No. 23-10362

IN THE UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Plaintiffs-Appellees,
v.
U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,
Defendants-Appellants,

and

DANCO LABORATORIES, LLC,
Intervenor-Appellant.

On Appeal from the United States District Court for the Northern District of Texas, No. 2:22-cv-00223-Z

APPENDIX OF EXHIBITS IN OPPOSITION TO AN EMERGENCY STAY PENDING APPEAL VOLUME 2 (ALLIANCE.APP. 115-174)

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TABLE OF EXHIBITS

The Danco Group

January 21, 2000

Division of Reproductive and
Urologic Drug Products (HFD-580)
Attention: Document Control Room 17B-20
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-687, Mifepristone 200mg Oral Tablets**
- Amendment 039 - Mifeprex® – Distribution Plan

Dear

As previously agreed, we are submitting Danco Laboratories, Inc.'s Distribution Plan for Mifeprex®. This is a comprehensive distribution plan that emphasizes control of mifepristone at all points in the supply chain, from manufacturers through to individual patients. This plan has been prepared in light of the unique situation surrounding abortion provision in the United States and not out of any medical safety concerns. However, in preparation of this plan, we have taken into account advice from the FDA that it is considering approving the NDA under "Subpart H—Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses, Sec. 314.520--Approval with restrictions to assure safe use."

Our position is that we are willing to agree with the FDA on appropriate distribution controls for mifepristone but that the application of Sec. 314.520 under Subpart H seems unnecessary, in light of our voluntary acceptance of some appropriate distribution controls.

Specifically, Sec. 314.520(a) states that the FDA can apply post-marketing restrictions if it "concludes that a drug product shown to be effective can be safely used *only* if distribution or use is restricted" (emphasis added). Regardless of the distribution system for mifepristone, the medical safety of this drug is well documented in our IND application and in the label and, thus, we believe that Sec. 314.520 does not apply.

This document constitutes trade secret and confidential commercial information exempt from public disclosure under 21 C.F.R. 20.61. Should FDA tentatively determine that any portion of this document is disclosable in response to a request under the Freedom of Information Act, Danco Laboratories, Inc. requests immediate notification and an opportunity for consultation in accordance with 21 C.F.R. 20.45. Contact telephone number is

On the contrary, scientific evidence demonstrates that mifepristone is an exceptionally safe drug. Mifepristone when taken by a woman whose pregnancy is ≤ 49 days LMP is associated with several relatively minor and predictable side effects. 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. There has never been a death related to the use of mifepristone in combination with misoprostol for medical termination of pregnancy. These details have been discussed and reported in our label and various submissions to the FDA.

In addition to concerns about patient safety, the possibility of teratogenic effects has previously triggered the application of section 314.520, as in the case of Thalomid (Thalidomide). These concerns relate to the inadvertent use of a known teratogen at the early stages of a pregnancy that was not scheduled for termination. In contrast, all women who will receive mifepristone will be known to be in early pregnancy and have elected to terminate that pregnancy. Of course, in the case of a successful application of mifepristone, concerns about teratogenicity are rendered moot as the woman will no longer be pregnant. Similarly, in the case of a failed medical abortion, women should have a surgical intervention to terminate the pregnancy and are counseled to do so before taking mifepristone and misoprostol. To date, there is no compelling evidence to suggest that either mifepristone or misoprostol produces teratogenic effects.

Based on the above reasons, we firmly believe that the NDA for mifepristone should not be approved under Sec. 314.520. In addition, applying Sec. 314.520 might draw increased and unwarranted attention to the product, the FDA, and to Danco and its manufacturers, in particular evoking queries about the product's safety. Nonetheless, given the contentious political climate surrounding *all* abortion provision in the United States, we feel that the distribution of mifepristone should be carefully monitored and controlled. Therefore, we have developed and are implementing a controlled distribution strategy and are submitting the details of this strategy in the enclosed Distribution Plan for your review and comment.

Sincerely,

/S/

President and Chief Executive Officer

/dns
Enclosure

cc:
Sandra P. Arnold – Population Council
Frederick H. Schmidt – Population Council
Patricia C. Vaughan, Esq. – Population Council

MIFEPREX®

DISTRIBUTION PLAN

January 21, 2000

MIFEPREX®

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MIFEPREX®

DISTRIBUTION PLAN

EXECUTIVE SUMMARY

This Distribution Plan for Mifeprex® demonstrates Danco Laboratories Inc.'s ("Danco") commitment to distributing Mifeprex® safely and efficiently while, at the same time, providing needed services and information to providers and patients in a confidential manner. Danco has a keen awareness of and sensitivity to the regulatory requirements, as well as the market and political dynamics, surrounding introduction of Mifeprex® in the United States. Therefore, Danco has established a **controlled distribution strategy** to best meet the goals of safe, efficient and confidential distribution of Mifeprex®.

This strategy ensures that Danco exerts positive control over distribution of Mifeprex® through all phases of manufacturing, storage, shipment and administration from manufacturer to patient. Key control elements throughout the distribution process include the following:

- Secure manufacturing, receiving and holding areas for Mifeprex®
- Secure shipping procedures, including tamper-proof seals
- Controlled returns procedures
- Tracking system ability to trace individual packages to patient level, while maintaining patient confidentiality
- Use of only [redacted] authorized distributors and a logistics partner, all of whom have necessary expertise, capabilities and industry experience to handle distribution requirements for Mifeprex®
- Required Account Registration and Order Form signed by providers, prior to any Mifeprex® order being shipped
- Mifeprex® availability only to registered providers, not through retail pharmacies
- Documented patient acknowledgment (informed consent), signed by patient and provider

Alongside key control elements, Danco also recognizes the need to provide support and access to training, services and information throughout the supply chain. The support that is built into the distribution system is as follows:

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Access to multi-media training materials and training programs with continuing medical education (CME) recognition and credits.

- Danco toll-free telephone information network for consumers and providers, with access to medical consultants for providers' medical questions
- Danco web site information network
- Trained service representatives for distributors' questions through the logistics partner

Danco has developed and assembled the infrastructure to ensure that Danco's goal of safe, efficient and confidential distribution of Mifeprex® is attained. The Distribution Plan for Mifeprex® details Danco's controlled distribution strategy, highlighting key control elements at each point in the supply chain.

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:

[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

[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)

(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:

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- 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)] 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 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

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.

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>).