UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD, Plaintiff, v. JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*, Defendants, and TIMOTHY K. MOORE and PHILIP E. BERGER, Intervenors.	Case No.: 1:23-cv-00077-WO-LPA

PLAINTIFF'S MOTION FOR LEAVE TO FILE AN AMENDED COMPLAINT AND TO EXPEDITE SUPPLEMENTAL BRIEFING ON INTERVENORS' MOTION TO DISMISS

TABLE OF CONTENTS

TABLE OF AUTHORITIES ii

PROCEDURAL BACKGROUND 2

ARGUMENT 5

I. Leave to Amend Should Be Granted 5

A. Plaintiff's Amendment Is Timely and Will Not Prejudice Defendants 6

B. Plaintiff Seeks Leave to Amend in Good Faith 8

C. Plaintiff's Amendment Is Not Futile 8

II. Any Supplemental Briefing on Intervenors' Motion to Dismiss Should Be Expedited 9

CONCLUSION 11

CERTIFICATE OF COMPLIANCE

CERTIFICATE OF SERVICE

TABLE OF AUTHORITIES

Cases

Davis v. Piper Aircraft Corp.,
615 F.2d 606 (4th Cir. 1980) 6, 9

Edwards v. City of Goldsboro,
178 F.3d 231 (4th Cir. 1999) 6, 7

Feit Elec. Co. v. Cree, Inc.,
No. 1:15-cv-535,
2016 WL 10587196 (M.D.N.C. June 20, 2016) 6

Foman v. Davis,
371 U.S. 178 (1962) 5

Hartford Fire Ins. Co. v. Hendrick Auto. Grp.,
No. 3:16-cv-133,
2016 WL 3344380 (W.D.N.C. June 13, 2016) 10

Island Creek Coal Co. v. Lake Shore, Inc.,
832 F.2d 274 (4th Cir. 1987) 5

Johnson v. Oroweat Foods Co.,
785 F.2d 503 (4th Cir. 1986) 6

Jones v. HSBC Bank USA, N.A.,
444 F. App'x 640 (4th Cir. 2011) 7

Laber v. Harvey,
438 F.3d 404 (4th Cir. 2006) 6

Pettiford v. City of Greensboro,
556 F. Supp. 2d 512 (M.D.N.C. May 30, 2008) 9

Sherron v. Corr. Care Dir. I,
No. 1:15-cv-852,
2016 WL 6069183 (M.D.N.C. Oct. 17, 2016) 6

Sherron v. Jones,
No. 1:15-cv-852,
2016 WL 6833982 (M.D.N.C. Nov. 18, 2016) 6

Smith v. 3M Co.,
No. 1:16-cv-00379,
2017 WL 11681454 (M.D.N.C. Dec. 15, 2017) 10

Syngenta Crop Prot., Inc. v. EPA,
222 F.R.D. 271 (M.D.N.C. 2004) 5

White v. Ctr. for Creative Leadership,
No. 1:15-cv-281,
2016 WL 1048044 (M.D.N.C. Mar. 11, 2016) 8

Wonasue v. Univ. of Md. Alumni Ass'n,
295 F.R.D. 104 (D. Md. 2013) 8

Rules

Fed. R. Civ. P. 15(a) 1, 5

Other Authorities

N.C. Sess. Law 2023-14 ..... 5, 7, 10

PLAINTIFF'S MOTION FOR LEAVE TO FILE AN AMENDED COMPLAINT AND TO EXPEDITE SUPPLEMENTAL BRIEFING ON INTERVENORS' MOTION TO DISMISS

Pursuant to Federal Rule of Civil Procedure 15(a), Plaintiff Amy Bryant, M.D. ("Plaintiff") hereby moves this Court for leave to file the proposed Amended Complaint attached as **Exhibit A**. The proposed Amended Complaint contains revised allegations and updated references to the challenged statutes, but asserts no new claims and adds no new parties. A redline showing differences between the original Complaint and the proposed Amended Complaint is attached as **Exhibit B**.

Given the procedural and factual situation presented by this Action, Plaintiff easily satisfies the requirements for leave to amend under Federal Rule of Civil Procedure 15(a). Precedent instructs that the Court should freely grant leave when justice so requires, and here, justice so requires. Plaintiff's complaint argues that North Carolina's restrictions on medication abortion are preempted by federal law. After the Complaint was filed, after Intervenors' Motion to Dismiss was filed, and after Plaintiff's opposition to that Motion to Dismiss was filed, the North Carolina

legislature —— of which Intervenors are the leaders —— voted to amend the statutes at issue in this Action. Rather than remedy the infirmities in those statutes, the North Carolina legislature enacted more restrictive legislation that only serves to create further conflict between federal and state law.

Leave to amend should accordingly be granted. Moreover, to avoid unnecessary cost and delay, the Court should treat Intervenors' pending motion to dismiss as applying to the Amended Complaint, Intervenors should be directed to supplement their motion to dismiss (if necessary) within one week following the grant of leave to amend, and Plaintiffs should be permitted to reply within one week thereafter. Plaintiffs notified Intervenors of their intent to file this motion, and Intervenors stated that they would determine their position after review of the motion and the proposed Amended Complaint.

PROCEDURAL BACKGROUND

On January 25, 2023, Plaintiff initiated this Action by filing the original Complaint. ECF No. 1.

On February 21, 2023, Intervenors Philip E. Berger, in

his official capacity as President *Pro Tempore* of the North Carolina Senate, and Timothy K. Moore, in his official capacity as the Speaker of the North Carolina House of Representatives, filed their Motion to Intervene. ECF No. 29. Intervenors' Motion to Intervene was granted on March 10, 2023. ECF No. 50.

On February 22, 2023, Defendants Attorney General Joshua Stein and Secretary of the Department of Health and Human Services Kody Kinsley filed their Answers to the Complaint. ECF Nos. 43, 41.

On March 24, 2023, Defendants Michaux R. Kilpatrick, Christine M. Khandelwal, Devdutta G. Sangvai, John W. Rusher, William M. Brawley, W. Howard Hall, Sharona Y. Johnson, Joshua D. Malcolm, Miguel A. Pineiro, Melinda H. Privette, Anuradha Roa-Patel, and Robert Rich, Jr., in their official capacity as board members of the North Carolina Medical Board (the "North Carolina Medical Board Defendants"), and Jeff Nieman filed their Answers to the Complaint. ECF Nos. 51, 52.

Also on March 24, 2023, Intervenors filed their Motion to Dismiss the Complaint. ECF No. 53.

On April 14, 2023, the North Carolina Medical Board

Defendants filed their Notice of No Position on Intervenors' Motion to Dismiss. ECF No. 58.

On April 28, 2023, Plaintiff filed her opposition to Intervenors' Motion to Dismiss the Complaint. ECF No. 68. Alongside that opposition, Attorney General Stein filed his Response in Opposition to the Intervenors' Motion to Dismiss. ECF No. 64. Likewise, Secretary Kinsley filed his Response to the Intervenors' Motion to Dismiss (ECF No. 67) and Jeff Nieman filed his Notice of No Position on Intervenors' Motion to Dismiss (ECF No. 66).

On May 2, 2023, with Intervenors' knowledge, Senator Joyce Krawiec and Representative Sarah Stevens offered a replacement bill for Senate Bill 20[1] that proposed to amend the provisions of the North Carolina General Statutes that Plaintiff challenges in her Complaint.

On May 3, the North Carolina House of Representatives passed Senate Bill 20. On May 4, the North Carolina Senate passed Senate Bill 20. On May 13, 2023, Governor Roy Cooper vetoed Senate Bill 20. The North Carolina legislature voted

[1] Prior to replacement on May 2, 2023, Senate Bill 20 was originally introduced on January 25, 2023, and contained proposed legislation relating to safe surrender of infants.

to override Governor Cooper's veto on May 16, 2023. Senate Bill 20 thus became North Carolina Session Law 2023-14 (attached as **Exhibit C**). The provisions of Session Law 2023-14 do not become effective until July 1, 2023.

On May 26, 2023, Intervenors filed their reply in support of their Motion to Dismiss the Complaint. ECF No. 72.

ARGUMENT

I. Leave to Amend Should Be Granted.

Rule 15(a) of the Federal Rules of Civil Procedure, which governs amendment of the pleadings, provides that "leave to amend shall be freely given when justice so requires." *See Foman v. Davis*, 371 U.S. 178, 182 (1962) (quotation marks omitted). The Fourth Circuit has consistently applied this standard under Rule 15(a) and granted leave when justice so requires. *See, e.g., Island Creek Coal Co. v. Lake Shore, Inc.*, 832 F.2d 274, 279 (4th Cir. 1987). The decision on whether to grant leave to amend falls within the discretion of the trial court, although "the federal rules strongly favor granting leave to amend." *Syngenta Crop Prot., Inc. v. EPA*, 222 F.R.D. 271, 278 (M.D.N.C. 2004) (quotation marks omitted). The law is well settled "that leave to amend a pleading should be denied only when the amendment would be

prejudicial to the opposing party, there has been bad faith on the part of the moving party, or the amendment would be futile." *Johnson v. Oroweat Foods Co.*, 785 F.2d 503, 509 (4th Cir. 1986); *see also Edwards v. City of Goldsboro*, 178 F.3d 231, 242 (4th Cir. 1999).

A. Plaintiff's Amendment Is Timely and Will Not Prejudice Defendants.

"Whether an amendment is prejudicial will often be determined by the nature of the amendment and its timing." *Laber v. Harvey*, 438 F.3d 404, 427 (4th Cir. 2006); *see also, e.g., Feit Elec. Co. v. Cree, Inc.*, No. 1:15-cv-535, 2016 WL 10587196, at *1 (M.D.N.C. June 20, 2016) (Osteen, J.) (allowing amendment after finding that "discovery in this case [has] not yet started, and any delay is not therefore prejudicial"). "The Fourth Circuit has further explained that 'absence of prejudice, though not alone determinative, will normally warrant granting leave to amend.'" *Sherron v. Corr. Care Dir. I*, No. 1:15-cv-852, 2016 WL 6069183, at *5 (M.D.N.C. Oct. 17, 2016) (quoting *Davis v. Piper Aircraft Corp.*, 615 F.2d 606, 613 (4th Cir. 1980)), *report and recommendation adopted sub nom. Sherron v. Jones*, 2016 WL 6833982 (M.D.N.C. Nov. 18, 2016).

As detailed above, Plaintiff could not have amended her complaint at an earlier date, as these statutory amendments were not ratified until May 16, only 2 weeks ago. In the interest of efficiency, Plaintiff files this Motion even before Session Law 2023-14 is effective, in the expectation that it will become effective as planned on July 1, 2023.

Unlike where leave to amend has been denied on timeliness grounds, Plaintiff here could not have revised her Complaint to address the revised statutory language contained in Session Law 2023-14 before it was ratified. *Compare Jones v. HSBC Bank USA, N.A.*, 444 F. App'x 640, 643 (4th Cir. 2011) (per curiam) (motion to amend denied because plaintiff "either knew or should have known of these facts considerably earlier"), *with Edwards*, 178 F.3d at 243 ("Prejudice to the Defendants could hardly flow from [] an addition" where plaintiff's amendment sought to add claims uncovered during discovery and to add specificity to existing claims). Here, while Intervenors and Defendants have answered or moved in response to the Complaint, discovery has not begun, and no scheduling order has been entered. Thus, Intervenors and Defendants are not prejudiced by the proposed Amended

Complaint.

B. Plaintiff Seeks Leave to Amend in Good Faith.

Plaintiff's request to amend her Complaint is a good faith attempt to update the statutory language and allegations in the Complaint to address the amended state laws concerning mifepristone. The proposed Amended Complaint asserts no new claims and does not seek to add parties. The proposed Amended Complaint represents nothing more than Plaintiff's good faith effort to capture the now-current laws implicated by her claim.

C. Plaintiff's Amendment Is Not Futile.

"Determining whether amendment would be futile does not involve an evaluation of the underlying merits of the case. Rather, the merits of the litigation are only relevant to the Court's ruling on a motion for leave to amend if a proposed amendment may clearly be seen to be futile, such as if the proposed amended complaint fails to state a claim under the applicable rules and accompanying standards." *White v. Ctr. for Creative Leadership*, No. 1:15-cv-281, 2016 WL 1048044, at *3 (M.D.N.C. Mar. 11, 2016) (quoting *Wonasue v. Univ. of Md. Alumni Ass'n*, 295 F.R.D. 104, 107 (D. Md. 2013)). "Unless a proposed amendment may clearly be seen to be futile because

of substantive or procedural considerations, conjecture about the merits of the litigation should not enter into the decision whether to allow amendment." *Davis*, 615 F.2d at 613 (citation omitted).

For the reasons discussed in Plaintiff's Opposition to Intervenors' Motion to Dismiss (ECF No. 68), both her Complaint and proposed Amended Complaint properly state a claim upon which relief can be granted. Plaintiff incorporates those arguments here.

II. Any Supplemental Briefing on Intervenors' Motion to Dismiss Should Be Expedited.

Should this Motion be granted, because Plaintiff asserts no new claims in the proposed Amended Complaint, it is appropriate that Intervenors' pending motion to dismiss be treated as applying to the Amended Complaint and, if additional briefing is deemed necessary, that Intervenors be directed to file a supplemental motion to dismiss to present any additional arguments in response to the Amended Complaint.

Supplemental motion to dismiss briefing in response to amended complaints is common. *See, e.g., Pettiford v. City of Greensboro*, 556 F. Supp. 2d 512, 516 (M.D.N.C. 2008)

("[T]he City filed a Motion to Dismiss and, after Plaintiffs' Amended Complaint, a Supplemental Motion to Dismiss"); *Smith v. 3M Co.*, No. 1:16-cv-00379, 2017 WL 11681454, at *2 (M.D.N.C. Dec. 15, 2017) (defendants "each filed a Supplemental Motion to Dismiss . . . to renew and incorporate their previously filed, unaddressed motions and supporting briefs in light of the Amended Complaint." (cleaned up)). Because no new claims are introduced by the proposed Amended Complaint, Intervenors' arguments in support of their Motion to Dismiss should not materially change, and supplemental briefing should be more than sufficient.

Likewise, an expedited timeline for any supplemental briefing (as other courts have considered and ordered) would be appropriate here. *See, e.g., Hartford Fire Ins. Co. v. Hendrick Auto. Grp.*, No. 3:16-cv-133, 2016 WL 3344380 (W.D.N.C. June 13, 2016) (ordering one week for defendants to supplement their motion to dismiss in response to amended complaint after motion to dismiss original complaint had been fully briefed, and one additional week for plaintiffs to respond). Intervenors, as leaders of the North Carolina legislature, are well versed in Session Law 2023-14 and are

well equipped to respond to the proposed Amended Complaint, which must have been expected given that this Action was pending when the legislation was introduced and passed.

Supplemental briefing on an expedited timeline is fair and appropriate in these circumstances. The parties have already devoted considerable time and resources to briefing Intervenors' motion to dismiss, and the amendments to Plaintiffs' complaint do not materially affect the arguments raised in Intervenors' motion. Restarting the briefing process from scratch would be unfairly prejudicial to Plaintiff and would cause unnecessary cost and delay for all parties —— especially given that the need for Plaintiff to amend her complaint resulted from the decision by the legislature, under Intervenors' leadership, to amend the challenged statutes at a time when briefing on Intervenors' motion was nearly complete.

CONCLUSION

In accordance with the foregoing, Plaintiff requests that her motion for leave to file the proposed Amended Complaint be granted and that the Court order expedited supplemental briefing (if necessary) on Intervenors' motion to dismiss.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I certify that the foregoing document complies with Local Rules 7.1(a) and 7.3(d) because it uses 13-point Courier New font; its top margin is not less than 1.25 inches and its bottom, left, and right margins are each one inch; and it contains 2,014 words.

Date: June 2, 2023

/s/ Chelsea Corey
Chelsea Corey
(NC Bar No. 48838)
Counsel for Plaintiff

CERTIFICATE OF SERVICE

I hereby certify that on June 2, 2023, the foregoing pleading was filed via the Court's CM/ECF System, which will effect service upon all registered counsel of record.

/s/ Chelsea Corey
Chelsea Corey
(NC Bar No. 48838)
Counsel for Plaintiff

Exhibit A

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD, Plaintiff, v. JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*, Defendants, and TIMOTHY K. MOORE and PHILIP E. BERGER, Intervenors.	Case No.: 1:23-cv-00077-WO-LPA **FIRST AMENDED COMPLAINT**

INTRODUCTION

1. Under well-settled principles of preemption that preserve American federalism, a State cannot impose laws that conflict with and frustrate the objectives of federal law. When Congress enacted the Risk Evaluation and Mitigation Strategies ("REMS") provisions of the Federal Food, Drug, and Cosmetic Act ("FDCA"), its clear objective was to ensure that REMS drugs are regulated in a way that is commensurate with

their risks while not imposing undue burdens on the healthcare system or patient access. The U.S. Food and Drug Administration ("FDA" or the "Agency") has acted pursuant to this authority to impose a precise set of controls on an FDA-approved drug, mifepristone. A State may not impose additional controls —— including restrictions that FDA has specifically rejected —— that upset the carefully balanced regulatory scheme established by federal law.

2. In the FDCA, Congress granted FDA exclusive authority to impose restrictions on the prescribing, dispensing, and administration of drugs that the Agency deems to pose particular risks but for which the importance of patient access justifies imposition of special controls. FDA imposes those controls by way of a REMS, which sometimes includes special Elements to Assure Safe Use ("ETASU"). *See* 21 U.S.C. § 355-1. In granting FDA (and only FDA) authority to impose drug-specific REMS and ETASU, Congress expressly charged the Agency with striking a balance between access to treatments and protection from identified risks, instructing FDA to impose only those restrictions necessary to ensure safety without imposing undue burdens on access or on the

healthcare delivery system. *See id.* § 355-1(f).

3. In 2000, after several years of review of voluminous data, FDA concluded that mifepristone is safe and effective and approved the drug for use under the trade name Mifeprex. Specifically, FDA approved mifepristone for the medical termination of intrauterine pregnancy, in a two-drug regimen with misoprostol. Exercising its authority first under regulation and subsequently under its exclusive REMS statutory authority, FDA has subjected Mifeprex to a carefully crafted set of regulatory controls that the Agency concluded were commensurate with the drug's risks while not unduly burdening patient access or the healthcare system. In doing so, FDA determined that any risk-mitigation benefits from additional restrictions would be outweighed by added burdens on patient access and the healthcare system.

4. During the more than two decades since FDA's approval of mifepristone as a safe and effective option for ending early pregnancy, medication abortion has been used by more than 5 million patients and now accounts for more than half of abortions nationwide. *See* Rachel K. Jones et al., Guttmacher Inst., *Medication Abortion Now Accounts for More*

than Half of All US Abortions (updated Dec. 1, 2022), https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions. Over that time, substantial additional evidence of safe and effective use has accumulated.

5. As more data and evidence have emerged, the Agency has revised and fine-tuned the Mifepristone REMS numerous times as part of its ongoing obligation under the REMS provisions of the FDCA. In its current form, the Mifepristone REMS requires providers to prescribe mifepristone under an FDA-approved Certified Prescriber Agreement, and to dispense mifepristone either directly or by issuing the prescription to a certified pharmacy. The Prescriber Agreement requires that providers be specially certified and possess certain qualifications, and that they agree to report any patient deaths to the drug sponsor. The Mifepristone REMS also requires providers to ensure that medication abortion patients receive specific counseling and information, including a copy of the mifepristone Medication Guide, and that they consent by using an FDA-approved Patient Agreement Form. *See* FDA, Single Shared System for Mifepristone 200 MG,

Risk Evaluation and Mitigation Strategy (REMS) (2023) ("2023 Mifepristone REMS"), attached as Ex. A. The Mifepristone REMS does *not* require, because FDA has affirmatively determined it should not, that mifepristone be provided by physicians only; that it be provided in person or in specially certified facilities; that it be preceded by in-person counseling, a 72-hour waiting period, an in-person examination by a physician, an ultrasound in all cases, or a determination of blood type; that the physician schedule an in-person follow-up visit with the patient; or that the physician report all adverse events potentially associated with the drug.

6. Rejecting the regulatory framework imposed by Congress and FDA, North Carolina has imposed (and recently expanded) a complex web of requirements relating to the provision of mifepristone that apply to all patients and medical providers in the state, including Plaintiff. Unlike FDA's framework, North Carolina's requirements —— including recent legislative amendments that are scheduled to take effect on July 1, 2023 —— state that abortion medications may be provided only in person, only by a physician, and only

after state-mandated in-person counseling, a 72-hour waiting period, an in-person physician examination, an ultrasound, and a determination of the patient's blood type. North Carolina also mandates that physicians use different patient consent forms than those required by FDA, schedule an in-person follow-up visit with every patient, and report any and all adverse events to the State and FDA within 3 days. *See* N.C. Gen. Stat. §§ 14-44, 14-45, 14-45.1, 90-21.82, 90-21.90; N.C. Sess. Law 2023-14 ("S.L. 2023-14"), Part I (changes effective July 1, 2023). North Carolina's restrictions conflict with federal law and upset the regulatory balance struck by FDA, creating an obstacle to the congressional objectives that FDA carried out in imposing the Mifepristone REMS.

7. Plaintiff is a physician who regularly provides care to patients of reproductive age and ability and who regularly prescribes mifepristone, as she is certified to do under the Mifepristone REMS. When prescribing mifepristone, Plaintiff complies with all of the Mifepristone REMS requirements, as she must to maintain her prescriber certification.

