BM data elements. However, it is preferred that ICSRs be submitted with E2BM data elements to allow for the most efficient processing of the submissions. For those who wish to use E2B data elements and the corresponding electronic transport format (ICH M2 Electronic Transmission of Individual Case Safety Reports Message Specification Final Version 2.3 Document Revision February 1, 2001 (ICH ICSR DTD Version 2.1)), please refer to documentation provided at https://www.fda.gov/downloads/drugs/ucm149932.pdf

[5] The term premarketing safety report refers to IND safety reports and IND-exempt BA/BE studies safety reports.

1. Submitting premarketing safety reports for CDER IND and IND-Exempt BA/BE

- AS2 Headers
  - Destination: "CDER"
  - XML files: AERS_PREMKT_CDER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CDER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CDER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CDER

2. Submitting premarketing safety reports for CBER IND

- AS2 Headers
  - Destination: "CBER"
  - XML files: AERS_PREMKT_CBER
  - PDF's: AERS_ATTACHMENTS_PREMKT_CBER

or

- Routing IDs
  - XML files: FDA_AERS_PREMKT_CBER
  - PDF's: FDA_AERS_ATTACHMENTS_PREMKT_CBER

C. XML Header

The addition of an XML header enables FDA to process ICSRs in an XML format successfully. FDA supports only the ISO-8859-1 character set for encoding the submissions.

1. For submissions of postmarketing safety reports for drug and biological products, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v2.1.dtd">

2. For submissions of postmarketing safety reports for combination products, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-

v2.2.dtd">

3. For submissions of premarketing safety reports, add the following XML header to the ICSR file:

<?xml version="1.0" encoding="ISO-8859-1"?>

<!DOCTYPE ichicsr SYSTEM "https://www.accessdata.fda.gov/xml/icsr-xml-v3.0.dtd">

D. ICSR Message Header Information

1. For submissions of postmarketing drug and biological product safety reports, use the value "2.1" for the DTD Descriptor <messageformatversion>:

<messageformatversion>2.1</messageformatversion>

2. For submissions of postmarketing combination product safety reports, use the value "2.2" for the DTD Descriptor <messageformatversion>:

<messageformatversion>2.2</messageformatversion>

3. For submissions of premarketing safety reports, use the value "3.0" for the DTD Descriptor <messageformatversion>:

<messageformatversion>3.0</messageformatversion>

E. ICSR File Extension

Use "xml" as the file extension for ICSRs in XML format. The name of the file should be 200 characters or less, excluding the three-digit extension. FDA does not support file names with multiple periods "." or the use of any special or foreign characters except underscore "_" and dash "-".

V. DATA ELEMENTS FOR ELECTRONIC SUBMISSIONS

A. Minimum Data Elements Requirements

For a submission to be successfully processed, submit an ICSR with the minimum data elements for reporting that are appropriate for the product type. If a sponsor submits an ICSR without the minimum data elements, they will receive a FAERS acknowledgement code 02 stating that the submission was not processed (see section III.B above). The minimum data elements for reporting are provided in Table 1 and the bullets that follow list the data elements to include in an ICSR by product type.

Table 1. Minimum Data Elements

Element	Data
B.1	Identifiable Patient
A.2	Identifiable Reporter
B.2	Reaction or Event
B.4	Suspect Drug Product

- Adverse event reports submitted for unapproved prescription drug products, unapproved nonprescription drug products and products approved for marketing under an abbreviated new drug application (ANDA), biologics license application (BLA), or new drug application (NDA), including combination products should have, at a minimum, the four data elements listed in Table 1.

- Adverse event reports for compounded drugs submitted by registered outsourcing facilities should have at a minimum, a suspect product and an adverse event.

- IND safety reports should include, at a minimum, the four data elements listed in Table 1 and the IND number under which the clinical trial where the event occurred is conducted.

- Serious adverse event reports from IND-exempt BA/BE studies should include, at a minimum, the four data elements listed in Table 1 and the pre-assigned ANDA number (hereafter referred as, Pre-ANDA number).

B. Administrative and Identification Elements

For FDA to successfully process your electronic ICSR submissions, populate the administrative and identification elements as indicated in Table 2.

Table 2. Detailed Description of Administrative Tags*

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
A.1.9	<fulfillexpeditecriteria>	1N	1= Yes (15-Day expedited) 2= No (non-expedited) 4= 5-Day 5= 30-Day 6= 7-Day expedited
A.1.0.1	<safetyreportid>	100AN	Sender's (Case) Safety Report Unique Identifier†
A.1.10.1	<authoritynumb>	100AN	Regulatory authority's case report number
A.1.10.2	<companynumb>	100AN	Other sender's case report number
A.3.1.2	<senderorganization>	60AN	Sender identifier
A.2.3.2^	<sponsorstudynumb>	35AN	IND or Pre-ANDA number under which the clinical trial where the event occurred is conducted
A.1.FDA.16††	<fdasafetyreporttype>	1N	1=IND Safety Report 2=IND-Exempt BA/BE Safety Report 3=Postmarketing Safety Report

* Include either <companynumb> or <authoritynumb> values. FDA cannot process the ICSR without one of these element values.

† The Sender's Safety Report Unique Identifier is comparable to the Manufacturer Report Number (also referred to as the Manufacturer Control Number (MCN)) provided on paper in FDA Form 3500A. This number is the company's unique case identification number, which is used for the life of the case.

^ For IND and IND-exempt BA/BE study safety reports only. An IND-exempt BA/BE study refers to a BA/BE study not conducted under IND.

†† The FDA Safety Report Type data element distinguishes premarketing (IND and IND-Exempt BA/BE) safety reports from postmarketing safety reports and is used to determine which reports are posted publicly. The FDA Safety Report Type data element is optional when using DTD 2.1 and 2.2 for postmarketing safety report submission but is mandatory when using DTD 3.0 for premarketing safety report submission.

C. Authorization/ Application Number Format

In the section designated for drug and biological products information, use the following format for the "Authorization/ Application Number" element (B.4.k.4.1) <drugauthorizationnumb> as indicated in Table 3 and described below.

- For approved drug and biological products marketed under an approved application, include the acronym "NDA" or "ANDA," followed by a space and then the number for the application (e.g., NDA 012345, ANDA 012345). For prescription drug products marketed without an approved application (Rx No Application), use "000000." For a nonprescription drug product marketed without an approved application (Non-Rx No

Application), use "999999." For adverse event reports for compounded drug products submitted by registered outsourcing facilities, use "COMP99."

- For marketed biological products, include the appropriate acronym "BLA," "STN," or "PLA" followed by a space and the primary six-digit number (e.g., STN 123456).

Table 3. Detailed Description of Application Number Formats

Type of Application	Recommended Format
NDA/ ANDA	NDA, ANDA 012345
STN/ BLA/ PLA	STN or BLA or PLA 123456
Rx No Application	000000
Non-Rx No Application	999999
Compounded Products	COMP99

D. Unique Case Identification Numbers for Initial and Follow-Up ICSRs

For the follow-up ICSR safety reports to be correctly linked to your initial ICSR report, follow these steps:

- Use the same <safetyreportid> for the E2BM elements in section A.1.0.1 for the initial ICSR and any of its follow-up ICSRs; this allows the follow-up report to be linked to the initial report in the FAERS database.

- If the initial ICSR was submitted on paper but its follow-up ICSR is submitted electronically, include the Manufacturer Control Number (MCN) listed in Box G9 of the FDA paper Form 3500A from the initial report in both A.1.0.1 <safetyreportid> and in A.1.10.2 <companynumb> field in the follow-up electronic submission.

- Always use the <safetyreportid> that was assigned to the initial ICSR when submitting follow-up reports. If you need to change the <safetyreportid> internally, note the internally reassigned <safetyreportid> in the narrative section of the follow-up report (i.e., element B.5.1) (e.g., "This ICSR has been reassigned to the Company ID number COA12345"). Do not use the internally reassigned <safetyreportid> for any follow-up reports.

- In the event that an incorrect <safetyreportid> has been used in a follow-up report, contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov so that the follow-up ICSR can be matched to the initial ICSR.

E. MedDRA Specific Elements

Use the ICH Medical Dictionary for Regulatory Activities (MedDRA) to code medical

terminology.[6] When possible, use the Lowest Level Term (LLT), and record the LLT as the MedDRA numeric code rather than the LLT name (e.g., the LLT name is Rash; the MedDRA numeric code for LLT Rash is 10378444).

1. Reaction/Event

a) Reaction/Event as reported by the primary source field

Record the original reporter's words verbatim and/or use short phrases to describe the reaction/event in element (B.2.i.0).

b) Reaction/Event MedDRA Term LLT numeric code or text field

Record the MedDRA LLT that most closely corresponds to the term reported by the original reporter in element (B.2.i.1).

c) Reaction/Event MedDRA Preferred Term (PT) numeric code or text field

Record the MedDRA PT that most closely corresponds to the term reported by the original reporter in element (B.2.i.2).

2. Other E2B Elements

For the E2B elements listed in Table 4, use either MedDRA text or, preferably, the corresponding numeric code.

Table 4. Additional E2B Elements for Preferred MedDRA Coding

Element	DTD Descriptor 2.1	Length
B.1.7.1a.2	<patientepisodename>	250 AN
B.1.8f.2	<patientdrugindication>	250 AN
B.1.8g.2	<patientdrugreaction>	250 AN
B.1.9.2b	<patientdeathreport>	250 AN
B.1.9.4b	<patientdetermineautopsy>	250 AN
B.1.10.7.1a.2	<parentmedicalepisodename>	250 AN
B.1.10.8f.2	<parentdrugindication>	250 AN
B.1.10.8g.2	<parentdrugreaction>	250 AN
B.3.1c	<testname>	100 AN
B.4.k.11b	<drugindication>	250 AN
B.4.k.17.2b	<drugrecuraction>	250 AN
B.4.k.18.1b	<drugreactionasses>	250 AN
B.5.3b	<senderdiagnosis>	250 AN

[6] Companies can license MedDRA from an international maintenance and support services organization (MSSO) (toll free number 877-258-8280; Direct 571-313-2574; fax 571-313-2345; e-mail MSSOhelp@mssotools.com).

F. Drug Description and Case Narrative Elements

To ensure the successful processing of your electronic ICSR submission, applicants are advised to populate the drug description and narrative elements as indicated in Table 5.

Table 5. Detailed Description of Drug(s) and Narrative Elements*†

Element	DTD Descriptor 2.1	Length	Element Values for DTD 2.1
B.4.k.1	<drugcharacterization>	1N	1=Suspect 2=Concomitant 3=Interacting 4=Drug not administered
B.4.k.2.1	<medicinalproduct>	70AN	Proprietary Medicinal Product Name
B.4.k.2.2	<activesubstancename>	100AN	Drug Substance Name
B.5.1	<narrativeincludeclinical>	20000AN	Case Narrative

*Include <medicinalproduct> and/or <activesubstancename>. FDA cannot process the ICSR without at least one of these elements.
†Appendix I lists various examples of correct drug element formats.

1. Recording Multiple Drugs

If you are submitting safety reports for products containing multiple drugs, you should follow these steps:

- List the proprietary drug product name in element (B.4.k.2.1) and/or list the drug substance name in element (B.4.k.2.2).
- List the characterization of each reported drug's role, such as suspect, concomitant, interacting, drug not administered, or similar device in element (B.4.k.1).

2. Medicinal Product Name and Active Drug Substance Name

FDA validates medicinal product names to the available Structured Product Labeling (SPL)[7], the submitted label (as ICSR attachment), and the Substance Registration System (SRS). These are further described below:

- When the product has an SPL, use the same naming convention as it appears in the SPL when submitting the ICSR.

[7] The SPL is a document markup standard approved by Health Level Seven (HL7) and adopted by FDA as a mechanism for exchanging product and facility information. See https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

- When submitting a product label as an attachment to an ICSR, use the name as it appears on the submitted product label.
- If no medicinal product is named and only the active substance is named, use the name of the active substance as it appears in the SRS.[8]

3. Case Narrative

a) Initial ICSR

Record all case narrative information including clinical course, therapeutic measures, outcome, and all additional relevant information in element (B.5.1). If the information exceeds the field length, consider describing the information using fewer words. Although the use of only the most widely used medical abbreviations is permissible if necessary, their use should be limited when possible.

b) Follow-up ICSR

Record both new information and corrections to previously submitted ICSRs in element (B.5.1).

G. Other Data Elements

1. Dosage Information Field

If dosage information cannot be captured in the structured fields in B.4.k.5, then use the element (B.4.k.6) <drugdosagetext>.

2. Pharmaceutical Form Field

Record the pharmaceutical form in element (B.4.k.7) <drugdosageform>. FDA accepts the European Medicines Agency (EMA) dosage codes or text.[9]

3. Route of Administration Field

Code the route of administration in element (B.4.k.8) <drugadministrationroute> as described in the ICH E2B(R2) guidance.

4. Receiver Field (A.3.2)

Complete the receiver using the code or text listed in Table 6.

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[8] https://www.fda.gov/ForIndustry/DataStandards/SubstanceRegistrationSystem-UniqueIngredientIdentifierUNII/default.htm.

[9] For a complete list of EMA dosage form codes and text, please refer to https://www.ema.europa.eu/documents/other/list-pharmaceutical-dosage-forms_en.xls

Table 6. Receiver Information

Element	DTD Descriptor 2.1	Code or Text
A.3.2.1	<receivertype>	2
A.3.2.2a	<receiverorganization>	FDA
A.3.2.2b	<receiverdepartment>	Office of Surveillance and Epidemiology
A.3.2.2d	<receivergivename>	FAERS
A.3.2.3a	<receiverstreetaddress>	10903 New Hampshire Avenue
A.3.2.3b	<receivercity>	Silver Spring
A.3.2.3c	<receiverstate>	MD
A.3.2.3d	<receiverpostcode>	20993
A.3.2.3e	<receivercountrycode>	US
A.3.2.3l	<receiveremailaddress>	faersesub@fda.hhs.gov

5. Message Receiver Field (M.1.6)

The following two message receiver identifiers are used by FDA to distinguish between test and production submissions:

- Test ICSRs: <messagereceiveridentifier>ZZFDATST</messagereceiveridentifier>
- Production ICSRs: <messagereceiveridentifier>ZZFDA</messagereceiveridentifier>

H. Data Elements for Electronic Submissions of Safety Reports for Postmarketing Combination Products

To ensure the successful processing of your electronic ICSR submission for a marketed drug- or therapeutic biologic led- combination product (e.g., a combination product containing a drug/biologic and device and marketed under an NDA or a BLA), you should populate the data elements indicated in Table 7.

Note: Some of the DTD descriptors listed in Table 7 are under existing E2B(R2) header elements, and some DTD descriptors are under new data elements. Those data element numbers that are new, have the word "FDA" incorporated into the number and are U.S.-specific regional elements related to reporting on combination products.

Table 7. Combination Product Data Elements

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
M.1.2	<messageformatversion>	Message Format Version	Version number of Message Format	3AN	2.2	Use value 2.2 if using icsr-xml-v2.2.dtd Use value 2.1 if using icsr-xml-v2.1.dtd
A.1	<safetyreport>	Header/ Entity	Identification of the case safety report			
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report		1N	1=Yes 2=No 4=5-Day 5=30-Day	Element values= 1 for 15-Day Expedited* and 2 for periodic non-expedited† Element value= 4 for remedial action to prevent an unreasonable risk of substantial harm to the public health Element value= 5 for malfunction with no associated adverse event Do not use element value of 3.
A.1.FDA.15	<combinationproductreport>	Combination Product Report Flag	Combination Product Report Flag	1N	1=Yes 2=No	
A.2	<primarysource>	Primary source(s) of information	Header/ Entity		Area below should be a repeatable block	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
A.2.1		Primary source(s)	Header			
A.2.1.3.FDA.4	<reporteremailaddress>	Reporter's Email Address		100AN		
B.1.1	<patientinitial>	Patient	Patient Identifier	10AN		If a single report is reported for a malfunction with no adverse event, the element value should be "NONE." If there are multiple malfunction reports with no adverse event, then the element value should be "SUMMARY."
B.4	<drug>	Drug(s) Information	Header/ Entity		Area below should be a repeatable block	
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1=Suspect 2=Concomitant 3=Interacting 5=Similar Device	If the product in the report is about a similar device, the element value should be 5=Similar Device.
B.4.k.2		Drug Identification	Header			
B.4.k.2.4.FDA.1a	<expirationdateformat>	Expiration date format	Product Expiration date	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.2.4.FDA.1b	<expirationdate>	Expiration date	Product Expiration date	8N		

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.2.FDA.5	<productavailableforevaluation>	Product available for evaluation	Indicate whether product is available for evaluation	1N	1=Yes 2=No 3=Return	
B.4.k.2.6.FDA.1a	<productreturndateformat>	Product return date format	Date Format	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.2.6.FDA.1b	<productreturndate>	Product return date	Date when Product was returned	8N		
B.4.k.20.FDA.1	<brandname>	Brand Name	The trade or proprietary name of the device constituent part of the suspect combination product as used in product labeling or in the catalog	80AN		At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for the device constituent part
B.4.k.20.FDA.2	<commondevicename>	Common Device Name	Generic or common name of the device constituent part of the suspect combination product or a generally descriptive name	80AN		At least one of the 3 must be reported <brandname> or <commondevicename> or <productcode> for device constituent part
B.4.k.20.FDA.3	<productcode>	Product Code	Product code	3AN	http://www.acce	At least one of the 3 must be