8. As a medical provider in North Carolina, Plaintiff

is also subject to North Carolina's requirements relating to providing mifepristone. Under the North Carolina restrictions, instead of having the option of seeing patients remotely via telehealth and either dispensing the medications or providing a prescription for a patient to fill from a pharmacy so that the patient may take the medication at the place of their choosing, as FDA expressly authorizes, Plaintiff must personally examine the patient; be physically present when the patient takes the mifepristone (which must be preceded by an ultrasound, a blood-type determination, state-mandated in person counseling, and a 72-hour waiting period); schedule and attempt to ensure that the patient returns for an in-person follow-up visit; and comply with the State's onerous and unnecessary reporting requirements.

9. These restrictions impose significant costs and burdens on both Plaintiff and her patients. As a North Carolina licensed physician, Plaintiff has a professional, legal, and ethical obligation to "use h[er] best judgment in the treatment and care of h[er] patient[s]" and to "exercise reasonable care and diligence in the application of h[er] knowledge and skill to [each] patient's case." *Hunt v.*

Bradshaw, 88 S.E.2d 762, 765 (N.C. 1955); *see* N.C. Med. Bd., Position Statements, *The Licensee-Patient Relationship* 2.1.1: (Mar. 2022) ("N.C. Med. Bd. Position Statement")[1] ("All licensees should exercise their best professional judgement when making patient care decisions" regardless of "the health care system or setting in which a licensee practices.").

10. The challenged restrictions impose unnecessary costs on Plaintiff and her practice and interfere with her ability to provide medical care to her patients according to her best medical judgment and in accordance with federal law. But for those restrictions, Plaintiff would be able to provide medication abortion care to a larger number of patients at lower cost. Further, medication abortion is inherently time-critical, and delaying such care can unnecessarily increase risk or even push patients outside the window for use of mifepristone, potentially forcing patients to have more involved and more expensive procedures (which will present heightened risks for some patients). Patients also must bear

[1] *Available at* https://www.ncmedboard.org/images/uploads/other_pdfs/Compendium_Final_03.25.2022.pdf.

all of the risks and costs of pregnancy during the delays caused by the challenged restrictions.

11. As part of its congressionally mandated regulatory balancing, FDA specifically considered and rejected the idea that mifepristone must be provided in person by a physician in a particular type of facility. FDA also considered and rejected more stringent physician adverse-event reporting requirements. FDA instead concluded that mifepristone can be safely prescribed by any certified healthcare provider either in person or via telehealth, obtained by the patient directly from or under the supervision of the healthcare provider or from a certified pharmacy, and taken by the patient in her home or other place of her choosing. And FDA expressly concluded that requirements like those imposed by North Carolina are unnecessary to ensure patient safety and contrary to the regulatory balance that Congress and FDA sought to achieve.

12. For North Carolina to impose restrictions that go beyond those FDA deemed warranted as part of its regulatory balancing, including restrictions that FDA specifically rejected, frustrates the objectives of federal law. In light

of FDA's heightened oversight and scrutiny of REMS drugs, as instructed by Congress in the REMS provisions of the FDCA, there is no room for North Carolina to impose additional restrictions and specific conditions for use that FDA, in the exercise of its congressionally delegated REMS authority, concluded are unwarranted and inappropriate. Simply put, North Carolina cannot stand in the shoes of FDA to impose restrictions on medication access that FDA determined are not appropriate and that upset the careful balance FDA was directed by Congress to strike.

13. Plaintiff seeks a declaratory judgment that North Carolina's restrictions on mifepristone are preempted insofar as they are inconsistent with the federal REMS, and an injunction prohibiting Defendants from enforcing those restrictions or taking any other action to restrict the ability of a provider to provide, or a patient to access, mifepristone in accordance with federal law.

PARTIES

14. Plaintiff, Dr. Amy Bryant, is a North Carolina board-certified and licensed physician with a medical practice in Orange County, North Carolina. Dr. Bryant

regularly provides medical care to patients of reproductive age and ability. In that capacity, she regularly counsels patients about the option of mifepristone for medical termination of intrauterine pregnancy, in a regimen with misoprostol. She also provides care through telemedicine for other patients, and she would provide telehealth abortion care if she could do so free from the risk of enforcement action by Defendants. She is certified to prescribe mifepristone as required by the REMS, and she regularly prescribes and dispenses mifepristone in accordance with the REMS. Plaintiff brings this action in her personal capacity.

15. Defendant Joshua Stein is the Attorney General for the State of North Carolina. He is the chief law enforcement officer of the State with the power to enforce the North Carolina restrictions at issue. He is sued in his official capacity.

16. Defendant Jeff Nieman is the District Attorney for North Carolina's 18th Prosecutorial District. He is responsible for criminal prosecutions under relevant North Carolina law occurring within Prosecutorial District 18, including in Orange County. *See* N.C. Const. art. IV, § 18(1);

N.C. Gen. Stat. §§ 7A-60, 7A-61. He is sued in his official capacity.

17. Defendant Kody H. Kinsley is the North Carolina Secretary of Health and Human Services, whose department is charged with (among other things) development of consent and physician declaration forms and printed and online materials required to be referenced in state-mandated pre-abortion counseling; licensing of hospitals and certification of clinics that provide abortion; denial, suspension, and revocation of facility certifications; and investigations of complaints relating to clinics that provide abortion. *See* N.C. Gen. Stat. §§ 90-21.83, 90-21.84; 10A N.C. Admin. Code 14E.0101, *et seq.*; S.L. 2023-14, sec. 1.2, §§ 90-21.83, 90-21.83A, 90-21.84. He is sued in his official capacity.

18. Defendant Michaux R. Kilpatrick, MD, PhD, is the President of the North Carolina Medical Board, an entity created by the North Carolina legislature and which establishes procedures and requirements for licensure as a physician in North Carolina. N.C. Gen. Stat. §§ 90-2, 90-9.1. The Medical Board has the power to sanction physicians, including placing them on probation and suspending or

revoking their licenses, for "[p]roducing or attempting to produce an abortion contrary to law." *Id.* § 90-14(a)(2); S.L. 2023-14, sec. 1.2, § 90-21.88A. She is sued in her official capacity.

19. Defendant Christine M. Khandelwal, DO, is a member and President-Elect of the North Carolina Medical Board. She is sued in her official capacity.

20. Defendant Devdutta G. Sangvai, MD, MBA, is a member and Secretary and Treasurer of the North Carolina Medical Board. He is sued in his official capacity.

21. Defendant John W. Rusher, MD, JD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

22. Defendant William M. Brawley is a member of the North Carolina Medical Board. He is sued in his official capacity.

23. Defendant W. Howard Hall, MD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

24. Defendant Sharona Y. Johnson, PhD, FNP-BC, is a member of the North Carolina Medical Board. She is sued in

her official capacity.

25. Defendant Joshua D. Malcolm, JD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

26. Defendant Miguel A. Pineiro, PA-C, MHPE, is a member of the North Carolina Medical Board. He is sued in his official capacity.

27. Defendant Melinda H. Privette, MD, JD, is a member of the North Carolina Medical Board. She is sued in her official capacity.

28. Defendant Anuradha Rao-Patel, MD, is a member of the North Carolina Medical Board. She is sued in her official capacity.

29. Defendant Robert Rich, Jr., MD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

JURISDICTION AND VENUE

30. This Court has original subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 because it arises under the Constitution and laws of the United States.

31. This Court has personal jurisdiction over Defendants

because they are domiciled in North Carolina and enactment and enforcement of the state laws at issue occurred and continues to occur within North Carolina.

32. Venue is proper within the Middle District of North Carolina under 28 U.S.C. § 1391(b)(2) because Plaintiff is located and practices medicine in this judicial district.

33. This Court has the authority to enter a declaratory judgment and provide injunctive relief pursuant to 28 U.S.C. §§ 2201 and 2202, Federal Rules of Civil Procedure 57 and 65, and this Court's inherent equitable powers.

34. Plaintiff has standing because the challenged provisions of North Carolina law directly operate against Plaintiff by regulating her conduct and subjecting her to a threat of enforcement when she prescribes mifepristone or advises patients regarding the use of mifepristone. As a North Carolina licensed physician, Plaintiff has a professional, legal, and ethical obligation to "use h[er] best judgment in the treatment and care of h[er] patient[s]" and to "exercise reasonable care and diligence in the application of h[er] knowledge and skill to [each] patient's case." *Hunt*, 88 S.E.2d at 765; *see* N.C. Med. Bd. Position

Statement 2.1.1 ("All licensees should exercise their best professional judgement when making patient care decisions" regardless of "the health care system or setting in which a licensee practices."). The challenged restrictions impose unnecessary costs on Plaintiff, her patients, and her practice and interfere with her ability to provide medical care to her patients according to her best medical judgment and in accordance with federal law. But for those restrictions, Plaintiff would be able to provide a wider range of mifepristone-related services to a larger number of patients at lower cost, including by providing flexible telehealth services to patients and by delegating some tasks related to medication abortion care to non-physician colleagues. Plaintiff would be subject to direct criminal, civil, and administrative penalties under North Carolina law if she were to violate its provisions.

35. Plaintiff's claims are ripe because the challenged North Carolina laws are currently in effect and enforceable and are presently impacting her ability to provide and offer medical advice regarding mifepristone to her patients according to her best medical judgment and in accordance with

federal law.

FACTUAL ALLEGATIONS

A. Statutory and Regulatory Background

36. Under the FDCA, no drug manufacturer, or "sponsor," can introduce its drug into interstate commerce unless and until that sponsor first obtains marketing approval from FDA. 21 U.S.C. §§ 321(p), 331(d), 355(a).

37. To seek approval under the FDCA, a drug sponsor must undertake a lengthy development program that typically includes, as it did in this case, significant clinical trial data, as well as extensive engagement with FDA in meetings and through written and oral feedback. The drug sponsor then submits a new drug application ("NDA") seeking FDA's authorization to sell and market the drug.

38. FDA reviews NDAs to ensure that they include adequate safety data and substantial evidence of efficacy, among other things. FDA may not approve an NDA unless it determines that the data and information included in the NDA demonstrate that the drug is both safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R.

§ 314.125(b).

39. Because all drugs have the potential for adverse effects, demonstrating safety necessary for approval does not require showing that a drug has no potential adverse effects, but rather that the drug's benefits outweigh its risks. *See Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013).

40. Congress created REMS as a risk management tool, codifying FDA's authority with respect to drugs that are expected to provide substantial benefits, but which FDA determines also pose risks that would otherwise result in FDA denying an application to sell or market those drugs. *See* Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, § 901, 121 Stat. 823, 926 (enacting 21 U.S.C. § 355-1); 21 U.S.C. § 355-1(a)(2) (extending the REMS authority to already-approved drugs). Within a REMS, FDA may impose requirements, including requiring information for patients and imposing restrictions on prescribers and distribution, that go above and beyond those that FDA is able to require in the absence of a REMS.

41. In enacting the REMS provision, Congress required FDA to consider both the risks associated with the drugs and

the burden of imposing various requirements, and to choose the least restrictive set of requirements sufficient to ensure a positive benefit-risk profile, *i.e.*, ensuring safe use of the drug by managing identified safety risks while also maximizing patient access to the drug and minimizing burdens on the healthcare system. *See, e.g.*, 21 U.S.C. § 355-1(a)(1), (f)(2), (f)(5), (g)(2)(C), (g)(4)(B); *see also* FDA, No. FDA-2018-D-4628, Draft Guidance for Industry: REMS Assessment: Planning and Reporting at 13 (Jan. 2019) ("REMS Assessment Draft Guidance")[2] (REMS with ETASU "shall, considering the risk, not be unduly burdensome on patient access, and, to the extent practicable, minimize the burden on the health care delivery system").

42. Congress provided a series of tools that FDA can incorporate in a particular REMS to strike the right balance between ensuring safe use and avoiding undue burdens on patient access or the healthcare delivery system. For instance, a REMS may include a medication guide or patient

[2] *Available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rems-assessment-planning-and-reporting.

package insert, *see* 21 U.S.C. § 355-1(e)(2); a communication plan, including letters to healthcare providers, *see id.* § 355-1(e)(3); and/or packaging and disposal requirements, *see id.* § 355-1(e)(4).

43. In addition to these relatively more modest requirements, a REMS can also include ETASU that FDA determines are necessary for the drug to be approved. *See* 21 U.S.C. § 355-1(f)(1). These additional elements may require that healthcare providers who prescribe the drug have particular training or experience or be specially certified; that pharmacies, practitioners, or health care settings that dispense the drug be specially certified; that the drug be dispensed to patients only in certain health care settings; that the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results; or that patients be subject to monitoring or be enrolled in a registry. *Id.* § 355-1(f)(3).

44. Because ETASU requirements have the potential to unduly restrict access to drugs with meaningful therapeutic benefits, Congress imposed strict limitations on their use. Any ETASU imposed by FDA must be "commensurate with" a

specific serious identified risk of the drug. 21 U.S.C. § 355-1(f)(2)(A). They must "not be unduly burdensome on patient access to the drug." *Id.* § 355-1(f)(2)(C). And they must be designed "to minimize the burden on the health care delivery system" of complying with the requirements. *Id.* § 355-1(f)(2)(D). In considering burdens on patient access, Congress directed FDA to give particular consideration to "(i) patients with serious or life-threatening diseases or conditions, (ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas), and (iii) patients with functional limitations." *Id.* § 355-1(f)(2)(C)(i)-(iii).

45. When FDA imposes ETASU requirements, Congress requires the Agency to seek input from patients, physicians, pharmacists, and other healthcare providers about how to design those requirements so as not to be unduly burdensome on patient access to the drug and to minimize the burden on the healthcare delivery system. 21 U.S.C. § 355-1(f)(5)(A).

46. Congress also charged FDA with continued monitoring and periodic re-assessment of REMS and ETASU to ensure that they continue to reflect the least restrictive set of

requirements necessary to ensure safety while protecting patient access, in light of the Agency's evolving understanding of a particular drug's risks and benefits. Every REMS thus includes a timetable for periodic assessments of the effectiveness of the risk mitigation strategy. *See* 21 U.S.C. § 355-1(c)(1), (d). FDA must "periodically evaluate" ETASU requirements to assess whether they are necessary to assure safe use, are not unduly burdensome on patient access to the drug, and minimize the burden on the healthcare delivery system; and the Agency must "modify" those requirements "as appropriate" in light of those evaluations and input received from patients, physicians, pharmacists, and other healthcare providers. 21 U.S.C. § 355-1(f)(5)(B), (C). Further, Congress obligated FDA to institute a REMS review and initiate modification of a REMS if at any time the Agency determines that the REMS should be modified to "minimize the burden on the health care delivery system of complying with the strategy." *Id.* § 355-1(g)(4)(B).

47. FDA guidance states that the process of identifying and minimizing potential burdens on the healthcare system and barriers to patient access "should begin during the REMS

design phase," when drug sponsors must demonstrate that they have considered and attempted to minimize potential burdens and barriers; and should continue during the post-approval implementation phase, when sponsors are required, as part of their periodic REMS assessments, to use metrics, data sources, and analytical tools "to assess REMS burdens" and "barriers to patient access." REMS Assessment Draft Guidance at 13-15.

48. Because REMS with ETASU are the most restrictive approach available for ensuring safe use of approved drugs, they are imposed on a very limited number of drugs. Of the more than 20,000 prescription drugs FDA has approved,[3] FDA's website lists only 56 currently approved REMS with ETASU.[4]

B. FDA's Approval of Mifepristone and the Mifepristone REMS

49. Mifepristone is used in medication abortion in a

[3] *See Fact Sheet: FDA at a Glance*, FDA.gov (Nov. 2021), https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance ("There are over 20,000 prescription drug products approved for marketing.").

[4] *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA.gov (2023), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

regimen with misoprostol. Typically a patient first takes mifepristone, which works by blocking the hormone progesterone, without which the pregnancy cannot continue; followed by misoprostol 24 to 48 hours later, which causes uterine contractions similar to an early miscarriage. Medication abortion typically involves cramping, pain, and bleeding; more serious complications are extremely rare, "occurring in no more than a fraction of a percent of patients." Nat'l Acads. of Scis., Eng'g, & Med., The Safety and Quality of Abortion Care in the United States 55 (2018), *available at* http://nap.nationalacademies.org/24950. These risks "are both low and similar in magnitude to the reported risks of serious adverse effects of commonly used prescription and over-the-counter medications," such as pain relievers like aspirin and ibuprofen and common antibiotics. *Id.* at 58.

50. FDA initially approved mifepristone in 2000 under the trade name Mifeprex (an abbreviated new drug application for a generic version of mifepristone was approved in 2019). FDA-approved product labeling specified that mifepristone was approved for the medical termination of intrauterine

pregnancy, in a regimen with misoprostol. Mifeprex (mifepristone) Prescribing Information (2000) ("2000 Prescribing Information"), attached as Ex. B.

51. Since its initial approval in 2000, FDA has closely monitored mifepristone and has made updates to the mix of regulatory controls FDA has imposed on the drug —— including changes to the approved labeling, the risk mitigation plan, and the REMS —— in 2004, 2005, 2009, 2016, 2019, 2021, and 2023.[5] In so doing, FDA has approved lifting or otherwise modifying certain of the REMS elements and ETASU when it determined that a particular ETASU or other REMS element was unduly burdensome or no longer necessary to maintain a favorable benefit-risk profile for the drug.

52. Each REMS modification reflects FDA's exercise of its congressionally mandated responsibility to continue to consider scientific evidence regarding the safe and effective use of mifepristone as well as burdens on patient access and the health care delivery system, and to adjust and refine the

[5] *See Drugs@FDA: NDA 020687*, FDA.gov, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=020687.

federal regulatory balance based on such consideration.

1. FDA's Initial Approval of Mifepristone in 2000

53. In initially considering whether to approve the Mifeprex NDA, FDA determined that medication abortion provides a meaningful therapeutic benefit to some patients. *See* 21 C.F.R. § 314.500; NDA 020687, Approval Letter from FDA to Sandra P. Arnold, Population Council at 1 (Sept. 28, 2000) ("Mifeprex Approval Letter"), attached as Ex. C (noting that the application was "approved under 21 CFR 314 Subpart H"); Memorandum from FDA to NDA 20-687 MIFEPREX (mifepristone) Population Council at 6 (Sept. 28, 2000) ("Mifeprex Approval Memorandum"), attached as Ex. D. It has never deviated from that determination. As FDA has recognized, "[p]regnancy can be a serious medical condition in some women" and is associated with numerous health risks, including preeclampsia and eclampsia; an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus; disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or

surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (*e.g.*, diabetes, lupus, cardiac disease, hypertension). Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch. to Donna Harrison, M.D., *et al.*, Denying Citizen Petition Asking FDA to Revoke Approval of Mifeprex at 4 (Mar. 29, 2016), attached as Ex. E. FDA further observed that continued pregnancy carries a significant risk that a patient may require a major surgical procedure and anesthesia, as well as endure depression, anxiety, and other conditions. *Id.* at 4-5.

54. In reviewing the NDA for Mifeprex, FDA determined that distribution restrictions were necessary in order to approve Mifeprex. The approved NDA for Mifeprex thus included a risk mitigation plan that included distribution restrictions under the regulations that predated the 2007 REMS statute. *See* 21 C.F.R. § 314.520; Mifeprex Approval Letter at 2 (Ex. C); Mifeprex Approval Memorandum at 6, (Ex. D).

55. FDA's initial 2000 approval required that Mifeprex could only be "provided by or under the supervision of a

physician" who had signed a Prescriber Agreement Form. Mifeprex Approval Letter at 2 (Ex. C). The Prescriber Agreement Form specified the qualifications that FDA had determined were necessary for a physician to become certified to prescribe mifepristone, including the ability to (a) assess duration of pregnancy (although, as described in the Mifeprex 2000 Prescribing Information (Ex. B), an ultrasonographic scan need only be used if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected); (b) diagnose ectopic pregnancies; (c) provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others; and (d) assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. Mifeprex (Mifepristone) Tablets, 200 mg Prescriber's Agreement (2000) ("2000 Prescriber Agreement"), attached as Ex. F.

56. The Prescriber Agreement Form required the signatory to have read and understood the prescribing information and to follow guidelines for use, including: (a) providing the patient with a copy of the Patient Agreement Form and the

Medication Guide; (b) fully explaining the procedure to each patient; (c) answering any questions the patient had about the procedure; and (d) signing and obtaining the patient's signature on the Patient Agreement Form. It also required the signatory to report "any hospitalization, transfusion, or other serious [adverse] event" to the drug's sponsor, 2000 Prescriber Agreement at 3 (Ex. F), which in turn was required to report it to FDA, 21 C.F.R. §§ 314.80, 314.81; Mifeprex Approval Letter (Ex. C).

57. According to FDA, the purpose of the Patient Agreement Form was to make sure that patients "understand the type of regimen they are about to commit to and its risks and benefits." Mifeprex Approval Memorandum at 3 (Ex. D). To that end, the form specified that the patient had been told about the risks and benefits of mifepristone and that she fully understood the treatment and its potential complications. It also included statements regarding the administration of mifepristone, *e.g.*, "I understand that I will take Mifeprex in my provider's office" and "I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and

that I am well." Mifeprex (mifepristone) Tablets Patient Agreement (2000), attached as Ex. G.

58. The Prescriber Agreement Form and Patient Agreement Form remain part of the ETASU under the Mifepristone REMS today, with modifications including those described below.