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
			assigned to the device constituent part based upon the medical device product classification		ssdata.fda.gov/premarket/ftparea/foiclass.zip	reported <brandname> or <commondevicename> or <productcode> for device constituent part
B.4.k.20.FDA.4	<manufacturer>	Manufacturer	Header/ Entity			
B.4.k.20.FDA.4a	<manufacturername>	Device Manufacturer Name	Manufacturer name of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4b	<manufactureraddress>	Manufacturer Address	Manufacturer address of the device constituent part of the suspect combination product	100AN		
B.4.k.20.FDA.4c	<manufacturercity>	Manufacturer City	Manufacturer city of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.4d	<manufacturerstate>	Manufacturer State	Manufacturer state of the device	40AN		

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
			constituent part of the suspect combination product			
B.4.k.20.FDA.4e	<manufacturercountry>	Manufacturer Country	Manufacturer country of the device constituent part of the suspect combination product	2AN	ISO3166	
B.4.k.20.FDA.5	<modelnumber>	Model Number	Model number of the device constituent part	30AN		
B.4.k.20.FDA.6	<catalognumber>	Catalog Number	Catalog number of the device constituent part	30AN		
B.4.k.20.FDA.7	<serialnumber>	Serial Number	Serial number of the device constituent part	30AN		
B.4.k.20.FDA.8	<udinumber>	Unique Identifier UDI#	Unique identifier of the device constituent part	50AN		
B.4.k.20.FDA.9a	<dateimplantedformat>	Device Implant Date Format	Date format of device implant in the patient	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
B.4.k.20.FDA.9b	<dateimplanted>	Device Implant Date	Date of device implant in the patient	8N		For medical devices that are implanted in the patient, provide the implant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10a	<dateexplantedformat>	Device Explant Date Format	Date format of device explant from the patient	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.10b	<dateexplanted>	Device Explant Date	Date of device explant from the patient	8N		If an implanted device was removed from the patient, provide the explant date or best estimate. If day is unknown, month and year are acceptable. If month and day are unknown, year is acceptable
B.4.k.20.FDA.11a	<deviceage>	Approximate age of device/ product	Age of device constituent part	5N		
B.4.k.20.FDA.11b	<deviceageunit>	Approximate age unit of device/	Age unit of device constituent part	3N	800=Decade 801=Year 802=Month	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		product			803=Week 804=Day 805=Hour	
B.4.k.20.FDA.12	<labeledsingleusedevice>	Single Use Device	Indicate whether the device constituent part was labeled for single use or not	1N	1=Yes 2=No	
B.4.k.20.FDA.13a	<devicemanufacturedateformat>	Device Manufacture Date Format	Device Manufacture Date format	3N	102=CCYYMMDD 610=CCYYMM 602=CCYY	
B.4.k.20.FDA.13b	<devicemanufacturedate>	Device Manufacture Date	Device Manufacture Date	8N		
B.4.k.20.FDA.14		Remedial action initiated/ Remedial action taken for the product	Header			
B.4.k.20.FDA.14.1a	<remedialactionrecall>	Recall	Recall initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1b	<remedialactionrepair>	Repair	Repair initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1c	<remedialactionreplace>	Replace	Replace initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1d	<remedialactionrelabel>	Relabeling	Relabeling initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1	<remedialactionnotify>	Notification	Notification	1N	1=Yes	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
e			initiated		2=No	
B.4.k.20.FDA.14.1f	<remedialactioninspection>	Inspection	Inspection initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1g	<remedialactionpatientmonitor>	Patient monitoring	Patient monitoring	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1h	<remedialactionmodifyadjust>	Modification/ Adjustment	Modification/ Adjustment initiated	1N	1=Yes 2=No	
B.4.k.20.FDA.14.1i	<remedialactionother>	Other	Other Remedial Action initiated	75AN		
B.4.k.20.FDA.15	<deviceusage>	Device Usage	Indicate the use of the device constituent part of the suspect combination product	1N	1=Initial Use of Device 2=Reuse 3=Unknown	
B.4.k.20.FDA.16	<devicelotnumber>	Device Lot Number	Lot number of the device constituent part of the suspect combination product	35AN		
B.4.k.20.FDA.17	<malfunction>	Malfunction	Malfunction of product	1N	1=Yes 2=No	
B.4.k.20.FDA.18		Follow-up type	Header			
B.4.k.20.FDA.18.1a	<followupcorrection>	Correction	Correction	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1b	<followupadditionalinfo>	Additional information	Additional information	1N	1=Yes 2=No	
B.4.k.20.FDA.18.1	<followupresponsetoFDA>	Response to	Response to FDA	1N	1=Yes	

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
c		FDA request	request		2=No	
B.4.k.20.FDA.18.1d	<followupdeviceevaluation>	Device Evaluation	Device Evaluation	1N	1=Yes 2=No	
B.4.k.20.FDA.19	<deviceproblemandevaluation>	Device Problem and evaluation codes	Header/ Entity		Area Below Should be a Repeatable Block	
B.4.k.20.FDA.19.1a	<evaluationtype>	Evaluation Type	Type of problem and/or the evaluation	2N	01=Device Problem 02=Method 03=Result 04=Conclusion	
B.4.k.20.FDA.19.1b	<evaluationvalue>	Evaluation Value	The FDA code value based on the respective evaluation type	6N		The value depends on the respective <evaluationtype> If <evaluationtype> = 01 --> https://www.fda.gov/media/146825/download If <evaluationtype> = 02 --> https://www.fda.gov/media/146827/download If <evaluationtype> = 03 --> https://www.fda.gov/media/146828/download If <evaluationtype> = 04 --> https://www.fda.gov/media/146829/download
B.4.k.20.FDA.20	<operatorofdevice>	Operator of	Operator of the	100AN		Use the value “Health

Data Element	DTD Descriptor 2.2	Title	Description	Length	Element Values for DTD 2.2	Notes
		the Device	Device			Professional" or "Lay User/Patient." If none applicable, then specify the "Other" value

* 21 CFR 314.80(c)(1) and 600.80(c)(1) use the term "15-day Alert reports." In the combination product PMSR final rule (21 CFR 4.101), these reports are defined as "Fifteen-day reports."

† Periodic non-expedited ICSRs are the reports required under 21 CFR 314.80(c)(2)(ii)(B) and 21 CFR 600.80(c)(2)(ii)(B) for serious, expected and nonserious adverse drug experiences.

I. Data Elements for Electronic Submissions of IND Safety Reports

To ensure the successful processing of your electronic IND ICSR submission, you should populate the following data elements as described in Table 8.

Table 8. Investigational New Drug Clinical Data Elements

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study
A.1.9	<fulfillexpeditecriteria>	Does this case fulfill the local criteria for an expedited report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Element value= 6 for 7-Day Expedited
A.1.12	<linkreportnumb>	Identification Number of the report which is linked to this report		100AN		Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						submitted as per (312.32(c)(1)(i)(B)) when a Narrative Summary Report is provided, this field should be populated in the IND Safety Report that contains the Narrative Summary Report.
A.2.3.1	<studyname>	Study Name		100AN	Study ID_$Abbreviated Trial Name	The Study ID should be the same value used in the study tagging file format of the eCTD submission.
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	IND number under which the clinical trial where the event occurred is conducted Use the “Parent” IND number* for reports submitted from an Aggregate Analysis as per (312.32(c)(1)(i)(C)) or for several events	Populate this field with the Primary IND in the first block and repeat block A.2 with elements A.2.3.2 and A.2.3.3.as noted below with element value= 5 for sponsor’s other INDs evaluating suspect product (where applicable) Include the acronym "IND" followed by a space and then the IND

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					submitted as per (312.32(c)(1)(i)(B)), from trials conducted under more than one IND	number for the application (e.g. IND 123456) See Appendix II (Case Scenarios) for additional information on how to submit reports from sponsor's other INDs (Cross-reporting).
A.2.3.3	<observestudytype>	Study type in which the Reaction(s)/ Event(s) were observed		1N	1= Clinical Trials 2= Individual Patient Use (e.g., 'Compassionate Use' or 'Named Patient Basis') 3= Other Studies (e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring) 4= Report from	Required if element value for A.1.4 is 2=Report from Study Repeat this field as needed with element value= 5 for each Cross-reported IND. The first block of this element in the report must not be 5. If element value 4 is chosen, then A.1.9= 1. See Appendix II (Case

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided 5= Cross-reported IND Safety Report	Scenarios) for additional information on how to submit reports from an Aggregate Analysis.
B.1.1	<patientinitial>	Patient Identifier		10AN		For a report from an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is provided, the element value should be "AGGREGATE"
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		For investigational drug and biological products without an established name (i.e. INN or USAN

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
						name), prior to submitting IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND, listing the names of the active drug substance/s and the medicinal product as they will be reported in E2B file submissions. The names should fit within the established E2B character length limits. Use company product code if no established name, for multi-ingredient products, or if name exceeds character length
B.4.k.2.2	<activesubstancename>	Active Drug Substance Names		100AN		
B.4.k.18	<drugreactionrelatedness>	Relatedness of Drug to				For IND Safety Reports, at least one suspect

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Reaction/ Event				product should have relatedness of drug to reaction/ event
B.4.k.18.1a	<drugreactionassesmeddra version>	MedDRA Version for Reaction Assessed		8AN		
B.4.k.18.1b	<drugreactionasses>	Reaction Assessed		250AN		
B.4.k.18.2	<drugassessmentsource>	Source of Assessment		60AN		Use the value “Sponsor” or “Investigator”. Include sponsor and investigator assessment when reporting both in separate blocks
B.4.k.18.3	<drugassessmentmethod>	Method of Assessment		35AN		Use the value “FDA”.
B.4.k.18.4	<drugresult>	Result		35AN	1=Suspected 2=Not suspected	For IND Safety Reports, at least one suspect product should have relatedness of drug to reaction/ event
B.5.1	<narrativeincludeclinical>	Case Narrative Including Clinical		20,000 AN		FDA strongly encourages sponsors to construct narratives that fit within the ICH E2B character

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
		Course, Therapeutic Measures, Outcome, and Additional Relevant Information				limit of 20,000 AN. If your narrative exceeds this limit, sponsors should include as much of the narrative as possible in this field and submit an ICSR attachment for any text that exceeds the character limit. Sponsors should not submit an ICSR attachment containing the entire narrative and leave the case narrative field empty. For reports from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) where PDF is attached, put "see attached Narrative Summary Report" in this field.

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
B.5.4	<sendercomment>	Sender's Comments		2000 AN		Identification and analysis of previously submitted events (as required by 312.32(c)(1)) should be reported in this field.

* The "parent IND" is the IND under which clinical investigations were initiated in the United States. (If the drug is being evaluated in multiple INDs, this is generally the IND with the lowest number.) NOTE: This may not be the same as the first A.2.3.2 block if the drug is being evaluated under multiple INDs.

NOTE: See FAERS Webpage for case scenario examples for reporting IND safety reports (e.g., IND safety reports where the sponsor is evaluating suspect product under more than one IND, IND safety reports that are a result of an aggregate analysis, and IND safety reports with unapproved and approved drugs listed as suspect products).

J. Data Elements for Electronic Submissions of ICSRs from IND-Exempt Bioavailability (BA)/ Bioequivalence (BE) Studies

For successful processing of your electronic ICSRs submissions for a BA/BE study not conducted under an IND, you should populate the following data elements as described in Table 9.

Table 9. Data Elements for IND-Exempt BA/BE Studies

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.4	<reporttype>	Type of Report		1N	1=Spontaneous 2=Report from Study 3=Other 4=Not Available to Sender (unknown)	Element value= 2 for Report from Study

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
A.1.9	<fulfillexpeditecriteria>	Does this Case Fulfill the Local Criteria for an Expedited Report?		1N	1=Yes 2=No 4=5-Day 5=30-Day 6=7-Day	Element value=1 for 15-Day Expedited Or Element value= 6 for 7-Day Expedited
A.2.3.1	<studyname>	Study Name		100AN	Abbreviated Trial Name	
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number		35AN	Pre-ANDA number for the IND-Exempt BA/BE Studies	Include the acronym "Pre-ANDA" followed by a space and then the Pre-ANDA number for the application (e.g. Pre-ANDA 123456)
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s)/ Event(s) were Observed		1N	1= Clinical Trials 2= Individual Patient Use (*e.g., 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g., Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis as per 312.32(c)(1)(i)(C) or for	Element value="1" for Clinical Trials.

Data Element	DTD Descriptor 3.0	Title	Description	Field Length	Element Values for DTD 3.0	Notes
					Several Events Submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary Report is Provided 5= Cross-Reported IND Safety Report	
B.4.k.2.1	<medicinalproduct>	Proprietary Medicinal Product Name		70AN		
B.4.k.1	<drugcharacterization>	Characterization of drug role		1N	1 = Suspect 2 = Concomitant 3 = Interacting 4 = Drug not administered	For no exposure to a study drug use 4=Drug not administered
B.4.k.2.2	<activesubstancename>	Active Drug Substance Name		100AN		
B.4.k.19	<drugadditional>	Additional Information on Drug		100AN	1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive) 5 = Other drug	Specify whether the product exposed is the Test drug, Reference drug, Placebo, Vehicle, Control or Other drug

VI. ELECTRONIC FORMAT FOR ICSR ATTACHMENTS

FDA can accept and archive ICSR attachments in PDF format. Currently approved formats for the non-structured component of an ICSR, such as ICSR attachments, are PDF versions 1.4 (current ICH standard) or 1.6 (current version in use at FDA). An ICSR attachment should be electronically submitted to FAERS after the associated ICSR has been submitted and accepted by FAERS.

A. Converting the ICSR Attachment to PDF

Applicants should provide an individual PDF file for each ICSR attachment. If you are submitting multiple ICSR attachments for a particular ICSR, include each attachment in the same PDF file and provide a PDF bookmark to distinguish each attachment. For example, if you are submitting a hospital discharge summary and an autopsy report for a single ICSR, include both in a single PDF file with a bookmark to the hospital discharge summary and a bookmark to the autopsy report.

B. Identification Information in the PDF Document Information Fields

Each PDF file contains fields to be completed by the author of the document. FAERS uses these fields to locate and retrieve the attachments to specific ICSRs. To enable FDA to match the attachment(s) to the correct ICSR, applicants should fill in the PDF document information fields with the appropriate E2B(R2) data elements for the ICSR as indicated in Table 10.

Table 10. Document Information Fields in ICSR Attachments

PDF Document Information Field	Include/ Optional	Document Information*	Length
Title	Include	A.1.0.1 <safetyreportid> Sender's (Case) Safety Report Unique Identifier	100AN
Subject	Include	A.1.10.1 <authoritynumb> Regulatory Authority's Case Report Number OR A.1.10.2 <companynumb> Other Sender's Case Report Number	100AN
Author	Optional	A.1.11.2 <duplicatenumb> Other Identification Number	100AN
Keywords	Optional	A.1.7b <receiptdate> Date of Receipt of the Most Recent Information for this ICSR	8N

* The information refers to the data elements in E2B(R2)

In addition:

- Use the ISO-8859-1 character set for the information fields.
- Do not exceed the character length indicated above for each information field.
- Avoid creating any custom fields with names identical to the information fields listed in Table 10.

If you need assistance, you can contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov.

VII. SUBMISSION RULES

The submission rules define the condition that shall result in a negative acknowledgement and not be accepted by FAERS.

Table 111. Submission Rules and Acknowledgement Status

Data Element	DTD Descriptor 2.1/2.2/3.0	Rejection Rule Description	Acknowledgement
NA	NA	ICSR submitted via AS2 Header where XML file: AERS or Routing ID where XML file: FDA_AERS and using DTD 3.0	reportacknowledgmentcode (B.1.8) = 02
NA	NA	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT and using DTD 2.1 or 2.2	reportacknowledgmentcode (B.1.8) = 02
A.1.FDA.16	<fdasafetyreporttype>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty	reportacknowledgmentcode (B.1.8) = 02
A.2.3.2	<sponsorstudynumb>	ICSR submitted via AS2 Header where XML file: AERS_PREMKT or Routing ID where XML file: FDA_AERS_PREMKT using DTD 3.0 and data value is empty or not prefixed with 'IND' or 'Pre-ANDA'	reportacknowledgmentcode (B.1.8) = 02

APPENDIX I. EXAMPLES OF CORRECT AND INCORRECT APPLICATION NUMBER AND DRUG ELEMENT FORMATS

Table 122. Examples of Application Number Formats and Drug Element Formats

Examples of Application Number Format		Comment
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>BLA 123456</drugauthorizationnumb>	
Correct	<drugauthorizationnumb>NDA 012345</drugauthorizationnumb> <drugauthorizationholder>COMPANYX</drugauthorizationholder>	
Incorrect	<drugauthorizationnumb>123456**/10300**</drugauthorizationnumb>	Use the appropriate prefix for the NDA/ ANDA/ STN/ BLA/ PLA. Do not include additional data after the application number
Incorrect	<drugauthorizationnumb>NDA **12-345;IND12,345** </drugauthorizationnumb>	Omit hyphens and commas in the application number. Do not populate the tag with two application numbers
Incorrect	<drugauthorizationnumb>**OTC Product**</drugauthorizationnumb>	For a non-prescription drug product marketed without an approved application (Non-Rx No Application), use “999999"
Incorrect	<drugauthorizationnumb>NDA 012345**(COMPANYX)**</drugauthorizationnumb> <drugauthorizationholder></></drugauthorizationholder>	Do not populate the company name in the <drugauthorizationnumb> tag