2. FDA's Approval of the Mifepristone REMS in 2011

59. When Congress enacted the statutory REMS provision in 2007, it expressly deemed certain drugs (including mifepristone) that had in effect an approved risk mitigation plan under 21 C.F.R. Subpart H to have approved REMS in effect, and it required those drugs' sponsors to submit proposed REMS for approval under the new statute. *See* FDAAA § 909(b), 121 Stat. at 950-51; FDA, Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313 (Mar. 27, 2008).

60. In June 2011, FDA approved the first REMS for mifepristone under the FDAAA. The 2011 Mifepristone REMS carried forward the distribution restrictions FDA had previously imposed on mifepristone and included as ETASU the

restrictions previously imposed in the 2000 Mifeprex risk mitigation plan: Physicians were required to be "specially certified" by completing the Prescriber Agreement; mifepristone was to be dispensed "only in certain health care settings, specifically clinics, medical offices, and hospitals"; and it was to be dispensed only with documentation of safe use conditions, including obtaining the patient's signature on the Patient Agreement. Physicians were still required to report "serious" adverse events (in addition to the sponsor's ongoing adverse event reporting requirement). The 2011 REMS also specified as a REMS element that the Medication Guide be provided with each Mifeprex prescription. FDA, NDA 20-687 Mifeprex (mifepristone) Tablets, 200 mg, Risk Evaluation and Mitigation Strategy (REMS) at 1-2 (2011) ("2011 Mifepristone REMS"), attached as Ex. H; *see also* NDA 020687/S-014, Supplement Approval Letter from FDA to Danco Labs., LLC at 1 (June 8, 2011), attached as Ex. I.

3. FDA's Modification of the Mifepristone REMS in 2016

61. In 2016, FDA "assessed the current REMS program to determine whether each Mifeprex REMS element remains

necessary to ensure that the drug's benefits outweigh the risks" in light of the extensive data and information about clinical practice collected since the original approval 16 years earlier. NDA 020687/S-020, Supplement Approval Letter from FDA to Danco Labs., LLC at 2 (Mar. 29, 2016), attached as Ex. J; *see also* FDA, NDA 020687/S-020, Risk Evaluation and Mitigation Strategy (REMS) Memorandum, REMS Modification at 2 (Mar. 29, 2016) ("2016 REMS Memorandum"), attached as Ex. K; FDA, NDA 020687/S-020, REMS Modification Review at 5, 10 (Mar. 29, 2016) ("2016 REMS Modification Review"), attached as Ex. L; FDA, NDA 020687/S-020, Addendum to REMS Modification Review § 3 (Mar. 29, 2016) ("2016 REMS Modification Review Addendum"), attached as Ex. M.

62. In light of its review, FDA approved several changes to the Mifepristone REMS that expanded the provision of medication abortion. *See* FDA, NDA 20-687 Mifeprex (mifepristone) Tablets, 200 mg, Risk Evaluation and Mitigation Strategy (REMS) (2016) ("2016 Mifepristone REMS"), attached as Ex. N. Among other things, the 2016 REMS allowed qualified healthcare providers other than physicians to become certified to prescribe mifepristone. *Compare* 2016

Mifepristone REMS, Prescriber Agreement Form (Ex. N) (stating that "Mifeprex must be provided by or under the supervision of *a healthcare provider* who prescribes and meets the following qualifications" (emphasis added)) *with* 2011 Mifepristone REMS, Prescriber's Agreement (Ex. H) (stating that "Mifeprex must be provided by or under the supervision of *a physician* who meets the following qualifications" (emphasis added)).

63. In addition, the 2016 modification revised the Patient Agreement to no longer state that the patient understood mifepristone would be *administered* in-person in the provider's office (while retaining the requirement that it be *dispensed* in-person in a clinic, medical office, or hospital). *Compare* 2016 Mifepristone REMS, Patient Agreement (Ex. N) (stating simply, "I understand . . . I will take Mifeprex on Day 1," with no location specified) *with* 2011 Mifepristone REMS, Patient Agreement (Ex. H) (stating, "I understand that I will take Mifeprex *in my provider's office*" (emphasis added)); *see also* 2016 Mifepristone REMS § II.A.2 (Ex. N) (continuing to specify locations where mifepristone could be dispensed); 2016 REMS Memorandum at 1-2 (Ex. K);

2016 REMS Modification Review at 5-7 (Ex. L); 2016 REMS Modification Review Addendum §§ 2.1.1.1, 2.2.1 (Ex. M). Consistent with its congressional mandate to assure safe use without burdening access, FDA concluded that in-person administration should not be required. *See* 2016 REMS Modification Review Addendum § 2.1.1.1 (Ex. M) (noting that the Patient Agreement was being modified to "revis[e] where Mifeprex . . . should be taken"). FDA also determined that in-person follow-up visits should not be required in all cases. *Compare* 2016 Mifepristone REMS, Patient Agreement (Ex. N) (stating, "I should follow up with my healthcare provider") *with* 2011 Mifepristone REMS, Patient Agreement (Ex. H) (stating, "I must return to my provider's office"); *see* Letter from Patrizia A. Cavazzoni, M.D., Dir., Ctr. For Drug Evaluation & Rsch. to Donna Harrison, M.D., *et al.*, Denying Citizen Petition at 13-14 (Dec. 16, 2021) ("AAPLOG Citizen Petition Denial Letter"), attached as Ex. P (noting FDA's conclusion that "appropriate follow-up . . . may be accomplished in multiple ways and not all require an in-clinic visit"). And FDA also determined that prescribers should no longer be required to report adverse events other

than death (although they could still report such events voluntarily, and the sponsor continued to be obligated to comply with post-approval reporting requirements). *See* 2016 Mifepristone REMS §§ II.A.1.b.vi, II.B.5 (Ex. N); 21 C.F.R. §§ 314.80, 314.81.

64. In considering the 2016 modifications, FDA also rejected certain REMS modifications the sponsor requested because FDA concluded those modifications would be inappropriate. For example, FDA did not approve the sponsor's application to remove the Patient Agreement Form requirement from the REMS because FDA determined that the form "would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care." Memorandum from Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch. regarding NDA 020687/S-020 (Mar. 28, 2016), attached as Ex. O.

4. FDA's Further Modification of the Mifepristone REMS in 2023

65. In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public

health emergency regarding the REMS ETASU requiring that mifepristone be dispensed only in certain healthcare settings (*i.e.*, the in-person dispensing requirement). Joint Motion to Stay Case Pending Agency Review, *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw. May 7, 2021), Doc. 148 ("*Chelius* Stay Motion"); *see* AAPLOG Citizen Petition Denial Letter at 5 (Ex. P).

66. Also in 2021, FDA "undertook a full review of the Mifepristone REMS Program," reviewing multiple sources of information, including published literature, safety information submitted to the Agency during the COVID-19 public health emergency, FDA Adverse Event Reporting System reports, the REMS assessment reports for mifepristone submitted in April 2020, and information provided by the sponsors, advocacy groups, and individuals. AAPLOG Citizen Petition Denial Letter at 6 (Ex. P); *see Chelius* Stay Motion at 2 ("FDA is reviewing the elements of the REMS for Mifeprex and its approved generic . . . in accordance with the REMS assessment provisions of Section 505-1 of the [FDCA]."); *see also* FDA, NDA 020687 & ANDA 91178, REMS Modification Rationale Review at 10, 19-36 (Dec. 16, 2021) ("REMS Modification

Rationale Review"), attached as Ex. Q.

67. Following that review, on December 16, 2021, FDA sent REMS modification notification letters to the mifepristone drug sponsors. In those letters, FDA stated that "[i]n accordance with section 505-1(g)(4)(B) of the [FDCA], we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks." NDA 020687, REMS Modification Notification Letter from FDA to Danco Labs., LLC at 1 (Dec. 16, 2021), attached as Ex. R.

68. In particular, FDA required that the Mifepristone REMS be modified to (1) remove the in-person dispensing requirement and (2) add a requirement that pharmacies that dispense the drug be specially certified. *Id.* at 1-2. FDA explained that "[r]emoval of the requirement for in-person dispensing" was "necessary" to "minimize the burden on the healthcare delivery system of complying with the REMS," and that the requirement was "no longer necessary to ensure the benefits of mifepristone outweigh the risks." *Id.* at 1-2; *see also* AAPLOG Citizen Petition Denial Letter at 6 (Ex. P)

("Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and . . . the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks.").

69. In January 2023, FDA approved a modification of the Mifepristone REMS that effectuated these changes. *See* 2023 Mifepristone REMS (Ex. A); *see also* NDA 020687/S-025, Supplement Approval Letter from FDA to Danco Labs., LLC (Jan. 3, 2023), attached as Ex. S. Consistent with FDA's 2021 directive, the 2023 modification removed the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (*i.e.*, the "in-person dispensing" requirement). It also added a certification requirement for pharmacies that dispense mifepristone in order to "ensure[] that pharmacies are aware of and agree to follow applicable REMS requirements, and [] that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers." FDA, NDA 020687/S-025 and ANDA 091178/S-004, Review of proposed Major REMS Modification at 13 (Jan. 3, 2023) ("2023

REMS Modification Review"), attached as Ex. T; *see also id.* at 4, 9. The 2023 modification also updated the REMS goals to add that mifepristone can be dispensed "by or under the supervision of certified prescribers, *or* by certified pharmacies on prescriptions issued by certified prescribers." 2023 Mifepristone REMS at 1 (Ex. A) (emphasis added).

70. FDA left in place the REMS requirement of healthcare provider certification, while concluding that the "[t]he burden of prescriber certification has been minimized to the extent possible." 2023 REMS Modification Review at 10 (Ex. T); REMS Modification Rationale Review at 14 (Ex. Q). FDA also determined that the Patient Agreement Form remains "an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients." 2023 REMS Modification Review at 11 (Ex. T); REMS Modification Rationale Review at 18 (Ex. Q).

71. FDA did not substantively change the prescriber certification requirements, but it did add requirements related to pharmacy certification to facilitate pharmacy dispensing. For example, for a pharmacy to become certified,

the authorized representative must sign a "Pharmacy Agreement Form" attesting that they have read and understood the Prescribing Information and that each location of the pharmacy will be able to receive Prescriber Agreement Forms, ship mifepristone under certain conditions, and adopt processes and procedures to fulfill the REMS requirements. 2023 REMS Modification Review at 12-15 (Ex. T); *see also* 2023 Mifepristone REMS at 3-4 & Pharmacy Agreement Form (Ex. A); REMS Modification Rationale Review at 40-41 (Ex. Q).

72. FDA explained that the 2023 modifications "will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients." 2023 REMS Modification Review at 13 (Ex. T); *see also id.* at 19-20.

73. Thus, as it currently stands, FDA's Mifepristone REMS requires (among other things) that: (1) mifepristone can only be prescribed by or under the supervision of a certified provider, *i.e.*, a healthcare provider who has signed and submitted a Prescriber Agreement Form; (2) mifepristone can be provided either directly by or under the supervision of a

certified prescriber or through a certified pharmacy to which a certified prescriber has sent a prescription; and (3) the patient must sign a Patient Agreement Form, including an attestation that the prescribing healthcare provider has provided information as necessary to comply with the Mifepristone REMS and that the patient has received a copy of the Medication Guide.

74. This means that under federal law, a certified healthcare practitioner (who need not be a physician) can prescribe mifepristone to a patient (either in person or through telemedicine), and either she or someone under her supervision can dispense the medication to the patient or she can provide a prescription for the patient to obtain the medication from a certified pharmacy and take the medication at home or another place of her choosing. FDA has concluded that this specific package of regulatory requirements is, in the Agency's view, commensurate with the risks of mifepristone and sufficient to ensure its safe use while not unduly burdening patient access or the healthcare delivery system. *See* 21 U.S.C. § 355-1(f)(2).

75. On January 22, 2023, President Biden issued a

memorandum noting that FDA, "after an independent and comprehensive review of the risks and benefits" of mifepristone pursuant to the REMS statute, had taken "evidence-based action" to modify the Mifepristone REMS to ensure that "healthcare providers and patients can continue to use telehealth to prescribe and receive mifepristone by mail" and that "pharmacies can now choose to become certified to dispense mifepristone to patients." President Biden explained: "These changes seek to reduce the burden on the healthcare delivery system while ensuring the benefits of the medication outweigh the risks. These changes also help ensure that patients can access mifepristone similarly to how they would access other prescribed medications." Memorandum on Further Efforts to Protect Access to Reproductive Healthcare Services (Jan. 22, 2023), https://www.whitehouse.gov/briefing-room/presidential-actions/2023/01/22/memorandum-on-further-efforts-to-protect-access-to-reproductive-healthcare-services/. And the President decried efforts by some state officials to "impose restrictions to limit access to this evidence-based, safe, and effective medication." *Id.*

C. North Carolina Law Imposes Unnecessary and Burdensome Requirements on Plaintiff's Prescribing of Mifepristone that Conflict with the FDA-Approved Regulatory Scheme

76. North Carolina's broad web of abortion laws imposes additional restrictions on the prescription and distribution of mifepristone that conflict with the regulatory balance struck by FDA's precisely calibrated REMS.

77. In North Carolina, medication abortion is legal only when performed in compliance with specific, onerous conditions and restrictions imposed by the State. *See* N.C. Gen. Stat. §§ 14-44, 14-45, 14-45.1. On May 16, 2023, the North Carolina legislature overrode the Governor's veto and passed Senate Bill 20 (which thus became Session Law 2023-14), amending North Carolina's laws with respect to surgical abortion and medication abortion with an effective date of July 1, 2023. Session Law 2023-14 carries forward or expands many of North Carolina's pre-existing restrictions on abortion, including restrictions that apply specifically to medication abortion. It also imposes onerous new restrictions on medication abortion.

78. Among other restrictions, currently operative North

Carolina law provides that "[t]he physician prescribing, dispensing, or otherwise providing any drug or chemical for the purpose of inducing an abortion shall be physically present in the same room as the patient when the first drug or chemical is administered to the patient." N.C. Gen. Stat. § 90-21.82(1)(a). Session Law 2023-14 maintains the requirement of in-person administration by a physician. *See* S.L. 2023-14, sec. 1.2, § 21.83A(b)(2)a; *id.* sec. 1.3, § 14-44.1.[6] In addition, when the amendments in Session Law 2023-

[6] In addition to requiring that mifepristone be provided in person by a physician, current North Carolina law strictly regulates the locations where such activities can take place. A physician can provide mifepristone only in a facility that the State deems "suitable," which means either a facility physically attached to or operated by a licensed hospital or a freestanding clinic certified by the State to provide abortion services. *See* N.C. Gen. Stat. § 14-45.1(a); 10A N.C. Admin. Code § 14E.0101(2). A hospital must meet numerous requirements to obtain and maintain state licensure, including facility requirements. *See generally* N.C. Gen. Stat. §§ 131E-75 *et seq.* A clinic not attached to or operated by a licensed hospital must likewise meet numerous facility requirements in order to be considered "a suitable facility for the performance of abortions," N.C. Gen. Stat. § 14-45.1(a), including (among other things) plan approval prior to construction, 10A N.C. Admin. Code §§ 14E.0104, .0105; regular facility inspections, *id.* § 14E.0111; N.C. Gen. Stat. § 14-45.1(a1); and specific building code requirements and specifications unnecessary for providing medication abortion,

14 take effect, North Carolina law will require the physician prescribing, administering, or dispensing mifepristone to examine the patient in person before providing the drug, schedule an in-person follow-up visit for the patient approximately seven to 14 days after providing the drug, and "make all reasonable efforts to ensure that the woman returns for the scheduled appointment." *Id.* sec. 1.2, §§ 90-21.83A(b)(4)(*l*), 90-21.83B, 90-21.93(b)(8)-(9).

79. North Carolina law also imposes onerous counseling requirements that must be satisfied before a medication abortion with mifepristone. It requires that a physician or qualified professional provide specific, state-mandated information to the patient prior to the abortion, including statements that are inconsistent with FDA-approved patient

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such as elevators, corridors, and doors large enough to accommodate a stretcher (N.C. Admin. Code §§ 14E.0203, .0204, .0205), ventilation and air supply requirements (*id.* § 14E.0206), and a "nourishment station with storage and preparation area for serving meals or in-between meal snacks" (*id.* § 14E.0207(14)). Under Session Law 2023-14, it appears that the facility requirement would not apply to medication abortion, while North Carolina law would still require that the physician be "physically present in the same room as the woman" when mifepristone is administered. S.L. 2023-14, sec. 1.2, § 21.83A(b)(2)a.

labeling for mifepristone and Plaintiff's expert medical judgment and irrelevant to the patient's care, and then wait at least 72 hours before performing the abortion. *See* N.C. Gen. Stat. §§ 90-21.82, 90-21.90. The amendments in Session Law 2023-14 will make the counseling requirements even more onerous, including by requiring that the counseling be provided in person. *See* S.L. 2023-14, sec. 1.2, §§ 90-21.83, 90-21.83A, 90-21.90. When those amendments take effect, North Carolina law will also mandate an ultrasound examination and a medically unnecessary blood-type determination (which may necessitate blood testing) for all medication abortion patients. *See id.* sec. 1.2, §§ 90-21.83A(b)(2)b, 90-21.83B(a)(2), 90-21.93(b)(6).[7]

80. Further, once Session Law 2023-14 takes effect, North Carolina will subject mifepristone prescribers to additional onerous and unreasonable reporting requirements that FDA has rejected. For example, the amendments made by

[7] Under current North Carolina law, an ultrasound is required for abortions performed in a clinic not attached to or operated by a licensed hospital. 10A N.C. Admin. Code § 14E.0305(d).

S.L. 2023-14 require physicians to report "any specific complications" from mifepristone to the State within 15 days of the patient's last appointment, and to report any "adverse event" to the State —— and to FDA —— within three days. S.L. 2023-14, sec. 1.2, § 90-21.93(b)(10), (c). The law defines both "complication" and "adverse event" broadly to encompass any "physical or psychological" conditions that may have arisen "as a primary or secondary result" of the abortion. *Id.* §§ 90-21.81(1b), (2a), 90-21.83(e)(2).

81. For those who fail to comply with these restrictions, North Carolina law threatens myriad and severe consequences, including criminal prosecution. A physician who "[p]roduce[s] or attempt[s] to produce an abortion contrary to law" is subject to disciplinary action by the North Carolina Medical Board, including fines and suspension or revocation of the physician's medical license, N.C. Gen. Stat. § 90-14(a)(2); S.L. 2023-14, sec. 1.2, § 90-21.88A, as well as other potential enforcement action, *see* N.C. Gen. Stat. §§ 14-44, 14-45, 14-45.1; S.L. 2023-14, sec. 1.2, § 90-21.81B. And a physician who performs an abortion in knowing or reckless violation of those requirements may be subject to

a civil action for damages and attorneys' fees. N.C. Gen. Stat. § 90-21.88; S.L. 2023-14, sec. 1.2, § 90-21.88.[8]

82. As explained above, in imposing and administering the Mifepristone REMS and performing its congressionally mandated balancing to ensure safety while minimizing burdens on patient access and the healthcare system, FDA has made a deliberate choice not to impose restrictions on mifepristone that are the same as or highly similar to restrictions imposed by North Carolina. For example, FDA specifically considered, initially imposed, and ultimately rejected requirements that mifepristone be provided in person by physicians in a specific type of medical facility. FDA has concluded that such requirements are not necessary to ensure safety and would unduly burden patient access and the healthcare delivery system. Instead, FDA concluded that it is appropriate for certified physicians, other certified healthcare providers, and healthcare providers operating under their supervision to

[8] Failure to comply with the facility certification requirements also may subject a provider to administrative action, including denial, suspension, or revocation of certification. *See* 10A N.C. Admin. Code § 14E.0110.

prescribe mifepristone in any type of facility or by telehealth, after providing the specific counseling information that is listed in the FDA-approved Patient Agreement and Medication Guide and without any waiting period; and for patients to obtain mifepristone directly from a certified prescriber or a healthcare provider working under the supervision of a certified prescriber, or from a certified pharmacy upon prescription of a certified prescriber, and take the medication in a place of the patient's choosing. FDA also has required that pregnancy be assessed by ultrasound only if the duration of the pregnancy is uncertain or an ectopic pregnancy is suspected. And FDA has determined that in light of mifepristone's well-characterized safety profile, prescribers should not be subject to reporting requirements like those North Carolina is now seeking to impose. *See* ¶¶ 50-76, *supra*.

CAUSE OF ACTION

83. Plaintiff realleges and incorporates by reference each of the preceding paragraphs as though set forth fully herein.

84. Under the Supremacy Clause of the United States

Constitution, federal laws made under the authority of the United States are "the supreme Law of the Land," the "Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Federal law thus preempts state law where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of federal law.

85. The restrictions imposed by North Carolina on the provision of mifepristone —— including the in-person examination, administration, and follow-up requirements; the in-person counseling and 72-hour waiting period requirement; the physician-only requirement; the ultrasound and blood-type requirements; and the physician adverse event reporting requirements —— conflict with and stand as an obstacle to the accomplishment and execution of the full purposes of objectives of federal law, as reflected in the FDCA and FDA's Mifepristone REMS.