Examples of Application Number Format		Comment
Correct	<medicinalproduct>TYLENOL</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	
Correct	<medicinalproduct>MIRACLE WONDER DRUG</medicinalproduct> <activesubstancename>ACETAMINOPHEN</activesubstancename>	
Incorrect	<medicinalproduct>AMAZING DRUG **OTC®**</medicinalproduct> <activesubstancename>ACETAMINOPHEN **500 mg**</activesubstancename>	
Incorrect	<medicinalproduct>NEW DRUG **40 mcg/mL**</medicinalproduct> <activesubstancename>NEWSUBSTANCE **Inj** </activesubstancename>	
Incorrect	<medicinalproduct>**MWD**</medicinalproduct> <activesubstancename>**APAP**</activesubstancename>	Do not use abbreviations for the brand name or active substance in the <medicinalproduct> and <activesubstance> tags

APPENDIX II. CASE SCENARIOS FOR IND SAFETY REPORTS SUBMITTED TO FAERS

The following case scenarios are intended to provide examples to sponsors on the use of ICH E2B data standard elements for submission of IND safety reports to FAERS that may differ from postmarketing safety reports.

1. For any IND safety report where the sponsor is evaluating the suspect product under more than one IND (i.e. "Cross-reporting")
    a. Repeat block A.2 for each IND
        i. Use first block A.2 to designate IND where the event occurred = "primary IND"
            1. A.2.3.2 = primary IND
            2. A.2.3.3 = data value could either be 1, 2, 3, or 4
            3. Other relevant information for the report to be populated in block A.2
        ii. Repeat block A.2 as many times as needed with only the following data elements for each IND that the sponsor holds where that suspect product is being evaluated:
            1. A.2.3.2 = IND number for each cross-reported IND

            and

            2. A.2.3.3 = 5

Table 133. Case Scenario 1. For IND Safety Reports Submitted to FAERS

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were observed	1= Clinical Trial 2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a Narrative Summary report is provided. 5=Cross-reported IND safety report

2. For an IND safety report that is a result of an aggregate analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided:

    a. Submit one IND safety report with the IND where the event occurred in A.2.3.2 <sponsorstudynumb> (or the "parent" IND if the events occurred in multiple INDs).

    For this IND safety report, populate the data elements below in addition to other relevant information regarding the event and suspect product.

        i. Use data element = 4 in A.2.3.3<observestudytype>

        ii. Use the term "AGGREGATE" in B.1.1 <patientinitial>

    b. Section VII.A.2. of the *FDA Guidance for Industry – "Safety Reporting Requirements for INDs and BA/BE Studies" (December 2012)* discusses several submission requirements for IND safety reports that are a result of an aggregate analysis. The following two sections describe these submission elements and how they are accomplished with electronic submission to FAERS.

        1. The guidance states that IND safety reports that are a result of an aggregate analysis should contain a narrative description of the event and the results of the analysis (hereafter referred to as a "narrative

summary report"). For IND reports submitted to FAERS, attach the narrative summary report to the IND safety report as a PDF attachment (do not put the narrative summary report in the E2B narrative field).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

2. The guidance states that all the individual cases that were analyzed in the aggregate analysis should be submitted. Use the repeatable block A.1.12 to link all the safety report numbers for the individual supportive ICSRs (i.e. the numbers in A.1.0.1 for all the individual cases that are summarized in the narrative summary report).

a. These instructions also apply to several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided.

b. IND safety reports previously submitted as ICSRs to FAERS do not have to be resubmitted (place the safety report numbers for these previously submitted reports in A.1.12).

c. For IND safety reports previously submitted in eCTD format, the sponsor should list the eCTD sequence number and date of submission in the narrative summary report. (The eCTD sequence number is the unique four-digit number for each IND submission the sponsor submits in the us-regional.xml file for the eCTD submission.)

d. IND safety reports previously submitted on paper should be attached to the IND safety report as PDF attachments.

Table 144. Case Scenario 2. For IND Safety Reports Submitted to FAERS

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.1.12	<linkreportnumb>	Identification number of the report(s) which are linked to this report	Used to link all individual cases (safetyreportid) that make up an IND Safety Report submitted as a result of an Aggregate Analysis as per 312.32(c)(1)(i)(C) or for several events submitted as per 312.32(c)(1)(i)(B) if a narrative summary report is provided
A.2.3.2	<sponsorstudynumb>	Sponsor Study Number	IND number under which the Clinical Trial where the event occurred is conducted

Data Element	DTD Descriptor 3.0	Title	Element Values for DTD
A.2.3.3	<observestudytype>	Study Type in Which the Reaction(s) were Observed	1= Clinical Trials 2= Individual Patient Use (*e.g. 'Compassionate Use' or 'Named Patient Basis'*) 3= Other Studies (*e.g. Pharmacoepidemiology, Pharmacoeconomics, Intensive Monitoring*) 4= Report from Aggregate Analysis 312.32(c)(1)(i)(C) 5=Cross-reported IND safety report
B.1.1	<patientinitial>	Patient Identifier	For a Report from an Aggregate Analysis, the element value should be "AGGREGATE"

3. For adverse events that occur with a marketed drug being evaluated under an IND that meets both IND and post-marketing safety reporting requirements (21 CFR 312.32 and 314.80, 600.80, or 310.305), sponsors must submit two separate ICSRs:

    a. for the marketed drug for the NDA/BLA

    and

    b. for the study drug for the IND (IND number in A.2.3.2)

APPENDIX III. CASE SCENARIOS FOR SAFETY REPORTS FROM IND-EXEMPT BA/BE STUDIES TO FAERS

Table 15 illustrates the ICH E2B data elements and element values for each IND-exempt BA/BE study exposure scenario described below:

Scenario 1: Exposure to a *study drug*:

This scenario applies to all drugs specified in the study protocol. For example, if a BA/BE study protocol for a generic opiate includes administration of naltrexone to each study subject prior to administration of a test or reference drug, naltrexone is a *study drug*, although it is not the test or reference drug. Similarly, a selective 5-HT3 receptor antagonist to prevent nausea and vomiting is considered a *study drug* if the BA/BE study protocol states that the drug is administered to each study subject prior to administration of a test or reference drug.

Scenario 2: Exposure to an *other drug*:

Other drugs are drugs taken by or administered to a subject that are not part of study conduct per protocol. For example, a subject with a diagnosis of hypertension has normal blood pressure while treated with a beta blocker. The subject meets study enrollment criteria and continues to take his beta blocker during study participation. In this situation, the beta blocker is an *other drug*. Similarly, if a subject develops symptoms of heartburn during participation in a BA/BE study and is permitted, by the investigator, to use a nonprescription antacid or H2 blocker for symptomatic relief, the nonprescription drug taken by the subject is an *other drug*.

Scenario 3: No exposure to a study drug:

A serious adverse event a subject experiences after enrollment to the study, but prior to exposure to a study drug, is subject to the expedited safety reporting requirement. To report a serious adverse event with no study drug exposure, the submitter should select values as shown in the Table 15, Scenario 3.

Table 155. ICH E2B Data Element & Value Selections for IND-Exempt BA/BE Study Exposures

Drug Exposure Scenario	Data Element	Element Values
Scenario 1: Exposure to a *study drug*	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	Select one from the following: 1 = Test drug 2 = Reference drug 3 = Placebo/Vehicle 4 = Control (negative or positive)
Scenario 2: Exposure to an *other drug*	B.4.k.1	Select one element value
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	5 = Other drug
Scenario 3: No exposure to a *study drug*	B.4.k.1	4 = Drug not administered
	B.4.k.2.1	Proprietary medicinal product name
	B.4.k.2.2	Drug substance name
	B.4.k.19	1 = Test drug

Exhibit 49

Declaration of Dr. Tyler Johnson

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. TYLER JOHNSON

I, Tyler Johnson, D.O., a citizen of the United States and a resident of Leo, Indiana, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I received my Bachelor of Science in Biology from the University of Saint Francis in Fort Wayne. I attended medical school at the Lake Erie College of Osteopathic Medicine. My residency was at Michigan State University's Kalamazoo Center for Medical Studies.
3. I am an emergency department physician certified by the American Board of Emergency Medicine. I practice in the emergency departments of hospitals in northern Indiana. My practice includes treating patients throughout rural northern Indiana into the inner-city of Fort Wayne. I am also the director of emergency medicine at Parkview Dekalb Hospital.
4. I am a member of the American Association of Pro-Life Obstetricians and Gynecologists (AAPLOG).
5. I am familiar with the U.S. Food and Drug Administration's (FDA) Risk Evaluation and Mitigation Strategy (REMS) drug safety program. I am also familiar with the REMS issued by the FDA for the chemical abortion drugs mifepristone and misoprostol in 2016.

6. The FDA's 2016 REMS for mifepristone and misoprostol expanded the acceptable gestational age for chemical abortion, eliminated the in-person administration requirement for these dangerous drugs, eliminated mandatory post-abortion follow-up visits, and eliminated the requirement for prescribers to report all non-fatal adverse events.
7. The FDA's actions harm both women and practitioners.
8. Mifepristone and misoprostol are dangerous drugs that have serious effects on a woman's body. Without the medical supervision, women taking these drugs are at risk of serious and life-threatening complications and even death.
9. I have seen at least a dozen cases of life-threatening complications from the use of abortifacient drugs over the years. These emergency situations are becoming more common as more women are turning to chemical abortion as the FDA has relaxed its regulations.
10. In one case, for example, I treated a woman in the emergency department who had been given an abortion pill from a clinic in Chicago. She took the pill and began to experience heavy bleeding on the drive back to Fort Wayne. By the time she arrived at the hospital, she was unconscious. I performed emergent treatment and gave her a necessary blood transfusion. The patient required further evaluation and observation in the hospital. I have seen multiple cases similar to this one.

11. About a month ago, I treated an 18-year-old woman in the emergency department who was experiencing severe pain. Although the situation was not life-threatening to her, she was terrified, and it was clear to me that she did not understand what she had been given. It is not uncommon for women who take mifepristone and misoprostol to come to the emergency department because the pain is so terrible.

12. Many of the patients I have treated for complications with chemical abortion experience trauma. They usually have no follow-up with the doctors who prescribed or dispensed the abortifacient drugs, and they are not adequately prepared to understand what the drugs will do to them. In these situations, it is clear to me that these women and girls could not have given informed consent to chemical abortion.

13. In many cases, women are hesitant to tell us that they have taken chemical abortion drugs. On multiple occasions I have treated women in the emergency department who are experiencing extremely heavy bleeding even after they have already passed the unborn child. The women will sometimes eventually explain that they took abortifacient drugs, which helps us understand what is happening to them. I understand that many women are told by staff at the dispensing clinics to tell emergency department doctors that they are experiencing a "miscarriage."

14. Because of the FDA's relaxed regulation of these dangerous drugs, it is extremely easy for women to obtain mifepristone and misoprostol with little

or no supervision. This leaves emergency physicians like me to deal with preventable emergent and life-threatening situations after these women have taken these drugs. The unsupervised administration of chemical abortion drugs simply harms women and physicians.

15. The FDA's actions have created a culture of chaos for emergency room physicians. In my experience, patients who are given abortifacient drugs at clinics do not understand what they have taken and are often reluctant to tell emergency doctors what they have taken. This puts me and my colleagues in a position where we have to treat women in emergency situations without crucial information. This culture puts us in increasingly higher risk situations, which increases our exposure to claims of malpractice and liability.

16. The increase in women presenting in the emergency department for complications with chemical abortions harms other patients too. Because more women are unnecessarily presenting in the emergency department, more of my time and attention is taken away from other patients who need it.

17. I also believe the FDA's elimination of reporting requirements for non-fatal adverse events harms women and practitioners. I believe we are not tracking these medications closely enough to know the extent of the negative side-effects commonly experienced. This also harms physicians' ability to practice evidence-based medicine. Moreover, women and girls cannot give informed

consent to chemical abortion when they do not receive accurate information about the risks associated with mifepristone and misoprostol.

18. Given my experience, I expect to see and treat more patients presenting themselves with complications from chemical abortion.

Executed this November 11, 2022.

By: _____
Tyler Johnson, D.O.

Exhibit 50

Declaration of Dr. Regina Frost-Clark

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. REGINA FROST-CLARK

I, Regina R. Frost-Clark, a citizen of the United States and a resident of Michigan, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am board-certified in obstetrics and gynecology. I practice with St. John OB/Gyn Associates, part of Ascension Medical Group.
3. I received my M.D. from Wayne State University and did my residency at St. John Hospital and Medical Center in Detroit, Michigan.
4. I am in a hospital owned practice and am often called to the emergency department for consultations.
5. I am familiar with the approval and regulatory changes by the United States Food and Drug Administration (FDA) regarding chemical abortion. Specifically, I am familiar with the relaxing of supervision requirements for administering these very serious drugs, and I am familiar with the relaxed reporting requirements for adverse events related to chemical abortions.
6. I believe these FDA actions will harm women, including my patients, and my practice.
7. As an OB/Gyn, I have treated several women who have suffered complications from chemical abortions.

8. The wider availability of chemical abortion drugs will result in an increase in the frequency of complications related to the drugs' use.

9. In at least a dozen cases, I have treated women who were suffering significant bleeding after taking chemical abortion drugs. Occasionally, women have to be admitted to the hospital for observation due to bleeding complications.

10. In my experience, women who have been given chemical abortion drugs often do not know what they were given or how much of a particular drug they took.

11. In most instances where I treat women who have complications from chemical abortion drugs, they have received it from an abortion facility. Recently a woman told me she obtained these drugs by herself—likely online—and took them without any medical supervision.

12. The FDA's suspension of the in-person dispensing requirement of mifepristone and misoprostol harms women and doctors because it has resulted in an increase in complications.

13. Without an in-person dispensing requirement for chemical abortion drugs, there is a greater chance that women with a molar or ectopic pregnancy will be given drugs that will be ineffectual, leaving them exposed to potentially deadly complications like a rupture or hemorrhage.

14. Similarly, without an in-person dispensing requirement, patients may be given chemical abortion drugs without a confirmed pregnancy or for an inappropriate gestational age.

15. In these instances, patients may avoid seeking appropriate medical care because they are unaware of the risks they potentially face, which puts them in greater danger of complications.

16. Women presenting with complications from chemical abortion pose a challenging situation because I may not have access to their medical history—either because I am unable to access any medical records from prescribers of the chemical abortion drugs or because they obtained the chemical abortion drugs without any medical oversight to begin with. Additionally, the patients themselves usually do not understand what they have been given, how much they have taken, or their follow-up instructions.

17. The lack of patient history and knowledge harms my ability to treat patients. For example, with patients experiencing bleeding, the course of treatment will vary if I believe the bleeding is regular or abnormal cyclical bleeding as opposed to bleeding resulting from attempted abortion.

18. I expect to see more and more women with chemical abortion complications as the use of the drugs increases. Because of the increased complications and the limited information available to me due to the FDA's actions, I fear that I will have greater exposure to liability in my practice.

19. The FDA's actions have led to more confusion for patients and providers. The FDA has forced my colleagues and me to make decisions about patient care based on limited information. It also requires me to spend a lot of time trying to reconstruct patient medical histories to best serve my patients.

20. The FDA's actions make it difficult for patients to have informed consent. Doctors cannot confirm the pregnancy, the location of the pregnancy, or the gestational age without an examination. In abortion clinic settings, it is unclear whether patients are seeing the same physician each time. And often there are no patient follow-up visits with the dispensing facility.

21. Under the current practice by those who prescribe chemical abortion drugs like mifepristone and misoprostol, there is no follow-up or additional care provided to patients and therefore no rapport between patients and their physicians. This makes it difficult to assess who is responsible for these patients when they experience complications.

22. The FDA's removal of the adverse event reporting requirement for all adverse events except death harms my ability to perform evidence-based medicine. I am unable to assess the risks present to women because the FDA's removal of reporting requirements undermines the legitimacy of risk data. For example, Ranitidine, commonly known as Zantac, was pulled from the market due to cancer associations after years of use. Without adverse event reporting, I cannot properly assess the risks that my patients face from abortifacient drugs.

23. I have not reported adverse events that I have witnessed as a result of chemical abortions because the process is so cumbersome. In addition to the burdensome paperwork, it is difficult to file an accurate report given that in many cases I am not certain what the patient was given by the chemical abortion prescriber.

Executed this November 13, 2022.

By: _____

Regina Frost-Clark, M.D.