86. Congress has directed FDA, when imposing REMS, and in particular REMS with ETASU, to strike a precise and careful balance between managing the risks of a drug and ensuring patient access to the drug. FDA is required to calibrate its restrictions to ensure patient safety while eschewing

unnecessary restrictions that would unduly burden patient access or the healthcare delivery system. In exercising that authority with respect to mifepristone, FDA has crafted, and regularly revisited and revised, a precise set of regulatory controls that the Agency views as striking the appropriate balance between safety and patient access, and has included only those ETASU that the Agency has deemed to be commensurate with the drug's risks and not unduly burdensome on patients or healthcare providers. In so doing, FDA has concluded that restrictions of the type imposed by North Carolina are unnecessary, inappropriate, and unduly burdensome.

87. The REMS are not a minimum standard on which states are free to build. Rather, as Congress instructed, they reflect FDA's expert conclusion as to the appropriate level of regulatory control for drugs that are expected to provide substantial benefits, but which FDA determines also pose risks that would otherwise result in FDA denying an application to sell or market those drugs. By attempting to impose a different regulatory balance from the one crafted by FDA under its REMS authorities, including by imposing restrictions on the provision of mifepristone that FDA itself

has specifically rejected, North Carolina law frustrates Congress's objective of empowering FDA to ensure safety while minimizing burdens on patient access and on the healthcare delivery system; upsets the deliberate and fine-tuned regulatory balance contemplated by federal law; and thus stands as an obstacle to the accomplishment and execution of the full purposes and objectives of federal law.

88. Plaintiff is accordingly entitled to a declaratory judgment that North Carolina's restrictions on mifepristone are preempted insofar as they are inconsistent with the federal Mifepristone REMS. Plaintiff is also entitled to an injunction prohibiting Defendants from enforcing those restrictions to prevent Plaintiff from providing mifepristone in accordance with federal law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays for the following relief.

1. A declaration pursuant to 28 U.S.C. § 2201 that North Carolina's restrictions on the provision of mifepristone are in conflict with and preempted by federal law;

2. Injunctive relief enjoining Defendants from enforcing North Carolina's restrictions on providing mifepristone or taking any other action to restrict the ability of a provider to provide, or a patient to access, mifepristone in accordance with federal law;

3. An order awarding Plaintiff her costs, expenses, and attorneys' fees; and

4. Such other and further relief as the Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff demands trial by jury on all issues so triable.

Dated: June 2, 2023

Respectfully submitted,

/s/ Chelsea Corey

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Exhibit A

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
    a. To become specially certified to prescribe mifepristone, healthcare providers must:
        i. Review the Prescribing Information for mifepristone.
        ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
            1) They have the following qualifications:
                a) Ability to assess the duration of pregnancy accurately
                b) Ability to diagnose ectopic pregnancies
                c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
            2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
    b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
        i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
        ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms “sign” and “signature” include electronic signatures.

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 57 of 357

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 58 of 357

2. Pharmacies that dispense mifepristone must be specially certified

   a. To become specially certified to dispense mifepristone, pharmacies must:

      i. Be able to receive *Prescriber Agreement Forms* by email and fax.

      ii. Be able to ship mifepristone using a shipping service that provides tracking information.

      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.

      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:

         1) Review the Prescribing Information for mifepristone.

         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:

            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.

            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.

            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.

            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.

            e) Track and verify receipt of each shipment of mifepristone.

            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.

            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.

            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.

            i) Maintain records of *Prescriber Agreement Forms*.

            j) Maintain records of dispensing and shipping.

            k) Maintain records of all processes and procedures including compliance with those processes and procedures.

            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.

            m) Train all relevant staff on the Mifepristone REMS Program requirements.

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 59 of 357

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form.*

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 60 of 357

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 61 of 357

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

Reference ID: 5103833
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 64 of 357

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   - **a.** I will take mifepristone on Day 1.
   - **b.** I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
    - Track and verify receipt of each shipment of Mifeprex.
    - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
    - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
    - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
    - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
    - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
    - Track and verify receipt of each shipment of mifepristone.
    - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
    - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
    - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
    - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
    - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
    - Train all relevant staff on the Mifepristone REMS Program requirements.
    - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

Exhibit B

MIFEPREX™ (mifepristone) Tablets, 200 mg
For Oral Administration Only

If Mifeprex* results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions on whom to call and what to do in the event of an emergency following administration of Mifeprex.

Prescribers should make sure that patients receive and have an opportunity to discuss the Medication Guide and the PATIENT AGREEMENT.

DESCRIPTION

Mifeprex tablets each contain 200 mg of mifepristone, a synthetic steroid with antiprogestational effects. The tablets are light yellow in color, cylindrical and biconvex, and are intended for oral administration only. The tablets include the inactive ingredients colloidal silica anhydrous, corn starch, povidone, microcrystalline cellulose, and magnesium stearate.

Mifepristone is a substituted 19-nor steroid compound chemically designated as 11ß-[*p*-(Dimethylamino)phenyl]-17ß-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is $C_{29}H_{35}NO_2$. Its structural formula is:

The compound is a yellow powder with a molecular weight of 429.6 and a melting point of 191-196°C. It is very soluble in methanol, chloroform and acetone and poorly soluble in water, hexane and isopropyl ether.

* Mifeprex is a trademark of Danco Laboratories, LLC.

CLINICAL PHARMACOLOGY

Pharmacodynamic Activity

The anti-progestational activity of mifepristone results from competitive interaction with progesterone at progesterone-receptor sites. Based on studies with various oral doses in several animal species (mouse, rat, rabbit and monkey), the compound inhibits the activity of endogenous or exogenous progesterone. The termination of pregnancy results.

Doses of 1 mg/kg or greater of mifepristone have been shown to antagonize the endometrial and myometrial effects of progesterone in women. During pregnancy, the compound sensitizes the myometrium to the contraction-inducing activity of prostaglandins.

Mifepristone also exhibits antiglucocorticoid and weak antiandrogenic activity. The activity of the glucocorticoid dexamethasone in rats was inhibited following doses of 10 to 25 mg/kg of mifepristone. Doses of 4.5 mg/kg or greater in human beings resulted in a compensatory elevation of adrenocorticotropic hormone (ACTH) and cortisol. Antiandrogenic activity was observed in rats following repeated administration of doses from 10 to 100 mg/kg.

Pharmacokinetics and Metabolism

Absorption

Following oral administration of a single dose of 600 mg, mifepristone is rapidly absorbed, with a peak plasma concentration of 1.98 mg/l occurring approximately 90 minutes after ingestion. The absolute bioavailability of a 20 mg oral dose is 69%.

Distribution

Mifepristone is 98% bound to plasma proteins, albumin and α_1-acid glycoprotein. Binding to the latter protein is saturable, and the drug displays nonlinear kinetics with respect to plasma concentration and clearance. Following a distribution phase, elimination of mifepristone is slow at first (50% eliminated between 12 and 72 hours) and then becomes more rapid with a terminal elimination half-life of 18 hours.

Metabolism

Metabolism of mifepristone is primarily via pathways involving N-demethylation and terminal hydroxylation of the 17-propynyl chain. *In vitro* studies have shown that CYP450 3A4 is primarily responsible for the metabolism. The three major metabolites identified in humans are: (1) RU 42 633, the most widely found in plasma, is the N-monodemethylated metabolite; (2) RU 42 848, which results from the loss of two methyl groups from the 4-dimethylaminophenyl in position 11ß; and (3) RU 42 698, which results from terminal hydroxylation of the 17-propynyl chain.

Excretion

By 11 days after a 600 mg dose of tritiated compound, 83% of the drug has been accounted for by the feces and 9% by the urine. Serum levels are undetectable by 11 days.

Special Populations

The effects of age, hepatic disease and renal disease on the safety, efficacy and pharmacokinetics of mifepristone have not been investigated.

Clinical Studies

Safety and efficacy data from the U.S. clinical trials and from two French trials of mifepristone are reported below. The U.S. trials provide safety data on 859 women and efficacy data on 827 women with gestation durations of 49 days or less (dated from the first day of the last menstrual period). In the two French clinical trials, safety evaluable data are available for 1800 women, while efficacy information is available for 1681 of these women. Success was defined as the complete expulsion of the products of conception without the need for surgical intervention. The overall rates of success and failure, shown by reason for failure, for the U.S. and French studies appear in Table 1.

In the U.S. trials, 92.1% of the 827 subjects had a complete medical abortion, as shown in Table 1. In 52 women (6.3%) expulsion occurred within two days, and resulted from the action of mifepristone (600 mg) alone, unaided by misoprostol, an analog of prostaglandin E_2. All other women without an apparent expulsion took a 400 µg dose of misoprostol two days after taking mifepristone. Many women (44.1%) in the U.S. trials expelled the products of conception within four hours after taking misoprostol and 62.8% experienced expulsion within 24 hours after the misoprostol administration. There were 65 women (7.9%) who received surgical interventions: 13 (1.6%) were medically indicated interventions during the study period, mostly for excessive bleeding; five (0.6%) interventions occurred at the patient's request; 39 women (4.7%) had incomplete abortions at the end of the study protocol; and eight (1.0%) had ongoing pregnancies at the end of the study protocol.

Women who participated in the U.S. trials reflect the racial and ethnic composition of American women. The majority of women (71.4%) were Caucasian, while 11.3% were African American, 10.9% were East Asian, and 4.7% were Hispanic. A small percentage (1.7%) belonged to other racial or ethnic groups. Women aged 18 to 45 were enrolled in the trials. Nearly two-thirds (66.0%) of the women were under 30 years old with a mean age of 27 years.

In the French trials, complete medical abortion occurred in 95.5% of the 1681 subjects, as shown in Table 1. In 89 women (5.3%), complete abortion occurred within two days of taking mifepristone (600 mg). About half of the women (50.3%) in the French trials expelled the products of conception during the first four hours immediately following administration of misoprostol and 72.3% experienced expulsion within 24 hours after taking misoprostol. In total, 4.5% of women in the French trials ultimately received surgical intervention for excessive bleeding, incomplete abortions, or ongoing pregnancies at the end of the protocol.

Table 1

Outcome Following
Treatment with Mifepristone and Misoprostol in the U.S. and French Trials

	U.S. Trials		French Trials	
	N	**%**	**N**	**%**
Complete medical abortion	**762**	**92.1**	**1605**	**95.5**
Timing of expulsion				
Before second visit	52	(6.3)	89	(5.3)
During second visit				
– less than 4 hrs after misoprostol	365	(44.1)	846	(50.3)
After second visit				
– greater than 4 hrs but less than 24 hrs after misoprostol	155	(18.7)	370	(22.0)
– greater than 24 hrs after misoprostol	68	(8.2)	145	(8.6)
Time of expulsion unknown	122	(14.8)	155	(9.2)
Surgical intervention	**65**	**7.9**	**76**	**4.5**
Reason for surgery				
Medically necessary interventions during the study period	13	(1.6)	NA	(NA)
Patient request	5	(0.6)	NA	(NA)
Treatment of bleeding during study	NA	(NA)	6	(0.3)
Incomplete expulsion at study end	39	(4.7)	48	(2.9)
Ongoing pregnancy at study end	8	(1.0)	22	(1.3)
Total	**827**	**100**	**1681**	**100**

Note: Mifepristone 600 mg oral was administered on Day 1, misoprostol 400 µg oral was given on Day 3 (second visit).

INDICATION AND USAGE

Mifeprex is indicated for the medical termination of intrauterine pregnancy through 49 days' pregnancy. For purposes of this treatment, pregnancy is dated from the first day of the last menstrual period in a presumed 28 day cycle with ovulation occurring at mid-cycle. The duration of pregnancy may be determined from menstrual history and by clinical examination. Ultrasonographic scan should be used if the duration of pregnancy is uncertain, or if ectopic pregnancy is suspected.

Any intrauterine device ("IUD") should be removed before treatment with Mifeprex begins.

Patients taking Mifeprex must take 400 µg of misoprostol two days after taking mifepristone unless a complete abortion has already been confirmed before that time (see DOSAGE AND ADMINISTRATION).

Pregnancy termination by surgery is recommended in cases when Mifeprex and misoprostol fail to cause termination of intrauterine pregnancy (see PRECAUTIONS).

CONTRAINDICATIONS

Administration of Mifeprex and misoprostol for the termination of pregnancy (the "treatment procedure") is contraindicated in patients with any one of the following conditions:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass (the treatment procedure will not be effective to terminate an ectopic pregnancy);
- IUD in place (see INDICATION AND USAGE);
- Chronic adrenal failure;
- Concurrent long-term corticosteroid therapy;
- History of allergy to mifepristone, misoprostol or other prostaglandin;
- Hemorrhagic disorders or concurrent anticoagulant therapy;
- Inherited porphyrias.

Because it is important to have access to appropriate medical care if an emergency develops, the treatment procedure is contraindicated if a patient does not have adequate access to medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and emergency resuscitation during the period from the first visit until discharged by the administering physician.

Mifeprex also should not be used by any patient who may be unable to understand the effects of the treatment procedure or to comply with its regimen. Patients should be instructed to review the Medication Guide and the PATIENT AGREEMENT provided with Mifeprex carefully and should be given a copy of the product label for their review.

Patients should discuss their understanding of these materials with their health care providers, and retain the Medication Guide for later reference (see PRECAUTIONS).

WARNINGS
(see CONTRAINDICATIONS)

1. Bleeding

Vaginal bleeding occurs in almost all patients during the treatment procedure. According to data from the U.S. and French trials, women should expect to experience bleeding or spotting for an average of nine to 16 days, while up to 8% of all subjects may experience some type of bleeding for 30 days or more. Bleeding was reported to last for 69 days in one patient in the French trials. In general the duration of bleeding and spotting increased as the duration of the pregnancy increased.

In some cases, excessive bleeding may require treatment by vasoconstrictor drugs, curettage, administration of saline infusions, and/or blood transfusions. In the U.S. trials, 4.8% of subjects received administration of uterotonic medications and nine women (1.0%) received intravenous fluids. Vasoconstrictor drugs were used in 4.3% of all subjects in the French trials, and in 5.5% of women there was a decrease in hemoglobin of more than 2 g/dL. Blood transfusions were administered in one of 859 subjects in the U.S. trials and in two of 1800 subjects in the French trials. Since heavy bleeding requiring curettage occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

2. Confirmation of Pregnancy Termination

Patients should be scheduled for and return for a follow-up visit at approximately 14 days after administration of mifepristone to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. Vaginal bleeding is not evidence of the termination of pregnancy. Termination can be confirmed by clinical examination or ultrasonographic scan. Lack of bleeding following treatment, however, usually indicates failure. Medical abortion failures should be managed with surgical termination.

PRECAUTIONS

General

Mifeprex is available only in single dose packaging. Administration must be under the supervision of a qualified physician (see DOSAGE AND ADMINISTRATION).

The use of Mifeprex is assumed to require the same preventive measures as those taken prior to and during surgical abortion to prevent rhesus immunization.

There are no data on the safety and efficacy of mifepristone in women with chronic medical conditions such as cardiovascular, hypertensive, hepatic, respiratory or renal

disease; insulin-dependent diabetes mellitus; severe anemia or heavy smoking. Women who are more than 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution because such patients were generally excluded from clinical trials of mifepristone.

Although there is no clinical evidence, the effectiveness of Mifeprex may be lower if misoprostol is administered more than two days after mifepristone administration.

Information for Patients

Patients should be fully advised of the treatment procedure and its effects. Patients should be given a copy of the Medication Guide and the PATIENT AGREEMENT. (Additional copies of the Medication Guide and the PATIENT AGREEMENT are available by contacting Danco Laboratories at 1-877-4 Early Option) (1-877-432-7596). Patients should be advised to review both the Medication Guide and the PATIENT AGREEMENT, and should be given the opportunity to discuss them and obtain answers to any questions they may have. Each patient must understand:

- the necessity of completing the treatment schedule, including a follow-up visit approximately 14 days after taking Mifeprex;
- that vaginal bleeding and uterine cramping probably will occur;
- that prolonged or heavy vaginal bleeding is not proof of a complete expulsion;
- that if the treatment fails, there is a risk of fetal malformation;
- that medical abortion treatment failures are managed by surgical termination; and
- the steps to take in an emergency situation, including precise instructions and a telephone number that she can call if she has any problems or concerns.

Another pregnancy can occur following termination of pregnancy and before resumption of normal menses. Contraception can be initiated as soon as the termination of the pregnancy has been confirmed, or before the woman resumes sexual intercourse.

Patient information is included with each package of Mifeprex (see Medication Guide).

Laboratory Tests

Clinical examination is necessary to confirm the complete termination of pregnancy after the treatment procedure. Changes in quantitative human Chorionic Gonadotropin (hCG) levels will not be decisive until at least 10 days after the administration of Mifeprex. A continuing pregnancy can be confirmed by ultrasonographic scan.

The existence of debris in the uterus following the treatment procedure will not necessarily require surgery for its removal.

Decreases in hemoglobin concentration, hematocrit and red blood cell count occur in some women who bleed heavily. Hemoglobin decreases of more than 2 g/dL occurred in 5.5% of subjects during the French clinical trials of mifepristone and misoprostol.

Clinically significant changes in serum enzyme (serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyltransferase (GT)) activities were rarely reported.

Drug Interactions

Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St. John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone).

Based on in vitro inhibition information, coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Due to the slow elimination of mifepristone from the body, such interaction may be observed for a prolonged period after its administration. Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies to evaluate the carcinogenic potential of mifepristone have been performed. Results from studies conducted *in vitro* and in animals have revealed no genotoxic potential for mifepristone. Among the tests carried out were: Ames test with and without metabolic activation; gene conversion test in *Saccharomyces cerevisiae* D4 cells; forward mutation in *Schizosaccharomyces pompe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; i*n vitro* test for gene mutation in V79 Chinese hamster lung cells; and micronucleus test in mice.

The pharmacological activity of mifepristone disrupts the estrus cycle of animals, precluding studies designed to assess effects on fertility during drug administration. Three studies have been performed in rats to determine whether there were residual effects on reproductive function after termination of the drug exposure.

In rats, administration of the lowest oral dose of 0.3 mg/kg/day caused severe disruption of the estrus cycles for the three weeks of the treatment period. Following resumption of the estrus cycle, animals were mated and no effect on reproductive performance was observed. In a neonatal exposure study in rats, the administration of a subcutaneous dose of mifepristone up to 100 mg/kg on the first day after birth had no adverse effect on future reproductive function in males or females. The onset of puberty was observed to be slightly premature in female rats neonatally exposed to mifepristone. In a separate study in rats, oviduct and ovary malformations in female rats, delayed male puberty,

deficient male sexual behavior, reduced testicular size, and lowered ejaculation frequency were noted after exposure to mifepristone (1 mg every other day) as neonates.

Pregnancy

Mifepristone is indicated for use in the termination of pregnancy (through 49 days' pregnancy) and has no other approved indication for use during pregnancy.

Teratogenic Effects

Human Data

Over 620,000 women in Europe have taken mifepristone in combination with a prostaglandin to terminate pregnancy. Among these 620,000 women, about 415,000 have received mifepristone together with misoprostol. As of May 2000 a total of 82 cases have been reported in which women with on-going pregnancies after using mifepristone alone or mifepristone followed by misoprostol declined to have a surgical procedure at that time. These cases are summarized in Table 2.

Table 2

Reported Cases (as of May 2000) of On-going Pregnancies Not Terminated by Surgical Abortion at the End of Treatment with Mifepristone Alone or with Mifepristone-Misoprostol

	Mifepristone Alone	**Mifepristone-Misoprostol**	**Total**
Subsequently had surgical abortion	**3**	**7**	**10**
No abnormalities detected	*2*	*7*	*9*
Abnormalities detected (sirenomelia, cleft palate)	*1*	*0*	*1*
Subsequently resulted in live birth	**13**	**13**	**26**
No abnormalities detected at birth	*13*	*13*	*26*
Abnormalities detected at birth	*0*	*0*	*0*
Other/Unknown	**26**	**20**	**46**
Total	**42**	**40**	**82**

Several reports in the literature indicate that prostaglandins, including misoprostol, may have teratogenic effects in human beings. Skull defects, cranial nerve palsies, delayed growth and psychomotor development, facial malformation and limb defects have all been reported after exposure during the first trimester.

Animal Data

Teratology studies in mice, rats and rabbits at doses of 0.25 to 4.0 mg/kg (less than 1/100 to approximately 1/3 the human exposure level based on body surface area) were carried out. Because of the antiprogestational activity of mifepristone, fetal losses were much higher than in control animals. Skull deformities were detected in rabbit studies at approximately 1/6 the human exposure, although no teratogenic effects of mifepristone have been observed to date in rats or mice. These deformities were most likely due to the mechanical effects of uterine contractions resulting from decreased progesterone levels.

Nonteratogenic Effects

The indication for use of Mifeprex in conjunction with misoprostol is for the termination of pregnancy through 49 days' duration of pregnancy (as dated from the first day of the last menstrual period). These drugs together disrupt pregnancy by causing decidual necrosis, myometrial contractions and cervical softening, leading to the expulsion of the products of conception.

Nursing Mothers

It is not known whether mifepristone is excreted in human milk. Many hormones with a similar chemical structure, however, are excreted in breast milk. Since the effects of mifepristone on infants are unknown, breast-feeding women should consult with their health care provider to decide if they should discard their breast milk for a few days following administration of the medications.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The treatment procedure is designed to induce the vaginal bleeding and uterine cramping necessary to produce an abortion. Nearly all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction. About 90% of patients report adverse reactions following administration of misoprostol on day three of the treatment procedure. Those adverse events that occurred with a frequency greater than 1% in the U.S. and French trials are shown in Table 3.

Bleeding and cramping are expected consequences of the action of Mifeprex as used in the treatment procedure. Following administration of mifepristone and misoprostol in the French clinical studies, 80 to 90% of women reported bleeding more heavily than they do during a heavy menstrual period (see WARNINGS, Bleeding for additional information). Women also typically experience abdominal pain, including uterine cramping. Other commonly reported side effects were nausea, vomiting and diarrhea. Pelvic pain, fainting, headache, dizziness, and asthenia occurred rarely. Some adverse reactions reported during the four hours following administration of misoprostol were judged by women as being more severe than others: the percentage of women who considered any particular adverse event as severe ranged from 2 to 35% in the U.S. and French trials. After the third day of the treatment procedure, the number of reports of adverse reactions declined progressively in the French trials, so that by day 14, reports were rare except for reports of bleeding and spotting.

Table 3

Type of Reported Adverse Events Following Administration of Mifepristone and Misoprostol in the U.S. and French Trials* (percentages)

	U.S. Trials	French Trials
Abdominal Pain (cramping)	96	NA
Uterine cramping	NA	83
Nausea	61	43
Headache	31	2
Vomiting	26	18
Diarrhea	20	12
Dizziness	12	1
Fatigue	10	NA
Back pain	9	NA
Uterine hemorrhage	5	NA
Fever	4	NA
Viral infections	4	NA
Vaginitis	3	NA
Rigors (chills/shaking)	3	NA
Dyspepsia	3	NA
Insomnia	3	NA
Asthenia	2	1
Leg pain	2	NA
Anxiety	2	NA
Anemia	2	NA
Leukorrhea	2	NA
Sinusitis	2	NA
Syncope	1	NA
Decrease in hemoglobin greater than 2 g/dL	NA	6
Pelvic pain	NA	2
Fainting	NA	2

* Only adverse reactions with incidence >1% are included.

OVERDOSAGE

No serious adverse reactions were reported in tolerance studies in healthy non-pregnant female and healthy male subjects where mifepristone was administered in single doses greater than threefold that recommended for termination of pregnancy. If a patient ingests a massive overdose, she should be observed closely for signs of adrenal failure.

The oral acute lethal dose of mifepristone in the mouse, rat and dog is greater than 1000 mg/kg (about 100 times the human dose recommended for termination of pregnancy).

DOSAGE AND ADMINISTRATION

Treatment with Mifeprex and misoprostol for the termination of pregnancy requires three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies. Physicians must also be able to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

Day One: Mifeprex Administration

Patients must read the Medication Guide and read and sign the PATIENT AGREEMENT before Mifeprex is administered.

Three 200 mg tablets (600 mg) of Mifeprex are taken in a single oral dose.

Day Three: Misoprostol Administration

The patient returns to the healthcare provider two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tablets (400 µg) of misoprostol orally.

During the period immediately following the administration of misoprostol, the patient may need medication for cramps or gastrointestinal symptoms (see ADVERSE REACTIONS). The patient should be given instructions on what to do if significant discomfort, excessive bleeding or other adverse reactions occur and should be given a phone number to call if she has questions following the administration of the misoprostol. In addition, the name and phone number of the physician who will be handling emergencies should be provided to the patient.

Day 14: Post-Treatment Examination

Patients will return for a follow-up visit approximately 14 days after the administration of Mifeprex. This visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

According to data from the U.S. and French studies, women should expect to experience bleeding or spotting for an average of nine to 16 days. Up to 8% of women may experience some type of bleeding for more than 30 days. Persistence of heavy or moderate vaginal bleeding at this visit, however, could indicate an incomplete abortion.

Patients who have an ongoing pregnancy at this visit have a risk of fetal malformation resulting from the treatment. Surgical termination is recommended to manage medical abortion treatment failures (see PRECAUTIONS, Pregnancy).

Adverse events, such as hospitalization, blood transfusion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol must be reported to Danco Laboratories. Please provide a brief clinical and administrative synopsis of any such adverse events in writing to:

Medical Director
Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4-Early Option (1-877-432-7596)

For immediate consultation 24 hours a day, 7 days a week with an expert in mifepristone, call Danco Laboratories at 1-877-4 Early Option (1-877-432-7596).

HOW SUPPLIED

Mifeprex will be supplied only to licensed physicians who sign and return a Prescriber's Agreement. Distribution of Mifeprex will be subject to specific requirements imposed by the distributor, including procedures for storage, dosage tracking, damaged product returns and other matters. Mifeprex is a prescription drug, although it will not be available to the public through licensed pharmacies.

Mifeprex is supplied as light yellow, cylindrical, bi-convex tablets imprinted on one side with "MF." Each tablet contains 200 mg of mifepristone. Tablets are packaged in single dose blister packets containing three tablets and are supplied in individual cartons (National Drug Code 6487500103).

Store at 25^0C (77^0F); excursions permitted to 15-30^0C (59-86^0F) [see USP Controlled Room Temperature].

Manufactured for:

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Exhibit C

SEP 28 2000

NDA 20-687

Population Council
Attention: Sandra P. Arnold
Vice President, Corporate Affairs
1230 York Avenue
New York, NY 10021

Dear Ms. Arnold:

Please refer to your new drug application (NDA) dated March 14, 1996, received March 18, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIFEPREX™ (mifepristone) Tablets, 200 mg.

We acknowledge receipt of your submissions dated April 19, June 20, July 25, August 15 and September 16 and 26, 1996; January 30, March 31, July 28, August 5, September 24, November 26, 1997; January 30 (2), February 19, April 27, June 25, October 26, December 8, 1998; February 8 and 22, March 31, April 28, May 10 and 20, June 3 (2), 15, 23, 25, and 30, July 14 (2) and 22, August 3, 13, 18 and 30, September 3, 8, 13 and 30, October 5, 26 and 28, November 16 and 29 (2), December 6, 7 and 23, 1999; and January 11, 21 and 28 (2), February 16 and 24, March 3, 6, 9, 10, 30 and 31 (2), April 20, May 3, 11 and 17, June 22 and 23, July 11, 13, 25 and 27, August 18, 21 and 24, September 8, 12, 15 (2), 19 (2), 20, 21, 22, 26 (2), and 27 (2), 2000. Your submission of March 30, 2000 constituted a complete response to our February 18, 2000 action letter.

This new drug application provides for the use of Mifeprex™ for the medical termination of intrauterine pregnancy through 49 days' pregnancy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to approve Mifeprex™ (mifepristone) Tablets, 200 mg, for use as recommended in the agreed upon labeling text. The application is approved under 21 CFR 314 Subpart H. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced regulations.

The final printed labeling (FPL) [including the professional labeling (Package Insert), the Medication Guide required for this product under 21 CFR Part 208, the Patient Agreement Form, and the Prescriber's Agreement Form] must be identical to the submitted draft labeling (Package Insert, Medication Guide, Patient Agreement Form, and the Prescriber's Agreement Form submitted September 27, 2000; and the immediate container and carton labels submitted July 25, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative

purposes, this submission should be designated "FPL for approved NDA 20-687." Approval of this submission by FDA is not required before the labeling is used.

Under 21 CFR 314.520, distribution of the drug is restricted as follows:

Mifeprex™ must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex™.
- Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, give her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well.
- Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an ongoing pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure.
- Must report any hospitalization, transfusion or other serious events to the sponsor or its designate.
- Must record the Mifeprex™ package serial number in each patient's record.

With respect to the aspects of distribution other than physician qualifications described above, the following applies:

- Distribution will be in accordance with the system described in the March 30, 2000 submission. This plan assures the physical security of the drug product and provides specific requirements imposed by and on the distributor including procedures for storage, dosage tracking, damaged product returns, and other matters.

We also note the following Phase 4 commitments, specified in your submission dated September 15, 2000. These commitments replace all previous commitments cited in the September 18, 1996 and the February 18, 2000 approvable letters. These Phase 4 commitments are:

1. A cohort-based study of safety outcomes of patients having medical abortion under the care of physicians with surgical intervention skills compared to physicians who refer their patients for surgical intervention. Previous study questions related to age, smoking, and follow-up on day 14 (compliance with return visit) will be incorporated into this cohort study, as well as an audit of signed Patient Agreement forms.

2. A surveillance study on outcomes of ongoing pregnancies.

You have agreed to provide the final Phase 4 protocols for these studies within six months.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also remind you that, under 21 CFR 314.550, after the initial 120 day period following this approval, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We are waiving the pediatric study requirement for this action on this application.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call [redacted]

Sincerely,

/S/

Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Exhibit D

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 28, 2000

FROM: /S/

SUBJECT:

TO: NDA 20-687 MIFEPREX (mifepristone) Population Council

This memo documents the approval action concerning the Population Council's NDA for mifepristone for the medical termination of intrauterine pregnancy through 49 days' pregnancy. The application was initially submitted to the Food and Drug Administration (FDA) on March 14, 1996. The Reproductive Health Drugs Advisory Committee met on July 19, 1996 and voted that benefits exceeded risk for this drug product with 6-yes, 0-no, and 2 abstentions. An approvable action letter was issued September 18, 1996 citing deficiencies in areas of Clinical (distribution system), Chemistry/Manufacturing and Controls, Biopharmaceutics, and Labeling. A complete response was received August 18, 1999. The last action by the Office was on February 18, 2000. That approvable action letter listed application deficiencies consisting of Chemistry/Manufacturing and Controls, Labeling, and the Distribution System issues. The Population Council submitted a complete response on March 30, 2000. After a brief summary of effectiveness and safety, this memo addresses those outstanding issues listed in the last action letter, Phase 4 commitments, and other issues.

Summary of Effectiveness and Safety

Effectiveness and safety data were derived from one U.S. clinical trial and two French trials. Effectiveness was defined as the complete expulsion of products of conception without the need for surgical intervention.

The U.S. trial consisted of 859 women providing safety data and 827 women providing effectiveness data for gestations of 49 days or less, dated from the last menstrual period. Demographic data showed racial composition of the U.S. trial was similar to the overall U.S. general population. Medical abortion was complete in 92.1% of 827 subjects. Surgical intervention was performed in 7.9% of subjects: 1.6% had medically indicated interventions (1.2% for heavy bleeding), 4.7% had incomplete abortions, 1.0% had ongoing pregnancies, and 0.6% had intervention at the patient's request. One of the 859 patients received a blood transfusion.

The two French trials enrolled a total of 1,681 women providing effectiveness outcomes and 1,800 women providing safety information. Medical abortion was complete in 95.5% of the 1681 subjects. Surgical intervention was performed in 4.5% of subjects: 0.3% for bleeding, 2.9% for incomplete abortions, and 1.3% for ongoing pregnancies. Of the 1,800 women, 2 patients received blood transfusions.

The Advisory Committee reviewed the French data in 1996 and voted 6-yes and 2-no for data supporting efficacy, 7-yes and 1-abstention for data supporting safety. As stated above, the overall vote for benefits exceeding risk was 6-yes, 0-no, and 2-abstentions. During the second review cycle in 1999, the committee received a copy of the U.S. study report, as they requested, to provide FDA with comments. None were received. The U.S. trial data confirms the effectiveness and safety of the product.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 92 of 357

Chemistry/Manufacturing

In May, 2000 the Population Council informed the Division of Reproductive and Urologic Drug Products that the bulk drug substance maker had changed manufacturing processes last summer. New analytic, physical, and stability data were received and reviewed and found to be adequate to ensure the quality of the drug manufacturing was preserved.

An inspection of the bulk drug substance maker was performed on July 24-28, 2000. Deficiencies were cited and the manufacturer corrected these. These corrections were found acceptable.

Because the drug is being distributed directly to qualified physicians, there is minimal chance for drug name confusion and I agree with the name, Mifeprex.

Labeling

Labeling is important to educate prescribers and patients about the safe and effective use of the drug and to inform health professionals about adverse event risks. The 1996 Advisory Committee strongly supported education of users of mifepristone. By coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic pregancies (and other requirements), goals of safe and appropriate use may be achieved. The drug's labeling is now part of a total risk management program that will be summarized below. The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement will together constitute the approved product labeling to ensure any future generic drug manufacturers will have the same risk management program.

The labeling for mifepristone has been revised to provide information about how to report adverse events. FDA and the Population Council agree that a black box will highlight special items related to the drug. In addition, FDA has determined that a Medication Guide for this drug will help ensure dispensers provide important information to patients to enhance compliance with the regimen for safety and efficacy. Furthermore, a patient agreement fosters active patient education and participation in this regimen. The Population Council will provide these educational materials (the professional labeling, the Medication Guide, the patient agreement form, and the Prescriber's Agreement form). The professional labeling, Medication Guide, Patient Agreement, and Prescriber's Agreement must be read, understood, and attested to by physicians who meet prescribing qualifications (discussed below).

Black Box

21 CFR 201.57(e) permits FDA to require a black box warning for special problems, particularly those that may lead to death or serious injury. The Population Council agreed in its July 5, 2000 submission to a black box warning. It was agreed that the box would contain the following:

> "If Mifeprex results in incomplete abortion, surgical intervention may be necessary. Prescribers should determine in advance whether they will provide such care themselves or through other providers. Prescribers should also give patients clear instructions of whom to call and what to do in the event of an emergency following administration of Mifeprex.
>
> Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

Misoprostol Administration

The approvable letter issued by FDA on 2/18/2000 agreed to the Population Council's statement that women could have the option of taking misoprostol on Day 3 either at home or at the prescriber's office. However, data provided by the Population Council supporting home use was re-reviewed and found not to provide substantial evidence for safety and efficacy. The data were anecdotal off-label experience with

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 93 of 357

a vaginal misoprostol regimen, an observational study about home use in Guadeloupe, and a U.S. clinical study of home use of a different regimen with different drug doses. The only study that commented on whether home use led to correct use was the Guadeloupe study reporting that 4% of patients who took misoprostol at home did it incorrectly. Returning to the health care provider on Day 3 for misoprostol, as in the U.S. clinical trial, assures that the misoprostol is correctly administered. This requirement has the additional advantage of contact between the patient and health care provider to provide ongoing care and to reinforce the need to return on Day 14 to confirm that expulsion has occurred.

Early in drug development, a mandatory observation period of 3-4 hours was instituted in clinical trials worldwide when a prostaglandin analogue, sulprostone, was used with mifepristone and felt to have some cardiovascular risk. This drug is no longer being used with mifepristone and is not a marketed drug in the U.S.; therefore, the rationale for an observation period is moot. There is no more likelihood of an adverse event occurring in the few hours after misoprostol administration than during the entire study period.

Therefore, as a consequence of this re-evaluation, the labeling currently reads that the patient returns on Day 3 for misoprostol and is given instructions about adverse events and whom to contact for questions and emergencies.

Access to Health Care and Emergency Services

FDA agreed with the Population Council that access to health care and emergency services is critical for the safe and effective use of the drug. The clinical trials ensured access to services. The labeling has a black box highlighting the possible need for surgical intervention and either the provision of access to these services by the prescriber or through referral. The labeling has a contraindication if there is no access to medical facilities for emergency services. The Patient Agreement emphasizes the need to know what to do in the case of an emergency.

Patient Agreement Form

Patients should be informed about the indication of the drug and how it is given. They must understand the type of regimen they are about to commit to and its risks and benefits. The signed agreement form will be given to the patient for her reference and another kept in the medical record. The Population Council has committed to auditing prescribers to ascertain whether they have obtained signed copies of the Patient Agreement forms.

Biopharmaceutics

This review cycle, the clinical biopharmaceutical reviewers evaluated new data in the published literature regarding the metabolism of mifepristone by the P450 3A4 system. Mifepristone is a substrate and this may inhibit drug metabolism of certain drugs and induce metabolism of others. This information was placed in the professional labeling and patients are instructed in the Medication Guide that use of other drugs may interfere with actions of mifepristone and misoprostol.

Pharmacology-Toxicology

Current literature on the effects of human fetal exposure to mifepristone and misoprostol or mifepristone alone was reviewed to ensure risk information was current. Many of the case reports of malformation concern the unsuccessful use of misoprostol for abortion, resulting in limb, facial, cranial, and other abnormalities. Many reports were retrospective in nature, subject to reporting and recall bias. Nevertheless, the risk of malformation is very important to address. This drug's indication is for pregnancy termination. The labeling, Medication Guide, process of obtaining patient agreement on medical abortion, and the commitment of the physicians through their signed Prescriber's Agreement are all meant to ensure women are completely informed about the process and make a commitment to follow through.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 94 of 357

The labeling for Mifeprex states that it is used with misoprostol for termination of pregnancy of 49 days or less. Human data on mifepristone and misoprostol used in this timeframe is available. Safety Update Report #3 submitted on March 31, 2000 contains [redacted] Periodic Safety Update Report #9 for the period of September 1, 1998 to November 30, 1999. It lists 38 on-going pregnancies with mifepristone plus misoprostol. The Lancet published a letter in July 1998 from [redacted] in which they mention that they had reviewed 71 cases of continuing pregnancies after failed early termination of pregnancy occurring from 1987 to 1998 and found no reported cases of malformation associated with use of mifepristone and misoprostol. There was one report of sirenomelia and cleft palate in a patient who had a therapeutic termination at week 7 gestation associated with mifepristone use alone. On July 6, 1999 the European Summary of Product Characteristics contains a statement for mifepristone that in humans, the reported cases do not allow a causality assessment for mifepristone alone or used with a prostaglandin. On August 21, 2000 the sponsor provided [redacted] 12/1/99 to 5/31/00 Periodic Safety Update on pregnancy outcomes following early pregnancy exposure. The current labeling has these new data on 82 pregnancies exposed to mifepristone only (40) and mifepristone used with misoprostol (42). FDA agrees that no conclusion can be made from the data at this time. Information on the possibility of a risk of malformation, including the above information as well as the anecdotal reports, is nevertheless included in the professional labeling, Medication Guide, and Patient Agreement. The Population Council has committed to continuing ongoing surveillance of human malformation risk.

Medication Guide

This product will be approved with a Medication Guide which dispensers must provide with the drug. It is important for patients to be fully informed about the drug, as well as the need for follow up, especially on Day 14 to confirm expulsion. A Medication Guide was determined to be necessary to patients' safe and effective use of the drug. The drug product is important to the health of women and the Medication Guide will encourage patient adherence to directions for use. Patient adherence to directions for use and visits is critical to the drug's effectiveness and safety.

Distribution System

Since 1996, FDA and the Population Council have agreed, as publicly discussed with the Reproductive Drug Products Advisory Committee, that once approved, the drug will be distributed directly to physicians. It will not be available from pharmacies. There were also discussions about the qualifications of the physicians receiving mifepristone for dispensing. The Committee also stated it was important that women have access to medical abortion as this new therapeutic option may offer women avoidance of a surgical procedure.

In January 2000, the Population Council provided its initial plan for drug distribution. This plan was resubmitted in its complete response of March 30, 2000. This plan had acceptably addressed the issue of physical security of the drug. The distribution system plan stated specific requirements imposed on and by distributors of the drug, including procedures for storage, dosage tracking, damaged product returns, and other matters. See Subpart H of this memo for more details. Other aspects of the distribution system are addressed below.

Physician Qualifications

Physician qualifications were discussed within CDER, the Agency, and with the Population Council. FDA also discussed physician qualifications with a special government employee with expertise in early pregnancy. The Population Council proposed that the drug be directly distributed to qualified physicians, as opposed to other types of health care professionals (midwives, physician's assistants, nurse practitioners, etc.). This restriction was supported by the discussions of the 1996 Advisory Committee. In fact, the clinical trial data was derived from the experience of physicians using this drug. Thus, physicians remain the initial population who will receive this drug for dispensing. This does not preclude another type of health care provider, acting under the supervision of a qualified physician, from

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 95 of 357

dispensing the drug to patients, provided state laws permit this. Should data be provided to amend the restriction to physicians, FDA will consider them.

The types of skills physicians had in the U.S. clinical trial were: 1) the ability to use ultrasound and clinical examination to date pregnancies and diagnose ectopic pregnancies, 2) the ability to perform surgical procedures, including dilation and curettage, vacuum suction, and/or surgical abortions, for bleeding or incomplete abortion, and, 3) they had privileges at medical facilities to provide emergency resuscitation, transfusion, hospitalization, etc. Physicians were trained to use the drug per protocol. Fourteen of the seventeen physicians in the U.S. clinical trial were obstetricians/gynecologists. All patients were within one hour of emergency facilities or the facilities of the principle investigator.

The role of ultrasound was carefully considered. In the clinical trial, ultrasound was performed to ensure proper data collection on gestational age. In practice, dating pregnancies occurs through using other clinical methods, as well as through using ultrasound. Ultrasound information can be provided to the prescribing physicians to guide treatment, but this information can be obtained through consultation referral from an ultrasound provider and does not necessarily need to be obtained by the prescriber him/herself. The labeling recommends ultrasound evaluation as needed, leaving it to the medical judgement of the physician.