Exhibit 51

Declaration of Dr. George Delgado

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. GEORGE DELGADO

I, George Delgado, a citizen of the United States and resident of San Marcos, California, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am board-certified in family medicine and in hospice and palliative medicine.
3. I serve as a medical advisor to the Abortion Pill Rescue Network and as director of medical affairs of Culture of Life Family Services (COLFS) Medical Clinic.
4. I received my medical degree from the University of California, Davis School of Medicine in 1988 and completed my residency at Santa Monica Hospital/ UCLA Medical Center in 1991.
5. I am a Natural Family Planning (NFP) Medical Consultant trained in NaProTechnology. I have also completed a one-year Certification Program in Health Care Ethics with the National Catholic Bioethics Center.
6. I performed the second recorded successful reversal of chemical abortion in the United States.
7. I established Abortion Pill Reversal, a program that connects women who regret taking the abortion-inducing drug, mifepristone (RU-486), and want to reverse the effects of the chemical abortion regimen.

8. I founded the Steno Institute, a non-profit organization, to conduct, promote and publish high-quality, morally sound health science and clinical research in pro-life areas, including chemical abortion reversal.

9. I published the first peer-reviewed article in the medical literature describing the reversal of the abortion-inducing drug, mifepristone (RU-486), using progesterone. The case study, "Progesterone Use To Reverse The Effects Of Mifepristone," presented a series of cases demonstrating successful reversal of mifepristone effects in women who chose to reverse the chemical abortion process. Four of six women who took mifepristone were able to carry their pregnancies to term after receiving intramuscular progesterone 200 mg.

10. I co-authored a peer-reviewed article, "A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone," published in Issues in Law & Medicine, Volume 33, Number 1, 2018. The results of the study concluded that the reversal of the effects of mifepristone using progesterone is safe and effective.

11. Based on my review of peer-reviewed studies, I can attest that there are higher levels of complications from chemical abortion than from surgical abortion. For example, the risk of severe bleeding with chemical abortion is five times higher than from surgical abortion.

12. In my family medicine practice, I continue to see patients one day per week while serving primarily in an administrative role.

13. I treat women with Abortion Pill Reversal in my office in addition to treating women who suffer complications from chemical abortions.

14. I see women who have a great deal of regret from undergoing the chemical abortion drug regimen. They are distressed, sad, and feel terrible about what they have done. While it is rewarding to offer these women a chance at reversing chemical abortion, this is some of the most emotionally taxing work I have done in my career.

15. For example, I spoke with one patient who sought to reverse a chemical abortion after taking mifepristone under duress by the abortion doctor. She recounted that the doctor at the abortion center rushed her to make a decision, placed the pill in her bare hand, and told her to take the pill before it melted in her hand and that it was very expensive. She took the pill because of the duress she was under and immediately regretted the decision. She successfully reversed her chemical abortion. This example illustrates how women and girls are not giving informed consent when undergoing chemical abortion and sometimes coerced into taking these drugs.

16. Given my experience, I expect to see and treat more patients presenting themselves with complications from chemical abortion and seeking reversal of mifepristone.

17. My practice renders early prenatal care to mothers and provides care to babies that are born. In doing so, my practice will bill a patient's insurance company for reimbursement for the costs of care. When my patients have

chemical abortions, there is a tangible financial loss to my practice in losing the opportunity to render professional prenatal care for the mother or to care for babies who are never born.

18. The FDA's elimination of necessary safeguards for pregnant women and girls, such as removing the requirement for an in-person follow-up examination after a chemical abortion, will increase the demands on my time in my family medicine practice and reduce the time I would like to spend with other patients. I will have to treat an increased number of patients due to abortion facilities' failure to provide follow-up care to women and girls.

19. Executed this November 14, 2022.

By: _____

George Delgado, M.D.

Exhibit 52

Declaration of Dr. Shaun Jester

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its members, and their members, and their members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

DECLARATION OF DR. SHAUN JESTER

I, Shaun Jester, a citizen of the United States and a resident of Dumas, Texas, declare under penalty of perjury under 28 U.S.C. § 1746 that the following is true and correct to the best of my knowledge.

1. I am over eighteen years old and make this declaration on personal knowledge.
2. I am a board-certified obstetrician and gynecologist and am the Medical Director of Moore County Ob/Gyn in Dumas, Texas. I have been board-certified since 2007.
3. I received my medical degree in 1999 from the Texas College of Osteopathic Medicine at the University of North Texas Health Science Center at Fort Worth.
4. I have a busy medical practice. I am one of three doctors on call. My practice includes cesarean section deliveries, hysterectomies, and other women's health treatments. My practice includes about thirty deliveries each month.
5. A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.
6. I understand that the FDA approved chemical abortion drugs for use in the United States in 2000.

7. I am also familiar with the FDA's regulatory changes regarding chemical abortion drugs, especially the REMS issued in 2016 and associated with the use of mifepristone and misoprostol for chemical abortions.
8. I understand that the FDA approved the use of mifepristone up to 70 days (or 10 weeks) of gestation in 2016, which is longer than the previous standard of 49 days (or 7 weeks).
9. I am familiar with the FDA's suspension and elimination of the in-person dispensing requirements for administering these dangerous drugs in 2021.
10. I am familiar with the removal of the requirement for an in-person, post-abortion office visit, which is when a physician determines whether any fetal parts or other products of conception remain. These visits are essential to ensure that women experience no complications after chemical abortion.
11. I am also familiar with the relaxed reporting requirements for adverse events related to chemical abortions.
12. I believe these FDA actions will harm my patients, women, and women's medicine.
13. I believe that the FDA's approval for using mifepristone at a later gestational age, and the elimination of the in-person dispensing requirement and follow-up visit requirement, are especially dangerous for women.
14. Based on my experience, mothers are often mistaken about how far along they are in pregnancy. According to the Listening to Mothers III survey, 26% of women's due dates are changed.

15. Without an in-person visit to obtain an ultrasound, there is no way to be certain about the gestational age of an unborn child. Women may be further along in pregnancy than is currently acceptable for chemical abortion. Similarly, without an in-person examination, it is impossible to rule out an ectopic pregnancy, which would not be terminated by a chemical abortion and could put women at an increased risk of rupture or even death.

16. Based on my experience treating patients, I believe unsupervised chemical abortions are dangerous and potentially life-threatening especially due to increased risk of hemorrhage and/or infection the further along they are after 6 weeks' gestation.

17. For instance, I treated a woman who traveled from Texas to obtain chemical abortion drugs from Planned Parenthood New Mexico to complete an abortion at 10 weeks' gestation. The woman returned to Texas, suffered from two weeks of moderate to heavy bleeding, and then developed a uterine infection. At the hospital, I provided her with intravenous antibiotics and performed a dilation and curettage procedure. If she had waited a few more days before receiving care, she could have been septic and died. I reported this adverse event to the FDA.

18. The FDA's actions harm my practice by causing unnecessary harm to my patients that could have been avoided by retention and enforcement of the REMS.

19. Doctors like me serve patients as professional health care providers. I provide care to all women and unborn children, and I give them the best professional services possible. Just like other employed obstetrical providers, my hospital will bill for the cost of obstetrical and medical services rendered. When my patients have chemical abortions, I lose the opportunity to provide these obstetrical and medical services to care for the woman and child through pregnancy and bring about a successful delivery of a new life.

20. Additionally, the wider availability of chemical abortion drugs will result in more patients experiencing complications and the number of patients in emergency situations will rise. These situations are naturally higher risk for both the patient and for the physician providing care. In the chemical abortion case that I reported as an adverse event to the FDA, I had no existing patient relationship or prior knowledge of the patient's medical history. Such cases can be a high-pressure, high-risk situation for practitioners like me.

21. The FDA's deregulation of these dangerous drugs increases our exposure to liability.

22. There are many contraindications to prescribing mifepristone, including adrenal failure, steroid use, severe anemia, bleeding disorders, the use of intrauterine devices, undiagnosed ectopic pregnancy, and others. I do not believe telemedicine can rule out all contraindications to prescribing

mifepristone because some of these conditions can only be ascertained with an in-person examination or lab work.

23. Telemedicine does not allow for a critical ultrasound assessment to rule out ectopic pregnancies and verify that the patients are within the 70 days allowed for chemical abortions. In this way, the FDA's loosening of regulations for abortifacient drugs harms women and practitioners by exposing them to increased risk of complications.

24. I believe the relaxed reporting requirements for adverse events related to chemical abortion drugs harm women and physicians because they create an inaccurate and false safety profile for the use of mifepristone and misoprostol. Many women and girls do not fully understand the nature of chemical abortion and the risks that these drugs present to them.

25. The elimination of mandatory follow-up visits after chemical abortion drugs have been administered is also dangerous and harms women and practitioners. Without follow-up visits, physicians cannot identify potential complications like sepsis and hemorrhage, lingering products of conception, and others until the patient is at a critical time or it is too late to help the patient.

26. I care for my patients and give them the best medical care and guidance that I can. I believe that chemical abortions harm women, including my patients, and harm the medical practice. The elimination of REMS critical to ensuring safe use of the chemical abortion drugs prevents doctors from fulfilling their

oath to "do no harm" by permitting the administration of abortifacient drugs to patients without full knowledge or appreciation for the impact those drugs would have on them.

27. As with my patient who suffered an adverse event, it disturbed me that she was not informed that it was not normal to bleed for multiple weeks and that if she had a routine follow-up visit, as required by past REMS, this situation could have been avoided before requiring overnight hospitalization and her being at risk for developing sepsis.

Executed this November 14, 2022.

By: _____, D.O.
Shaun Jester, D.O.

CIVIL COVER SHEET

The JS 44 civil cover sheet and the information contained herein neither replace nor supplement the filing and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. *(SEE INSTRUCTIONS ON NEXT PAGE OF THIS FORM.)*

I. (a) PLAINTIFFS

Alliance for Hippocratic Medicine, et al

(b) County of Residence of First Listed Plaintiff Potter County, TX
(EXCEPT IN U.S. PLAINTIFF CASES)

(c) Attorneys *(Firm Name, Address, and Telephone Number)*

Please see attached

DEFENDANTS

U.S. Food and Drug Administration, et al.

County of Residence of First Listed Defendant Montgomery County, MD
(IN U.S. PLAINTIFF CASES ONLY)

NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED.

Attorneys *(If Known)*

Please see attached

II. BASIS OF JURISDICTION *(Place an "X" in One Box Only)*

- ☐ 1 U.S. Government Plaintiff
- ☐ 3 Federal Question *(U.S. Government Not a Party)*
- ☒ 2 U.S. Government Defendant
- ☐ 4 Diversity *(Indicate Citizenship of Parties in Item III)*

III. CITIZENSHIP OF PRINCIPAL PARTIES *(Place an "X" in One Box for Plaintiff and One Box for Defendant)*

(For Diversity Cases Only)

	PTF	DEF		PTF	DEF
Citizen of This State	☐ 1	☐ 1	Incorporated *or* Principal Place of Business In This State	☐ 4	☐ 4
Citizen of Another State	☐ 2	☐ 2	Incorporated *and* Principal Place of Business In Another State	☐ 5	☐ 5
Citizen or Subject of a Foreign Country	☐ 3	☐ 3	Foreign Nation	☐ 6	☐ 6

IV. NATURE OF SUIT *(Place an "X" in One Box Only)*

Click here for: Nature of Suit Code Descriptions.

CONTRACT
- ☐ 110 Insurance
- ☐ 120 Marine
- ☐ 130 Miller Act
- ☐ 140 Negotiable Instrument
- ☐ 150 Recovery of Overpayment & Enforcement of Judgment
- ☐ 151 Medicare Act
- ☐ 152 Recovery of Defaulted Student Loans (Excludes Veterans)
- ☐ 153 Recovery of Overpayment of Veteran's Benefits
- ☐ 160 Stockholders' Suits
- ☐ 190 Other Contract
- ☐ 195 Contract Product Liability
- ☐ 196 Franchise

REAL PROPERTY
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

TORTS

PERSONAL INJURY
- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers' Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Personal Injury - Medical Malpractice

PERSONAL INJURY
- ☐ 365 Personal Injury - Product Liability
- ☐ 367 Health Care/ Pharmaceutical Personal Injury Product Liability
- ☐ 368 Asbestos Personal Injury Product Liability

PERSONAL PROPERTY
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

CIVIL RIGHTS
- ☐ 440 Other Civil Rights
- ☐ 441 Voting
- ☐ 442 Employment
- ☐ 443 Housing/ Accommodations
- ☐ 445 Amer. w/Disabilities - Employment
- ☐ 446 Amer. w/Disabilities - Other
- ☐ 448 Education

PRISONER PETITIONS

Habeas Corpus:
- ☐ 463 Alien Detainee
- ☐ 510 Motions to Vacate Sentence
- ☐ 530 General
- ☐ 535 Death Penalty

Other:
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition
- ☐ 560 Civil Detainee - Conditions of Confinement

FORFEITURE/PENALTY
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 690 Other

LABOR
- ☐ 710 Fair Labor Standards Act
- ☐ 720 Labor/Management Relations
- ☐ 740 Railway Labor Act
- ☐ 751 Family and Medical Leave Act
- ☐ 790 Other Labor Litigation
- ☐ 791 Employee Retirement Income Security Act

IMMIGRATION
- ☐ 462 Naturalization Application
- ☐ 465 Other Immigration Actions

BANKRUPTCY
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

PROPERTY RIGHTS
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 835 Patent - Abbreviated New Drug Application
- ☐ 840 Trademark
- ☐ 880 Defend Trade Secrets Act of 2016

SOCIAL SECURITY
- ☐ 861 HIA (1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g))
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g))

FEDERAL TAX SUITS
- ☐ 870 Taxes (U.S. Plaintiff or Defendant)
- ☐ 871 IRS—Third Party 26 USC 7609

OTHER STATUTES
- ☐ 375 False Claims Act
- ☐ 376 Qui Tam (31 USC 3729(a))
- ☐ 400 State Reapportionment
- ☐ 410 Antitrust
- ☐ 430 Banks and Banking
- ☐ 450 Commerce
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced and Corrupt Organizations
- ☐ 480 Consumer Credit (15 USC 1681 or 1692)
- ☐ 485 Telephone Consumer Protection Act
- ☐ 490 Cable/Sat TV
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 890 Other Statutory Actions
- ☐ 891 Agricultural Acts
- ☐ 893 Environmental Matters
- ☐ 895 Freedom of Information Act
- ☐ 896 Arbitration
- ☒ 899 Administrative Procedure Act/Review or Appeal of Agency Decision
- ☐ 950 Constitutionality of State Statutes

V. ORIGIN *(Place an "X" in One Box Only)*

- ☒ 1 Original Proceeding
- ☐ 2 Removed from State Court
- ☐ 3 Remanded from Appellate Court
- ☐ 4 Reinstated or Reopened
- ☐ 5 Transferred from Another District *(specify)*
- ☐ 6 Multidistrict Litigation - Transfer
- ☐ 8 Multidistrict Litigation - Direct File

VI. CAUSE OF ACTION

Cite the U.S. Civil Statute under which you are filing ***(Do not cite jurisdictional statutes unless diversity)***:
5 U.S.C. §§ 553, 701-706, equitable cause of action for judicial review

Brief description of cause:
Challenge to agency actions in violation of federal statutes and regulations

VII. REQUESTED IN COMPLAINT:

☐ CHECK IF THIS IS A **CLASS ACTION** UNDER RULE 23, F.R.Cv.P.

DEMAND $ Injunction, Vacatur , D.J.

CHECK YES only if demanded in complaint:
JURY DEMAND: ☐ Yes ☒ No

VIII. RELATED CASE(S) IF ANY

(See instructions): JUDGE _____ DOCKET NUMBER _____

DATE 11/18/2022

SIGNATURE OF ATTORNEY OF RECORD /s/ Erik C. Baptist

FOR OFFICE USE ONLY

RECEIPT # _____ AMOUNT _____ APPLYING IFP _____ JUDGE _____ MAG. JUDGE _____

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
AMARILLO DIVISION

ALLIANCE FOR HIPPOCRATIC MEDICINE, on behalf of itself, its member organizations, their members, and these members' patients; **AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS**, on behalf of itself, its members, and their patients; **AMERICAN COLLEGE OF PEDIATRICIANS**, on behalf of itself, its members, and their patients; **CHRISTIAN MEDICAL & DENTAL ASSOCIATIONS**, on behalf of itself, its members, and their patients; **SHAUN JESTER, D.O.**, on behalf of himself and his patients; **REGINA FROST-CLARK, M.D.**, on behalf of herself and her patients; **TYLER JOHNSON, D.O.**, on behalf of himself and his patients; and **GEORGE DELGADO, M.D.**, on behalf of himself and his patients,

Plaintiffs,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration; **JANET WOODCOCK, M.D.**, in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration; **PATRIZIA CAVAZZONI, M.D.**, in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration; **U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**; and **XAVIER BECERRA,** in his official capacity as Secretary, U.S. Department of Health and Human Services,

Defendants.

Case No. _____

ATTACHMENT TO CIVIL COVER SHEET

I. Plaintiffs' Attorneys

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II. Defendants

U.S. Food and Drug Administration;
Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs, U.S. Food and Drug Administration;
Janet Woodcock, M.D., in her official capacity as Principal Deputy Commissioner, U.S. Food and Drug Administration;
Patrizia Cavazzoni, M.D., in her official capacity as Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration;
U.S. Department of Health and Human Services; and
Xavier Becerra, in his official capacity as Secretary, U.S. Department of Health and Human Services.

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