The Population Council proposed that any physician who could date pregnancies and diagnose ectopic pregnancies should be able to receive the drug from the distributor. These two qualifications alone limit the number of physicians who will be eligible to receive mifepristone from the Population Council's distributor(s) to those physicians who are very familiar with managing early pregnancies. These two qualifications also are performance-based standards and do not limit providers of mifepristone to specific medical subspecialties. Education about the use of the drug is described above in the Labeling section of this memo. Because qualified physicians will be using this drug, there is no need for special certification programs. The current labeling and distribution system states physician need not have skills for handling surgical interventions, but could provide referral to services for incomplete abortion and emergency care. The Population Council stated that current medical practice is structured on referral of patients who need surgery (for example, women with a spontaneous incomplete abortion or a cardiologist's patient who needs by-pass grafts) to a physician possessing the skills to address the problem. Moreover, within the U.S. clinical trial, 11 patients out of roughly 850 patients needed surgical intervention to handle bleeding, the most important urgent adverse event associated with this drug, and 3 of these patients were handled by non-principal investigators such as the emergency room and non-study gynecologist. This suggests that patients will get the needed surgical intervention by either their physician or another physician with the needed skills. Referral to a hospital for emergency services does not mean having admitting privileges, but having the ability and the responsibility to direct patients to hospitals, if needed. The professional labeling and the Medication Guide highlight that surgery may be needed and patients need to know if the provider of mifepristone will furnish surgical intervention or if the patient will be referred. If the latter, the treating health care provider must give the patient the name, address, and phone number of this referred provider. To ensure that the quality of care is not different for patients who are treated by physicians who have the skill for surgical intervention (as in the clinical trials) compared to those treated by physicians who must refer patients for surgical intervention, FDA has proposed and the Population Council has agreed to structure a Phase 4 monitoring study. This monitoring study incorporates study questions of four of the original six Phase 4 commitments. See Phase 4 Commitments for additional information.

Finally, the one hour travel distance restriction in the clinical trial was intended to ensure access by patients to emergency or health care services. This concern has been dealt with through the labeling, which makes it clear that if there isn't adequate access to emergency services, the medication is contraindicated.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 96 of 357

Subpart H

In the February 18, 2000 approvable letter, FDA stated that the eventual approval of this drug would be under Subpart H. (21 CFR 314.500-314.560). This subpart applies to certain new drugs that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. FDA has determined that the termination of an unwanted pregnancy is a serious condition within the scope of Subpart H. The meaningful therapeutic benefit over existing surgical abortion is the avoidance of a surgical procedure. Subpart H applies when FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. In the case of mifepristone, the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications. Under 21 CFR 314.520, distribution of mifepristone is restricted as described below.

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record

- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

The Population Council agreed to approval under Subpart H in their letter of September 15, 2000.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 97 of 357

Phase 4 Commitments

In 1996, the Population Council committed to 6 post-marketing studies: 1) to monitor the adequacy of the distribution and credentialing system; 2) to follow up on the outcome of a representative sample of mifepristone treated women who have surgical abortion because of method failure; 3) to assess the long term effects of multiple use of the regimen; 4) to ascertain frequency with which women follow the complete treatment regimen and the outcome of those who do not; 5) to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke; 6) to ascertain the effect of the regimen on children born after treatment failure.

During this review cycle, items 1, 2, 4 and 5 were revised and integrated into a monitoring study to ensure providers who did not have surgical intervention skills and referred patients for surgery had similar patient outcomes as those patients under the care of physicians who possessed surgical skills (such as those in the clinical trial). This study specifically addresses adequacy of qualifications (#1). FDA reviewed the protocols from the Population Council submitted on September 7, 2000 and provided a revised protocol on September 13, 2000 in which the investigators collect data on safety outcomes (#2), return for their follow up visits (#4), and include all ages (#5) and collect smoking status (#5). Commitment #2 was defined by the Advisory Committee discussions of 1996 surrounding the question of whether certain physician specialties would have higher rates of problems encountered with medical abortion. This study specifically will investigate the performance of specialties with surgical skills compared to those that refer for surgical interventions with respect to incidence of medical abortion failures.

The Population Council agrees to study ongoing pregnancies and their outcomes through a surveillance, reporting, and tracking system (#6). This protocol summary and a summary for the monitoring system was received on September 19, 2000 and both were found to be adequate.

The Population Council asked that Commitment #3 (to assess the long term effects of multiple use of the regimen) be waived because it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug, especially given privacy issues. In addition, the pharmacology of mifepristone does not suggest any carry over effect after one-time administration. The Agency agrees with this assessment.

As a note, this cycle the Population Council provided new data concerning Commitment #5 (to study the safety and efficacy of the regimen in women under age 18, over age 35, and who smoke), from Spitz et al. This study had 106 women ages 35 years or older as well as 51 subjects under age 20, all of whom were 49 days or less since their last menstrual period. The data on the older women is informative and of meaningful sample size. FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Sptiz data actually suggests a trend towards increased success of medical abortion with younger patients. However, as these age groups were not part of the NDA indication and the data on safety and effectiveness were only reviewed for the indication's age group (18-35 years of age), the trials excluded patients younger than 18 years old, and the raw data from Sptiz have not been submitted for review, the labeling states the safety and efficacy in these groups have not been studied. The Population Council will collect outcomes in their Phase 4 studies of women of all ages to further study this issue. With respect to smokers, the Population Council will study smokers of various ages to collect safety information. In sum, the changes in postmarketing commitments reflect current postmarketing questions given establishment of final labeling, Medication Guide, and distribution system, along with availability of additional clinical data with the drug since 1996.

The postmarketing audit of signed Patient Agreement forms was discussed above.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 98 of 357

Public Comments Considered

The Food and Drug Administration received over 1,000 letters or emails from the public about mifepristone. Most comments objected to various restrictions of the drug's distribution. For example, many letters opposed press reports of an alleged FDA public registry of doctors who dispense mifepristone. Other letters focused on the research uses of mifepristone for neurologic and oncologic diseases and the concern that restricting distribution after approval would constrain off-label uses. Still other letters expressed misunderstanding that experimental indications that are subject to INDs would be limited by an approval of mifepristone with distribution restrictions. These comments were reviewed and considered.

Risk Management Program

Risk management for a drug has the goal of optimizing the use of a product by maximizing its benefits and minimizing its risks. Interventions to manage risk include education to physicians, patients, and the public, labeling (including warnings, precautions, contraindications, dosage and administration, and Medication Guide), restriction of product use or supply, and packaging changes. This drug is being approved under Subpart H (restrictions on distribution) as part of the risk management program. The Population Council and FDA have identified the areas below, among others, that contribute to drug safety and effectiveness:

1. Proper selection of patients via physicians who are qualified to do so by dating pregnancies and diagnosing ectopics,
2. Qualified physicians to administer or supervise the administration of the medication
3. Compliance with the regimen by physicians and patients through education and monitoring
4. Safety and effectiveness information that fully informs patients and physicians about the risks and benefits of the treatment
5. Evaluation of physician qualifications through Phase 4 studies has been discussed in above sections.
6. Physical packaging in unit of dosing to ensure proper dose and provision of Medication Guide with each dose
7. Active patient participation in the treatment through the Patient Agreement and Medication Guide with an audit of signed Patient Agreement to ensure compliance
8. Active programs to get physicians to report adverse events and ongoing pregnancies to provide accurate risk information
9. Commitment to review and revise the risk management program for improved public health

All components of this risk management program have been discussed above, including the Medication Guide, the labeling that includes the Prescriber's and Patient Agreement forms, approval under Subpart H, and Phase 4 studies to evaluate risk management interventions and to gather data on risks.

In summary, all approval issues related to the NDA have been addressed adequately.

APPEARS THIS WAY
ON ORIGINAL

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 99 of 357

Exhibit E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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Silver Spring, MD 20993

MAR 29 2016

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Re: Docket No. FDA-2002-P-0364

Dear Drs. Harrison and Rudd and Ms. Nance:

This letter responds to your citizen petition submitted on August 20, 2002, to the Food and Drug Administration (FDA or Agency) on behalf of the American Association of Pro Life Obstetricians and Gynecologists (AAPLOG), the Christian Medical Association (CMA) (n/k/a the Christian Medical and Dental Associations), and Concerned Women for America (CWA) (Petition).[1] Your Petition requests that the Agency stay FDA's approval of Mifeprex (mifepristone, also known as RU-486), thereby halting the distribution and marketing of the drug pending final action on the Petition. The Petition also requests that the Agency revoke FDA's approval of Mifeprex and requests a full audit of the French and U.S. clinical trials submitted in support of the new drug application (NDA) for Mifeprex.

We have carefully considered the information submitted in your Petition, comments on your Petition submitted to the docket, other submissions to the docket, and other relevant data available to the Agency. Based on our review of these materials and for the reasons described below, your Petition is denied.

[1] The citizen petition was originally assigned docket number 2002P-0377/CP1. The number was changed to FDA-2002-P-0364 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This citizen petition was submitted by AAPLOG, CMA, and Sandy Rios, the then-President of CWA. We have addressed this response to CWA's current CEO and President, Penny Young Nance.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 20-687). The application was approved under 21 CFR part 314, subpart H, "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments. Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the approval letter, including a requirement that Mifeprex be provided by or under the supervision of a physician who meets eight qualifications specified in the letter.

The September 28, 2000, approval letter also listed two Phase 4 commitments[2] that the then-applicant of the Mifeprex NDA (i.e., the Population Council)[3] agreed to meet. In addition, the letter stated that FDA was waiving the pediatric study requirement in 21 CFR 314.55.

II. DISCUSSION OF ISSUES RAISED

You maintain that good cause exists for granting an immediate stay of the Mifeprex approval and for the subsequent revocation of that approval under 21 CFR 314.530 (Petition at 3). You contend that:

- The approval of Mifeprex in 2000 violated the Administrative Procedure Act's (APA's) prohibition against agency action that is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (5 U.S.C. 706(2)(A));

- The 2000 approval violated section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) because Mifeprex does not satisfy the safety and labeling requirements of that section; and

- FDA approved Mifeprex in 2000 despite the presence of substantial risks to women's health, including fatal hemorrhage and serious bacterial infections.

You make eight arguments for the stay and revocation of the 2000 Mifeprex approval, as follows (Petition at 4-7):

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[2] For purposes of this petition response, the term 'Phase 4 commitments' refers to the postmarketing studies that the Mifeprex sponsor agreed to perform as a condition of approval.

[3] Effective October 31, 2002, the Population Council transferred ownership of the Mifeprex NDA to Danco Laboratories, LLC (Danco), which had been licensed to manufacture and market Mifeprex.

- That the approval of Mifeprex in 2000 violated the legal requirements of the accelerated approval regulations under 21 CFR Subpart H.
- That Mifeprex was not proven safe and effective in 2000 as required by law.
- That the Mifeprex regimen requires that Mifeprex be used in conjunction with another drug, misoprostol, which has not been separately approved as an abortifacient.
- That the Mifeprex regimen was approved in 2000 without adequate safety restrictions.
- That the drug's sponsor, following the approval in 2000, neglected to require Mifeprex providers to adhere to the restrictions contained in the regimen approved at that time.
- That the safeguards employed in one of the clinical trials that supported the 2000 approval were not mirrored in the regimen that FDA approved.
- That FDA improperly waived a requirement for pediatric studies in connection with the 2000 Mifeprex approval.
- That FDA did not require the sponsor of Mifeprex to honor its commitments for Phase 4 studies.

We respond to each of these arguments below.

We note your petition challenges the original approval of Mifeprex in 2000, and therefore this response is addressed to the 2000 approval and to the labeling that was approved at that time. Today, the Agency is approving a supplemental NDA submitted by Danco Laboratories, LLC (Danco), the holder of the Mifeprex NDA. This supplemental NDA proposed modified labeling for Mifeprex, including an updated dosing regimen, and included data to support the new labeling. After reviewing Danco's supplemental NDA, FDA determined that it met the statutory standard for approval. The fact that the previously approved regimen is no longer included in the labeling does not reflect a decision that there were safety or effectiveness concerns with the previously approved regimen.

A. Approval of Mifeprex Was Consistent With Subpart H

You maintain that FDA's 2000 approval of Mifeprex under the subpart H regulations was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law, and thus violated the APA (Petition at 18-23). You state that pregnancy, without major complications, is not a serious or life-threatening illness; instead, you claim it is a normal physiological state experienced by most females one or more times and is rarely accompanied by life-threatening complications (Petition at 19). You contend that Mifeprex does not provide meaningful therapeutic benefit to patients over existing treatments because surgical abortion is a less dangerous, more effective alternative for the termination of pregnancy, and that Mifeprex does not treat any subset of the female population that is unresponsive to or intolerant of surgical abortion

(Petition at 21-23). Thus, you assert that the approval of Mifeprex did not meet the requirements for product approval under subpart H (Petition at 23).

We disagree with your conclusion that we inappropriately approved Mifeprex under subpart H. As stated in section I above, the accelerated approval regulations apply to new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (§ 314.500). As FDA made clear in the preamble to the final rule for subpart H, the subpart H regulations are intended to apply to serious or life-threatening conditions, as well as to illnesses or diseases.[4] The Agency also made clear that a condition need not be serious or life-threatening in all populations or in all phases to fall within the scope of these regulations.[5] Unwanted pregnancy falls within the scope of subpart H under § 314.500 because unwanted pregnancy, like a number of illnesses or conditions, can be serious for certain populations or under certain circumstances.

Pregnancy can be a serious medical condition in some women.[6] Pregnancy is the only condition associated with preeclampsia and eclampsia and causes an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus. Additionally, there is a significant risk of a major surgical procedure and anesthesia if a pregnancy is continued; for 2013 (the most recent data available), the Centers for Disease Control and Prevention reported an overall 32.7 percent rate of cesarean sections in the United States.[7] Other medical concerns associated with pregnancy include the following: disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (e.g., diabetes, lupus, cardiac disease, hypertension). In addition, approximately 50 percent of all pregnancies in the United States each year are unintended.[8] According to the

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[4] See, e.g., 57 FR 58942, 58946 (Dec. 11, 1992).

[5] Id.

[6] According to data from the Centers for Disease Control and Prevention (CDC), for 2012 (the most recent year for which data are available), the pregnancy-related mortality ratio in the United States was 15.9 maternal pregnancy-related deaths per 100,000 live births. See CDC, Pregnancy Mortality Surveillance System, available on the CDC Web page at http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html. A 2012 study by Raymond and Grimes provides a comparison for the mortality rate associated with legal abortion to live birth in the United States for the earlier period from 1998 through 2005. Investigators reported that over the study period, the pregnancy related mortality rate among women who delivered live neonates was 8.8 deaths per 100,000 live births. This lower rate excludes deaths from ectopic pregnancies, stillbirths, gestational trophoblastic disease, etc. During the same period, the rate of abortion related mortality was 0.6 per 100,000 abortions. The risk of childbirth related death was therefore approximately 14 times higher than the rate associated with legal abortion. Raymond, EG and DA Grimes, Feb. 2012, The Comparative Safety of Legal Induced Abortion and Childbirth in the United States, Obstet Gynecol, 119 (2, Part 1):215-219.

[7] See CDC, Nov. 5, 2014, Trends in Low-risk Cesarean Delivery in the United States, 1990-2013, National Vital Statistics Report, 63(6), available at http://www.cdc.gov/nchs/data/nvsr/nvsr63/nvsr63_06.pdf .

[8] Guttmacher Institute, Feb. 2015, Unintended Pregnancy in the United States, at 1, available at http://www.guttmacher.org/pubs/FB-Unintended-Pregnancy-US.pdf. See also Institute of Medicine, 2011,

Institute of Medicine, women experiencing an unintended pregnancy may experience depression, anxiety, or other conditions.[9]

Furthermore, consistent with § 314.500, medical abortion through the use of Mifeprex provides a meaningful therapeutic benefit to some patients over surgical abortion.[10] Although FDA provided several examples in the preamble to the final rule to illustrate how the term "meaningful therapeutic benefit" might be interpreted, the Agency did not suggest that the meaning of the term was limited to the examples provided.[11] In the Phase 3 clinical trial of Mifeprex conducted in the United States, medical termination of pregnancy avoided an invasive surgical procedure and anesthesia in 92 percent of the 827 women with an estimated gestational age (EGA) of 49 days or less.[12] Complications of general or local anesthesia, or of intravenous sedation ("twilight" anesthesia), can include a severe allergic reaction, a sudden drop in blood pressure with cardiorespiratory arrest, death, and a longer recovery time following the procedure. Medical (non-surgical) termination of pregnancy provides an alternative to surgical abortion; it is up to the patient and her provider to decide whether a medical or surgical abortion is preferable and safer in her particular situation.[13]

Clinical Preventive Services for Women: Closing the Gaps (Closing the Gaps), at 102-110, available at http://books.nap.edu/openbook.php?record_id=13181 (stating that "[u]nintended pregnancy is highly prevalent in the United States").

[9] See Closing the Gaps, supra note 8, at 103.

[10] For a discussion of how FDA interprets the phrase "meaningful therapeutic benefit to patients over existing treatments" in 21 CFR 314.500, see FDA guidance for industry, *Expedited Programs for Serious Conditions—Drugs and Biologics*, at 3-4, 16-17, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[11] 57 FR 58942, 58947 (Dec. 11, 1992).

[12] FDA, 1999, Medical Officer's Review of Amendments 024 and 033: Final Reports for the U.S. Clinical Trials Inducing Abortion Up to 63 Day Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments (Medical Officer's Review), at 11 (Table 1) and 16, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf. Spitz, IM, et al., 1998, Early Pregnancy Termination With Mifepristone and Misoprostol in the US, NEJM, 338:1241-1243.

[13] CDC data indicate that for the 730,322 abortions reported in 2011, there were 2 deaths. The CDC's calculated case fatality rate over the period from 2008 to 2011 (the most recent year for which data are available), the case fatality rate was 0.73 legal induced abortion-related deaths per 100,000 reported legal abortions. http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6410a1.htm?s_cid=ss6410a1_e. Mortality rates identified by type of abortion (medical or surgical) were not available. However, the evidence suggests that the risk of mortality associated with medical abortion is quite low. Confirmation of the low risk of medical abortion is provided in a study by Trussell, et al., which recorded no deaths for 711,556 medical abortions performed by Planned Parenthood clinics under the buccal misoprostol administration protocol (Trussell J, D Nucatola, et al., Mar. 2014, Reduction in Infection-Related Mortality Since Modifications in the Regimen of Medical Abortion, Contraception, 89(3):193-6). We note that one study reported a comparatively high occurance of fatality (1 death in a study of 11,155 early medical abortions); however, this apparent high occurence of fatality is likely due to instability in the estimate as a result of the small sample size (Goldstone P, J Michelson, et al., Sept. 3, 2012, Early Medical Abortion Using Low-Dose Mifepristone Followed by

You cite a study by Jensen, et al., as support for your claim that surgical abortion is less dangerous and more effective than Mifeprex (Petition at 21-22 (citing Jensen, JT, et al., 1999, Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study, Contraception, 59:153-159 (Jensen study)). This study was a prospective, nonconcurrent cohort analysis comparing the patients from one site in the U.S. phase 3 trial and a separate group of patients (who were not part of the U.S. phase 3 trial) who underwent surgical abortion at the same facility. The populations that were compared were not randomized to treatment (i.e., medical or surgical abortion) and the treatment periods did not overlap.[14] In addition, the data on medical abortion cited in the Jensen study are based on the 178 subjects at a single site in the phase 3 U.S. Mifeprex trial that enrolled 2,121 women. This small subset of the U.S. trial included patients with pregnancies of up to 63 days' gestation. Although you cite a surgical intervention rate of 18.3 percent in the Mifeprex patients, the surgical intervention rate for Mifeprex patients with an EGA ≤ 49 days was 12.7 percent (9 of 71), which, because of the small number of patients in the two groups, is not statistically significantly different from the 3.9 percent rate for re-intervention in the comparative surgical group (3 of 77).[15] Furthermore, the 3.9 percent who first had a surgical abortion and then required surgical re-intervention ultimately required *two* surgical interventions, not one, thereby exposing them twice to the risks inherent in invasive surgical procedures and anesthesia. Finally, although you state that the medical abortion patients in the Jensen study reported significantly longer bleeding than did surgical patients, there was not a greater amount of bleeding in the medical abortion group, nor was there a significant difference between the two treatment groups in the incidence of anemia as determined by the overall change in hemoglobin concentrations.

You state that FDA "viewed [s]ubpart H as the only available regulatory vehicle that had the potential to make Mifeprex safe" (Petition at 23 (footnote omitted)). The question of whether subpart H was "the only available regulatory vehicle" is not relevant here. As described above, Mifeprex met the criteria for approval under subpart H. Additionally, as stated in the September 28, 2000, memorandum to NDA 20-687 (Mifeprex Approval Memorandum), "the Population Council proposed and FDA agreed that this drug will be directly distributed via an approved plan that ensures the physical security of the drug to physicians who meet specific qualifications" that were set out in the approval letter and the Prescriber's Agreement.[16]

Buccal Misoprostol: A Large Australian Observational Study, Med J Aust, 197(5):282-6). Much more accurate and meaningful data are provided by Trussell's study covering >700,000 medical abortions.

[14] We are not suggesting that in order to be adequate and well-controlled a trial must be concurrently controlled. As discussed below in section II.B.1, FDA's regulations in § 314.126 recognize a number of different types of controls.

[15] In addition, the mean surgical intervention rate for all Mifeprex patients with gestational ages ≤ 49 days in the Phase 3 U.S. trial was 7.9 percent (65 of 827 evaluable patients).

[16] FDA, Sept. 28, 2000, Memorandum to NDA 20-687 MIFEPREX (mifepristone) Population Council (Mifeprex Approval Memorandum), available at http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111366.pdf

Furthermore, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[17] The2011 REMS for Mifeprex incorporated the restrictions under which the drug was approved. Indeed, there is substantial overlap between the requirements of subpart H and the statutory criteria for REMS set out in Title IX.

Given all of the above, the Mifeprex NDA was appropriately approved in 2000.

B. The French and U.S. Clinical Trials of Mifeprex Provided Substantial Evidence to Support Approval

You contend that the studies on which the Population Council relied in support of its NDA for Mifeprex do not meet the statutory and regulatory requirements for the quality and quantity of scientific evidence needed to support a finding that a new drug is safe and effective (Petition at 24).

Our review of Mifeprex was thorough and consistent with the FD&C Act and FDA regulations, including the requirements under section 505(d) of the FD&C Act that: (1) there be adequate tests to show that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1)) and (2) there be substantial evidence that the drug will have the effect it purports or is recommended to have under the conditions of use prescribed, recommended, or suggested in the labeling (section 505(d)(5)). The Mifeprex NDA was thoroughly reviewed, and the drug product was found to be safe and effective for its approved indication. In addition, as noted in the Mifeprex Approval Memorandum (at 1), FDA's Reproductive Health Drugs Advisory Committee (Advisory Committee) voted 6 to 0 (with 2 abstentions) on July 19, 1996, that the benefits of Mifeprex exceeded the risks. As set forth below, we disagree with your claims concerning the clinical trials that form the basis for the approval of Mifeprex.

1. The Clinical Trials Used to Support the Mifeprex NDA Were in Accordance With the FD&C Act and Applicable Regulations

You argue that because neither the French clinical trials nor the U.S. clinical trial of mifepristone were blinded, randomized, or concurrently controlled, these trials were inadequate to establish the safety and effectiveness of Mifeprex (Petition at 24-25 and 32-34). In addition, you assert in the response you submitted on October 10, 2003, to the comments in opposition to the Petition submitted by the Population Council and Danco (Response to Opposition) that the clinical trials of Mifeprex were not historically controlled but instead were uncontrolled.[18] You state that the

[17] 73 FR 16313 (Mar. 27, 2008).

[18] Response to Opposition at 5. You also state that because the Mifeprex regimen was the first drug regimen that FDA approved to induce abortions, the applicant should have compared the new drug regimen to surgical abortions performed during the first 49 days after a woman's last menstrual period (Response to Opposition at

applicant did not describe any historical control group in the French clinical trials, and did not indicate that any of the scientific guidelines for selecting a proper control group before beginning a historically controlled study were used for these trials (id. at 5-6). You also reject the applicant's claim that the available information on surgical abortion constitutes historically controlled data (id. at 6).

We disagree with your conclusion that the French and U.S. clinical trials of mifepristone were not clinically and legally adequate to support the approval of Mifeprex. The data from these three clinical trials (a large U.S. trial and two French trials) constitute substantial evidence that Mifeprex is safe and effective for its approved indication in accordance with section 505(d) of the FD&C Act. The labeling approved in 2000 for Mifeprex was based on data from these three clinical trials and from safety data from a postmarketing database of over 620,000 women in Europe who had had a medical termination of pregnancy (approximately 415,000 of whom had received mifepristone together with misoprostol).[19]

The U.S. trial of Mifeprex involved 2,121 subjects enrolled at 17 sites. Of these, 827 had an EGA of ≤ 49 days and were included in the efficacy evaluation.[20] Medical termination of pregnancy was complete (without the need for surgical intervention) in 762 of these subjects (92 percent).[21] Sixty-five of the subjects in the U.S. trial who were evaluable for efficacy were classified as having had a "treatment failure." The reasons for treatment failure (and number of subjects experiencing each) were: incomplete pregnancy termination (n = 39), still pregnant (n = 8), subject request for surgical intervention (n = 5), and medical indication (bleeding, n = 13).[22] The two French trials enrolled a total of 1,681 subjects providing effectiveness outcomes. Among the French subjects, the success rate for medical termination of pregnancy was 95.5 percent.[23]

In the U.S. trial, 859 subjects with an EGA of ≤ 49 days were evaluated for safety. Among these subjects, there were no deaths, one transfusion, and nine instances in which subjects received intravenous fluids.[24] The safety profile of the patient group in the French trials with an EGA of ≤ 49 days did not differ significantly from the safety profile of the same patient group in the U.S.

5, note 20). The fact that a drug might be the first one approved for a particular indication is not a factor in determining what type of control is adequate for a clinical trial of that drug for that indication. As discussed above, FDA's regulations provide for a variety of different types of controls (see 21 CFR 314.126(b)), and do not require comparison of a proposed drug product to an active control group to establish the safety and effectiveness of the drug. Therefore, the clinical trials to support the approval of Mifeprex were not required to have a surgical comparator arm.

[19] Mifeprex labeling, Sept. 28, 2000, PRECAUTIONS, Teratogenic Effects: Human Data, *Pregnancy,* available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf.

[20] Mifeprex Approval Memorandum, supra note 16, at 1; Medical Officer's Review, supra note 12, at 10.

[21] Medical Officer's Review, supra note 12, at 11 (Table 1) and 16.

[22] Id. at 11 (Table 1).

[23] Mifeprex Approval Memorandum, supra note 16, at 1.

[24] Medical Officer's Review, supra note 12, at 12-13.

trial, and the percentage of patients in the French and U.S. trials requiring hospitalization and blood transfusion and experiencing heavy bleeding was comparable.[25] There were no deaths in the French trials.[26]

Section 505(d) of the FD&C Act states, in part, that FDA must refuse to approve an application if the Agency finds that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the drug's proposed labeling. Section 505(d) defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."

As stated in 21 CFR 314.126(a), the purpose of conducting clinical investigations of a drug is to distinguish the effect of the drug from other influences, such as a spontaneous change in the course of the disease or condition, placebo effects, or biased observation. Reports of adequate and well-controlled investigations serve as the main basis for determining whether there is substantial evidence to support the claims of effectiveness for a drug.

We agree that randomization and the use of concurrent controls are two principal means of ensuring that clinical trial data are reliable and robust. However, that does not mean that in order to be adequate and well-controlled, a clinical trial must use a randomized concurrent control design. Section 314.126(b) lists the characteristics of an adequate and well-controlled study. Contrary to your assertion (Petition at 24), FDA regulations do not require that a study be blinded, randomized, and/or concurrently controlled. Among the characteristics of an adequate and well-controlled study is that it uses a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect (§ 314.126(b)(2)). A historical control is one of the recognized types of control (§ 314.126(b)(2)(v)), and one in which the results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment in comparable patients or populations (id.). Unlike some other types of control (e.g., placebo concurrent control (§ 314.126(b)(2)(i)) or dose-comparison concurrent control (§ 314.126(b)(2)(ii))), use of a historical control does not include randomization or blinding. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances, including studies in which the effect of the drug is self-evident.[27] Thus, in the proper setting,

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[25] Id. at 18.

[26] FDA, May 21, 1996, Statistical Review and Evaluation (May 21, 1996, Statistical Review), at 4 and 7, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[27] 21 CFR 314.126(b)(2)(v). We note your contention that the effects of the regimen approved in 2000 are not self-evident because "[t]he Sponsor's focus on this dyadic set of possibilities (failure (0) or success (1)) obscures a whole range of less easily measurable, but critically important, outcomes," including "tissue retention, life-threatening hemorrhaging, persistent bleeding, infection, teratogenicity, pain, continued fertility, and psychological effects" (Response to Opposition at 8). We disagree with your argument. From a clinical perspective, there are two outcomes associated with the use of Mifeprex for medical abortion: either there is a complete abortion (without the need for surgical intervention) or there is not. The "outcomes" you

historically controlled trials can be considered adequate and well-controlled, and there is no need for the other types of control listed in § 314.126(b)(2).[28]

The use of historical controls in the Mifeprex clinical trials was appropriate for two reasons. First, the natural history of a viable pregnancy is adequately documented (a pregnancy continues on average for 40 weeks' gestation).[29] Second, the effect of Mifeprex is dramatic, occurs rapidly following treatment, and has a low probability of having occurred spontaneously.[30] Furthermore, contrary to your assertion (Petition at 32-34), the use of a historical control in these circumstances is consistent with ICH's guidance for industry, *E10 Choice of Control Group and Related Issues in Clinical Trials* (E10 Guidance).[31] The E10 Guidance addresses external controls (including historical controls) that are used in externally controlled trials to compare a group of subjects receiving the test treatment with a group of patients external to the study, rather than with an internal control group consisting of patients from the same population assigned to a different treatment.[32] The guidance states that the "external control may be defined (a specific group of patients) or non-defined (a comparator group based on general medical knowledge of outcome)."[33]

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cite are complications that can be associated with all abortions (including surgical abortion, missed abortion (non-viable pregnancy that has not been expelled from the uterus), and spontaneous abortion).

[28] You cite to a statement in the May 21, 1996, Statistical Review regarding the two French trials that "[i]n the absence of a concurrent control group in each of these studies, it is a matter of clinical judgement whether or not the sponsor's proposed therapeutic regimen is a viable alternative to uterine aspiration for the termination of pregnancy" (Petition at 27). FDA's finding that Mifeprex was safe and effective for its labeled indication was based on data from three trials, one in the U.S. and two in France, as well as from safety data from a database of over 620,000 women in Europe who had had a medical termination of pregnancy (and approximately 415,000 of whom had received the combination of mifepristone and misoprostol). The Medical Officer's Review, supra note 12, also states that the "U.S. clinical trials confirm the safety and efficacy of mifepristone and misoprostol found in the pivotal French studies for women seeking medical abortions with gestations of 49 days duration or less" (Id. at 18-19). As stated previously, it is up to the physician and his/her patient to decide whether a medical or surgical abortion is preferable and safer in the patient's particular situation.

[29] MacDonald, PC, NF Gant, et al., 1996, Williams Obstetrics (20th ed.), Appleton and Lange, at 151.

[30] Although sources and studies differ somewhat, the 92% success rate following mifepristone/misoprostol use far exceeds the rate of spontaneous abortion (spontaneous miscarriage). One source states: "No less than 30% and as much as 60% of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. Most recognized pregnancy losses occur before 8 weeks' gestation, and relatively few occur after 12 weeks" (Fritz, M and L Speroff, 2011, Clinical Gynecologic Endocrinology and Infertility (8th ed.), Lippincott Williams & Wilkins, Philadelphia, at 1193). Other sources indicate that 15% of all pregnancies between 4-20 weeks of gestation spontaneously abort (See Speroff, L, et al., 1989, Clinical Gynecologic Endocrinology and Infertility (4th ed.), Williams and Wilkins, Baltimore, at 535; see also Stenchever, MA, 2001, Comprehensive Gynecology (4th ed.), Mosby, at 414). According to the National Library of Medicine, "[a]mong women who know they are pregnant, the miscarriage rate is about 15-20%. Most miscarriages occur during the first 7 weeks of pregnancy." (Miscarriage, available on the MedlinePlus Web site at http://www.nlm.nih.gov/medlineplus/ency/article/001488.htm.

[31] E10 Guidance, available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm, at 6.

[32] Id.

[33] Id.

Moreover, the E10 Guidance clearly states that, notwithstanding certain limitations of external controls, including the possibility of bias, external controls can be appropriate under circumstances where the effect of the treatment is dramatic and the usual course of the disease or condition is highly predictable.[34] In other words, historical controls can be appropriate in circumstances such as medical termination of early pregnancy. The use of the expected rate of spontaneous abortion during early pregnancy as the control in the Mifeprex clinical trials was appropriate and fully consistent with FDA regulations and guidance. The applicant could rely on the data from the three trials to support approval because they were adequate and well-controlled, using a historical control.[35]

It is not uncommon for the drug product review divisions in FDA's Center for Drug Evaluation and Research (CDER) to accept for filing and approve applications that rely on clinical trials employing historical controls to support approval for drug products in which the outcome of the condition is well known and the effect of the drug is anticipated to be markedly different from that of a placebo. Examples include FDA's approval of numerous oncology drug products, including, for example, Xalkori (crizotinib) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test, and Adcetris (brentuximab vedotin) for the treatment of patients with Hodgkin lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. Other examples include iPlex (mecasermin rinfabate [rDNA origin] injection) for treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH; Myozyme (alglucosidase ALFA) for use in patients with Pompe disease (GAA deficiency); Ferriprox (deferiprone) for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate; Voraxaze (glucarpidase) for treatment of toxic (>1 micromole per liter) plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function; and Elelyso (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease. Similarly, it is not unusual for the CDER review divisions to accept for filing applications relying on historically controlled clinical trials. Examples of reproductive drug products for which a historical control is often relied on in the drug approval process include contraceptive drug products (e.g., most birth control pills, Mirena intrauterine device, NuvaRing (an intravaginal hormonal contraceptive), and Implanon (an implanted hormonal contraceptive)) and menopausal hormonal therapy products with the addition of a progestin to prevent endometrial cancer secondary to unopposed estrogen stimulation.

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[34] Id. at 27.

[35] We disagree with your statement that the sponsor's failure to identify precisely a historical control group is fatal to its claim that the trials supporting the approval of Mifeprex were historically controlled (Response to Opposition at 5-6). In situations where an investigational product is anticipated to have an effect that is readily discernible and greatly exceeds that which would be expected otherwise, the historical control may be relied upon without explicitly describing it as such. Examples of situations where this arises include, as here, the use of a drug for early medical abortion, given that the majority of pregnancies continue to term, and the use of a drug as a contraceptive, given that the pregnancy rate in sexually active women between 18 and 35 years old in the absence of contraception for one year is well documented at approximately 85% (Hatcher, RA, et al., 2012, Contraception Technology (20th ed.), Ardent Media, Inc., at 780.

You state that FDA did not conduct a statistical review of the results of the U.S. clinical trial (Petition at 29). The Agency, however, concluded that the clinical results of the supporting U.S. clinical trial were "similar enough to the results of the European studies" (the studies used to support the original approval of Mifeprex in Europe) that a statistical evaluation of the results of the U.S. trial was not required.[36]

You maintain that the Mifeprex approval is not in accordance with Agency guidance[37] on when only one effectiveness trial may be necessary for approval because: (1) mifepristone had not been approved for any use in any population in the United States and (2) no one had ever presented to FDA any evidence from adequate and well-controlled trials regarding any use for mifepristone.[38] As stated above, our approval of Mifeprex was based on not one but three studies that met the requirements of § 314.126. Therefore, Agency guidance concerning reliance on only one effectiveness trial is not relevant to the approval of Mifeprex.

You argue that FDA's acceptance of the French and U.S. clinical trial data violated § 314.126(e), which states that uncontrolled studies or partially controlled studies are not acceptable as the sole basis for approval of claims of effectiveness (Petition at 34-36). As explained above, the Mifeprex clinical trials were neither uncontrolled nor partially controlled. They were historically controlled, and the use of an historical control was appropriate under § 314.126(b)(2)(v). Consequently, § 314.126(e) is inapplicable.

Citing § 314.500, you contend that the approval of Mifeprex under subpart H was improper because FDA did not require the concurrent testing of mifepristone with surgical abortion to test the proposition that mifepristone provides a meaningful therapeutic benefit over the standard method for terminating pregnancies (Petition at 37-40). You maintain that Mifeprex is the only drug that we have approved under § 314.520 (approval with restrictions to assure safe use) without requiring "that safety and efficacy be scientifically demonstrated through blinded, comparator-controlled, and randomized clinical trials" (Petition at 37).

Nothing in subpart H requires that an applicant conduct comparative clinical trials in order to demonstrate that a drug product provides meaningful therapeutic benefit to patients over existing treatments. Furthermore, nothing in the concept of "meaningful therapeutic benefit" requires concurrent testing of a proposed drug with an existing treatment.[39] We have approved other drugs

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[36] FDA Memorandum to NDA 20-687 re: Statistical comments on Amendment 024, Feb. 14, 2000, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_statr.pdf.

[37] FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (Effectiveness Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[38] Petition at 31-32 (citing Effectiveness Guidance at 5-17).

[39] You state that "[c]onducting a concurrently-controlled randomized trial comparing surgical abortion with the mifepristone-misoprostol regimen is readily achievable" (Petition at 32, note 145). You add that "[t]here are study designs that would have also allowed for blinding" (Id.). Assuming, arguendo, that it may have been feasible to design a randomized, concurrently-controlled study, such study was not required under our regulations; as described previously in this response, the clinical trials supporting the approval of Mifeprex

under subpart H based on clinical trials that do not directly compare the drug to an existing therapy, including Gleevec (imatinib mesylate), Tracleer (bosentan), and Xyrem (sodium oxybate). We also note that the latter two referenced drug products, Tracleer (bosentan) and Xyrem (sodium oxybate), were approved under the restricted distribution provisions at 21 CFR 314.520. As previously explained in this response, Mifeprex was deemed to have in effect an approved REMS under Title IX of FDAAA. The Mifeprex REMS, which was approved in June 2011 and is still in effect, incorporated the subpart H restrictions under which the drug was approved.

As evidenced by the foregoing, the studies supporting the 2000 approval of Mifeprex were consistent with the FD&C Act and FDA regulations, including § 314.126 and subpart H.

2. There Is No Need for an Audit of the French Clinical Data

You assert that FDA allowed "tainted data" to support the Mifeprex NDA by failing to require a comprehensive audit of the French clinical trial data after discovering violations of good clinical practices (Petition at 40-41). You maintain that we should therefore conduct a complete audit of all of the French clinical trial data to determine whether other trials must be conducted (Petition at 41 and 89).

We disagree with your characterization of both the French data and FDA's reliance on that data. You reference the Form FDA 483 issued on June 28, 2006, to Dr. Elisabeth Aubeny, as well as the Summary of Findings related to that Form FDA 483. It is not uncommon to have trial sites receive a Form FDA 483, listing the FDA investigator's observations regarding non-compliance with good clinical practice, at the conclusion of an inspection. The investigator will draft an Establishment Inspection Report (EIR) that reviews the violations noted and will recommend an action, taking into consideration the nature of the inspectional findings, any actions that occurred following the findings, and Agency policy. For products regulated by CDER, compliance reviewers in the Division of Clinical Compliance Evaluation in the Office of Scientific Investigations (previously, the Division of Scientific Investigations) review the EIR, the Form FDA 483, and the evidence collected during the inspection, as well as any written response submitted timely by the inspected party, to determine whether the recommended action is appropriate and is supported by adequate evidence. This review evaluates each violation's effect on the timeliness, accuracy, and/or completeness of the data collected from the site to ascertain if the data are reliable. In this particular case, although there were violations cited on the Form FDA 483 and discussed in the EIR, the violations were determined not to affect the reliability of the data provided by that site. The statement you quote from the Summary of Findings reflects this conclusion. We note that, although the French studies were not performed under a U.S. investigational new drug application (IND), this is typical of many approved drugs that originally were developed or studied outside the United States, and is fully permissible under 21 CFR 312.120 (Foreign clinical studies not conducted under an IND) (including the version of the provision in effect at the time of the 2000

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were historically controlled, which was appropriate under § 314.126(b)(2)(v). Furthermore, your suggestion that there are study designs that would have allowed for blinding raises ethical issues that go beyond the scope of your Petition and this response.

approval of Mifeprex). FDA concluded that the French trials were conducted in accordance with good clinical practice,[40] and the Agency was able to validate the data from those studies.

It is worth noting that in 1996, when the Advisory Committee reviewed the French data without considering the U.S. data, the committee voted 6 to 2 that the French data alone demonstrated efficacy and 7 to 0 (with one abstention) that the French data supported safety.[41] The subsequent approval of Mifeprex was based not only on the data from the two French trials but also on the data from the large Phase 3 U.S. trial. The Advisory Committee received a report on the U.S. trial (the article by Spitz, et al., referenced in note 12 above) and had no comments.

For the foregoing reasons, there is no scientific or regulatory need for us to further review the French clinical data on Mifeprex.

3. Your Request for an Audit of the U.S. Clinical Data

In addition to your request that FDA conduct a full audit of the data from the French trials, you request that FDA conduct a full audit of all data from the U.S. trial (Petition at 1-2 and 89). Other than one footnote referring to a letter from the NDA sponsor to FDA (Petition at 89, note 384), you have provided no information supporting this request. Accordingly, we do not address this request further, other than to note that we do not believe there is any scientific or regulatory need to further review the U.S. clinical trial data relied on for approval of the Mifeprex NDA.

C. FDA Lawfully Approved Labeling for Mifeprex for Use with Misoprostol

You contend that FDA's "de facto" approval of misoprostol for use with Mifeprex as part of a medical abortion regimen was unlawful because the holder of the only approved NDA for misoprostol[42] did not submit a supplemental NDA for this new use (Petition at 41-45). You further

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[40] The regulations in effect at the time of the Mifeprex approval in 2000 refer to FDA accepting such studies when they are "well designed, well conducted, performed by qualified investigators, and conducted in accordance with ethical principles acceptable to the world community" FDA has generally interpreted that language as incorporating the principles of "good clinical practice" (see, e.g., ICH guidance for industry, *ICH E6 Good Clinical Practice: Consolidated Guidance* (E6 Guidance), available on the FDA Drugs Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm), which is the term used in the current regulations. The E6 Guidance states that GCP:

> is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that clinical trial data are credible

(E6 Guidance at 1).

[41] Mifeprex Approval Memorandum, supra note 16, at 1.

[42] Two abbreviated new drug applications (ANDAs) for misoprostol have been approved since Mifeprex was approved: ANDA 076095 (IVAX Pharmaceuticals, Inc., approved July 10, 2002) and ANDA 091667 (Novel Laboratories Inc., approved July 25, 2012).

argue that FDA not only sanctioned, but participated in, the promotion of an off-label use of misoprostol by overseeing the creation of Mifeprex promotional materials that discuss the off-label use of misoprostol and by disseminating information about the off-label use in documents such as the press release announcing Mifeprex's approval (Petition at 46-47).

The approval of Mifeprex was based on evidence from three adequate and well-controlled clinical trials using the treatment regimen of administration of mifepristone on day one, followed approximately 48 hours later (i.e., on day three) by the administration of misoprostol (unless a complete abortion has already been confirmed before that time). Neither the FD&C Act nor FDA regulations require the submission of a supplemental NDA by the sponsor of the misoprostol NDA for the use of misoprostol as part of the approved treatment regimen for Mifeprex. In this situation, the "drug product" subject to section 505(b) of the FD&C Act (21 U.S.C. 355(d)) was Mifeprex.[43] The NDA for Mifeprex appropriately contained the full reports of investigations which have been conducted to show whether or not "such drug" is effective in use (§ 505(b)(1) of the FD&C Act), and FDA appropriately found that the Mifeprex NDA met the approval requirements in § 505(d) of the FD&C Act.

There are a number of drug products that FDA has approved as safe and effective in combination with another drug for a use that was not sought by the applicant of the second drug product, and for which the Agency did not require any change in the labeling of the second product (i.e., that the second product's labeling include the indication for use with the newly approved drug product). Examples of approved drug labeling that refer to the concomitant use of another drug without there being a specific reference to the combined therapy in the previously approved labeling for the referenced drug include the following:

- Xeloda (capecitabine) for treatment of metastatic breast cancer in combination with Taxotere (docetaxel) after failure of prior anthracycline-containing therapy[44]

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[43] In the Response to Opposition, you reference a July 2, 2002, letter submitted by the Population Council to Docket 01E-0363 re: Determination of Regulatory Review Period for Purposes of Patent Extension; Mifeprex (Response to Opposition at 12-13). In its July 2, 2002, letter, the Population Council made several statements regarding what it believed should be considered "the approved human drug product" for purposes of 21 CFR 60.22(a)(1), for purposes of patent term restoration. In the Agency's October 24, 2002, notice amending FDA's previous determination of the regulatory review period for Mifeprex (67 FR 65358), we addressed — and rejected — the Population Council's assertions. We stated that "[t]he applicant tries to characterize Mifeprex as mifepristone 'in combination with another active ingredient' in an attempt to take advantage of portions of the definition of 'human drug product' in 35 U.S.C 156(f), that is, a human drug product means 'the active ingredient of a new drug * * * as a single entity or in combination with another active ingredient.' The applicant points to the definition of 'combination product' at 21 CFR 3.2(e) in this effort. A more useful description of a drug 'in combination with another active ingredient' is found at 21 CFR 300.50 (two or more drugs combined in a single dosage form). Mifeprex is not mifepristone 'in combination with another active ingredient.' Mifeprex is single entity mifepristone" (67 FR 65358, note 2).

[44] We note your assertion that when Xeloda and Taxotere are used together, each is being used for an FDA-approved use (Response to Opposition at 11). Taxotere (docetaxel) was approved on May 14, 1996; its current labeling states that it is indicated as a single agent for treatment of locally advanced or metastatic breast cancer after failure of prior chemotherapy, and in combination with doxorubicin and cyclophosphamide as adjuvant treatment of patients with operable node-positive breast cancer. Xeloda (capecitabine), which

- Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin for *H. pylori* eradication
- Persantine (dipyridamole) as an adjunct to coumarin anticoagulants for prevention of postoperative thromboembolic complications of cardiac valve replacement
- Herceptin (trastuzumab) in combination with paclitaxel for treatment of metastatic breast cancer
- Vistide (cidofovir) administered with probenecid for treatment of CMV retinitis in patients with AIDS
- Daraprim (pyrimethamine) for treatment of toxoplasmosis when used conjointly with a sulfonamide

You maintain that the labeling for Mifeprex is misleading because it directs physicians to use misoprostol for a purpose that FDA never approved and because it creates the false expectation that misoprostol is approved for medical abortion (Petition at 47). We disagree that the labeling for Mifeprex is misleading by virtue of the fact that it includes instructions for the use of misoprostol as part of the approved treatment regimen for Mifeprex. The Mifeprex labeling appropriately describes the clinical trial treatment regimen in which Mifeprex was shown to be safe and effective. The labeling for Mifeprex makes clear that Mifeprex tablets contain mifepristone, not misoprostol, and although the Indication and Usage section in the 2000 labeling does address the use of misoprostol in a regimen with Mifeprex, the labeling is clearly addressed to Mifeprex.

You claim that Mifeprex is misbranded because, per 21 CFR 201.6(a), the references to misoprostol in the Mifeprex labeling constitute a false or misleading representation that misoprostol itself is approved for medical termination of pregnancy (Petition at 48). In addition, you contend that Mifeprex is misbranded under section 502(j) of the FD&C Act (21 U.S.C. 352(j)) because it is unsafe when used as directed in the 2000 approved labeling (id.).

The references to misoprostol in the Mifeprex labeling do not render Mifeprex misbranded as described in § 201.6(a) because the labeling does not make any false or misleading representations with regard to misoprostol. We determined, and the labeling reflects, that Mifeprex is safe and effective for the termination of early pregnancy when used in combination with misoprostol. The approval was based on evidence from adequate and well controlled clinical trials in which misoprostol was administered two days after mifepristone to help stimulate uterine contractions; accordingly, the approved labeling describes the use of Mifeprex in combination with misoprostol.

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originally was approved on April 30, 1998, for the treatment of metastatic breast cancer that is resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated, is currently approved (in addition to other indications) for use in combination with docetaxel for treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. The indication to which this response refers is the concomitant use (i.e., use in combination) of the two drugs, a use that is not referenced in the labeling for Taxotere. Your arguments with respect to Actos (pioglitazone) in combination with a sulfonylurea, metformin, or insulin; Viread (tenofovir disproxil fumarate) in combination with other antiretroviral agents; and Nexium (esomeprazole magnesium) in combination with clarithromycin and amoxicillin (id.) are similarly inapposite.

Additionally, the approved labeling in no way implies that misoprostol alone would be safe and effective for the termination of pregnancy. Thus, the statements in the labeling are neither false nor misleading with regard to the use of misoprostol.

With regard to section 502(j) of the FD&C Act, Mifeprex is not misbranded under that provision because, as discussed in the following section, the approved regimen for Mifeprex is not "dangerous to health when used in the dosage or manner; or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof."

D. Mifeprex Is Safe for Its Approved Use and the Conditions of Approval Do Not Lack Essential Safeguards

You contend that FDA "approved mifepristone for use in a deregulated regimen that lacks key safeguards" (Petition at 5). You claim that in 2000, the Population Council repudiated distribution restrictions that it had proposed in 1996, and that FDA subsequently approved a regimen that does not embody restrictions sufficient to address legitimate safety concerns (Petition at 49). You note that the February 18, 2000, Mifeprex approvable letter stated that restrictions (per § 314.520) on the distribution and use of Mifeprex were needed to ensure safe use of the drug but that in March 2000, the Population Council said such restrictions were unwarranted (Petition at 51-52). You claim that we later yielded to the applicant on several important issues (Petition at 54-55).

FDA has found that Mifeprex is safe and effective for its intended use. It is true that, before the 2000 approval of Mifeprex, FDA and the applicant were not always in full agreement about the distribution restrictions. It is not unusual for such differences to emerge during the course of the review process for a proposed drug product. We ultimately determined that the distribution restrictions stated in the approval letter were appropriate to ensure the safety of Mifeprex for its intended use.[45] Three adequate and well-controlled clinical trials supported the safety of Mifeprex for its intended use, and over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support the safety of this drug product.[46] Further, we approved a risk evaluation and mitigation strategy (REMS) for Mifeprex in June 2011, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Following is our response to the specific safety issues you raise in the Petition.

1. Ultrasound Dating

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[45] We note your reference in your Response to Opposition to the statement by the Reproductive Health Drugs Advisory Committee that it had concerns about the distribution proposal discussed at the July 19, 1996, meeting (Response to Opposition at 4 (referencing the minutes from the 1996 Reproductive Health Drugs Advisory Committee meeting)). In light of FDA's determination in 2000 that the distribution restrictions stated in the approval were appropriate to ensure that Mifeprex was safe for its intended use, as well as the 2011 approval of the Mifeprex REMS, the Committee's reservations in 1996 are not applicable.

[46] See, e.g., Raymond, EG, et al., 2013, First-Trimester Medical Abortion With Mifepristone 200 mg and Misoprostol: A Systematic review, Contraception, 87:26-37 In this article, 87 trials were reviewed and 91 references were cited.

You maintain that the Mifeprex regimen is unsafe because it does not require ultrasound examination. Specifically, you maintain that the use of transvaginal ultrasound is necessary to accurately date pregnancies and to identify ectopic pregnancies, and you note both that Mifeprex was approved in 2000 only for women through 49 days' gestation and that it is contraindicated for women with a confirmed or suspected ectopic pregnancy (Petition at 57-61).

Although the protocol for the U.S. clinical trial required a transvaginal sonogram (TVS) for each patient at Visit 1 and stated that the test should be used "as indicated" at Visits 2 and 3, this does not mean that a TVS is essential to ensure the safe use of Mifeprex.[47] As stated in the Mifeprex Approval Memorandum, during the review process, the Agency carefully considered the role of ultrasound.[48] In the clinical trials, ultrasound was performed to ensure proper data collection on gestational age, but in clinical practice, pregnancies can also be (and frequently are) dated using other clinical methods. (As discussed in section II.F below, safeguards employed during clinical trials are not always essential for safe use of the approved drug product.) As part of the restricted distribution of Mifeprex put in place in 2000, each provider must have the ability to accurately assess the duration of pregnancy and to diagnose ectopic pregnancy. We determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider.

You claim that the only way to date a pregnancy accurately enough to exclude EGA > 49 days is by using TVS (Petition at 58). That is incorrect. As noted above, using TVS (or any other method) does not ensure complete accuracy in dating a pregnancy. In most cases, a provider can accurately make such a determination by performing a pelvic examination and obtaining a careful history, which would include the following: date of last menstrual period, regularity of menses, intercourse history, contraceptive history, and (if available) home pregnancy test results.[49] If in doubt, the provider can order an ultrasound and/or a blood test measuring the quantitative beta-human chorionic gonadotropin (hCG) to further assist in dating the gestational age.

Furthermore, use of a TVS does not guarantee that an existing ectopic pregnancy will be identified. As of April 30, 2015, there were 89 unduplicated reports in FDA's Adverse Event Reporting System (FAERS) database of ectopic pregnancy in women in the United States who had received mifepristone for termination of pregnancy since the approval of Mifeprex in the United States. In

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[47] We note that the French clinical trials did not require an ultrasound examination; rather, the decision as to whether an ultrasound was needed was left to the discretion of the investigator.

[48] Mifeprex Approval Memorandum, supra note 16, at 5.

[49] See, e.g., Fielding, SL, et al., 2002, Clinicians' Perception of Sonogram Indication for Mifepristone Abortion up to 63 Days, Contraception, 66:27-31 (discussing the results of a prospective study of 1,016 women in a medical abortion trial at 15 sites that concluded that "clinicians correctly assessed gestational age as no more than 63 days in 87% of women. In only 1% (14/1013) of their assessments did clinicians underestimate gestational age. We conclude that the clinicians felt confident in not using ultrasound in most cases").

42.7% (38 of89) of the reported cases, an ultrasound was completed. Of the 38 cases that had an ultrasound completed, 55.3% (21 of 38) showed no changes indicative of ectopic pregnancy.[50] In light of the fact that Mifeprex is contraindicated for women with a confirmed or suspected ectopic pregnancy, we believe it is reasonable to expect that the women's providers would not have prescribed Mifeprex if a pelvic ultrasound examination had clearly indicated an ectopic pregnancy; this strongly suggests, therefore, that ultrasound examinations were falsely negative for ectopic pregnancy in these women. The currently approved labeling for Mifeprex reflects this, stating that the "presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed Mifeprex."[51]

2. Physician Training and Admitting Privileges

You contend that the administration of Mifeprex should have been restricted to physicians who have formal training in both pharmaceutical and surgical abortion and who have admitting privileges to emergency facilities (Petition at 62-65).

Although we did not restrict the administration of Mifeprex to physicians with the specific requirements you list in your Petition, we did conclude in 2000 that Mifeprex had to be provided by a physician who, among other qualifications, either (1) has the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or (2) has made plans to provide such care through other qualified providers and facilities.

During the clinical trials for Mifeprex, the principal investigators were trained in surgical abortions and were able to conduct any necessary surgical interventions.[52] The protocol for the U.S. trial was designed such that the studies were conducted at 17 centers where the principal investigators could perform abortions by either vacuum aspiration or dilatation and curettage and had access to facilities that provided blood transfusions and performed routine emergency resuscitation procedures.

During the NDA review process, the issue of physician qualifications and certification was thoroughly discussed within the Agency, with the applicant, and with an outside consultant with expertise in early pregnancy termination. Although the distribution of Mifeprex was not restricted to any particular medical specialist, the Agency did determine in 2000 that certain restrictions were

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[50] Seventeen cases were identified as having an ultrasound with a possible ectopic pregnancy. Fourteen of these 17 (82.3%) cases noted appropriate follow-up procedures, such as additional hCG monitoring, ultrasounds, appointments, or emergency room referral, while two cases did not include any additional follow-up information. In the remaining case, a diagnosis of a heterotopic gestation (simultaneous ectopic pregnancy and intrauterine pregnancy) was noted.

[51] Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. .

[52] Additionally, it is common in drug development that the clinical investigators who conduct pivotal Phase 3 clinical trials have more specialized training than may be necessary to ensure the safe use of a drug post-approval. Examples are trials for male erectile dysfunction (typically conducted by urologists), hypertension (internists), depression (psychiatrists), and endometriosis (gynecologists).

necessary under § 314.520. In accordance with this determination, the Prescriber's Agreement for Mifeprex stated the following:[53]

> Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:
>
> - Ability to assess the duration of pregnancy accurately.
> - Ability to diagnose ectopic pregnancies.
> - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have [sic] made plans to provide such care through others, and are [sic] able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
> - Has read and understood the prescribing information of Mifeprex....

As noted in the Mifeprex Approval Memorandum, the requirement that a physician certify, by signing the Prescriber Agreement, that he or she has the qualifications described in that Agreement limited the physicians who would be eligible to receive Mifeprex from the sponsor to those who are familiar with managing early pregnancies.[54] Because only such qualified physicians would be using or would oversee the use of Mifeprex, we concluded that there was no need for special certification programs or additional restrictions. Additionally, as noted in the Mifeprex Approval Memorandum, in the U.S. clinical trial of Mifeprex, 11 out of roughly 850 patients needed surgical intervention to treat bleeding, and three of these patients were treated by non-principal investigators such as emergency room physicians and a non-study gynecologist.[55] These data suggested that patients would receive any needed surgical intervention from either their physician or another physician with the needed skills.[56] The Mifeprex Approval Memorandum also pointed out that the Mifeprex labeling and the Medication Guide approved at that time highlight that surgery may be needed and that patients must understand whether the provider will furnish any necessary medical intervention or whether they will be referred to another provider and/or facility.[57]

In addition, one of the Phase 4 commitments accompanying the approval of Mifeprex was a cohort-based study of safety outcomes when Mifeprex is prescribed by physicians with the skills for surgical intervention compared to physicians who refer patients for surgical intervention. In a February 2008 submission, the applicant stated that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful

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[53] Mifeprex labeling (June 8, 2011), Mifeprex (mifepristone) tablets, 200 mg, Prescriber's Agreement, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020687s014lbl.pdf.

[54] Mifeprex Approval Memorandum, supra note 16, at 5.

[55] Id.

[56] Id.

[57] Id.

study to assess this specific issue. After review of this submission, the Agency: (1) concurred with the applicant regarding the non-feasibility of conducting a meaningful study and (2) concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. Accordingly, on September 26, 2008, the Agency released the applicant from this commitment.

The provisions of the currently approved labeling (including the REMS) that relate to provider training and admitting privileges are substantially similar to the labeling provisions approved in 2000. Under current labeling, healthcare providers who administer Mifeprex must be licensed to prescribe, and must have the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also (1) be able to provide any necessary surgical intervention, or (2) have made arrangements for others to provide for such care. Healthcare providers must be able to ensure that women have access to medical facilities for emergency care, and must agree to other responsibilities, including reviewing and signing the Patient Agreement Form with the patient and providing each patient with a copy of the signed Patient Agreement Form and the Medication Guide.[58]

3. "Dear Health Care Provider" Letter and FDA "Mifepristone Questions and Answers"; Adverse Events Discussed in Response to Opposition

You maintain that your concerns about the safety of Mifeprex are validated by the April 19, 2002, "Dear Health Care Provider" letter issued by Danco and by statements in the "Mifepristone Questions and Answers" (Mifepristone Q&A) document (placed on FDA's Web site on April 17, 2002) about reports of serious adverse events, including ruptured ectopic pregnancies and serious systemic bacterial infections (Petition at 65-71). You argue that FDA understated the possibility that the Mifeprex regimen caused the serious adverse events referred to in the letter and inappropriately attempted to link those events to the unapproved vaginal administration of misoprostol (Petition at 67-68).

The fact that Danco and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 (or that a subsequent Dear Health Care Provider letter and a Dear Emergency Room Director letter were issued on September 30, 2004) does not imply that the approved Mifeprex regimen is unsafe. It is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."[59] The intent of the two "Dear Health Care Provider" letters and the "Dear Emergency Room Director" letter was to provide health care personnel with new safety information regarding the use of Mifeprex. Similarly, when these letters were issued, we posted Mifepristone Q&A documents to

[58] Mifeprex REMS, available at http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=35

[59] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm.

address questions that might arise as a result of the issuance of the letters. We disagree that we have in any way "inappropriately attempted to link" the adverse events to the intravaginal use of misoprostol. Rather, the April 2002 Mifepristone Q&A document accurately stated that in all of the adverse event cases at that time,[60] the misoprostol was given vaginally not orally; that we did not know what role, if any, the use of Mifeprex and vaginal misoprostol may have in the development of serious infections; and that FDA had not reviewed data on the safety and effectiveness of vaginal administration of misoprostol.

You maintain that it is particularly important for FDA to respond to these adverse events because the clinical trials in support of Mifeprex allegedly did not adhere to the Agency's scientific methodology for such trials (Petition at 70). As explained above, however, the clinical trials supporting the approval of Mifeprex were adequate and well-controlled, and they provided substantial evidence of the safety and effectiveness of the drug product in accordance with the FD&C Act and FDA regulations.

In your Response to Opposition, you state that the serious adverse events reported to date are consistent with concerns expressed before approval (Response to Opposition at 16). You refer to the death of Holly Patterson on September 17, 2003, after she had taken Mifeprex and misoprostol to terminate her pregnancy. You state that Ms. Patterson's apparent death from a serious systemic bacterial infection after taking Mifeprex is "not the first such death since FDA approved Mifeprex," referring to a fatality due to serious systemic bacterial infection mentioned in the April 2002 "Dear Health Care Provider Letter" (Response to Opposition at 16-17). You also question whether adverse events for Mifeprex will be adequately reported to FDA (Response to Opposition at 18).

As with all approved drug products, we continue to monitor the safety of Mifeprex. Since the approval of Mifeprex, the Agency has issued two public health advisories (one in July 2005[61] and one in March 2006[62]) and posted multiple MedWatch safety alerts (in November 2004[63] and July 2005, the latter with updates in November 2005 and March 2006[64]). As referenced above, Danco has issued two Dear Health Care Provider letters and one Dear Emergency Room Director letter. Furthermore, since you submitted your Response to Opposition, Danco has revised the labeling for

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[60] The April 2002 Mifepristone Q&A document refers to cases of ectopic pregnancy, sepsis, and heart attack.

[61] Available at, http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051734.htm.

[62] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051196.htm.

[63] Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166463.htm.

[64] Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111339.htm.

Mifeprex (including the prescribing information, the Medication Guide, and the Patient Agreement), in November 2004, December 2004, July 2005, and April 2009[65] to provide prescribers and women with additional information about infection, vaginal bleeding, and ectopic pregnancy.

The boxed warning for Mifeprex currently states the following:

> Serious and sometimes fatal infections and bleeding occur very rarely following spontaneous, surgical, and medical abortions, including following MIFEPREX use. No causal relationship between the use of MIFEPREX and misoprostol and these events has been established.
>
> • Atypical Presentation of Infection. Patients with serious bacterial infections (e.g., *Clostridium sordellii*) and sepsis can present without fever, bacteremia, or significant findings on pelvic examination following an abortion. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. A high index of suspicion is needed to rule out serious infection and sepsis.
>
> • Bleeding. Prolonged heavy bleeding may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed. Advise patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding.
>
> Because of the risks of serious complications described above, MIFEPREX is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the MIFEPREX REMS Program.
>
> Before prescribing MIFEPREX, inform the patient about the risk of these serious events. Ensure that the patient knows whom to call and what to do, including going to an Emergency Room if none of the provided contacts are reachable, if she experiences sustained fever, severe abdominal pain, prolonged heavy bleeding, or syncope, or if she experiences abdominal pain or discomfort, or general malaise (including weakness, nausea, vomiting or diarrhea) for more than 24 hours after taking misoprostol.
>
> Advise the patient to take the Medication Guide with her if she visits an emergency room or a healthcare provider who did not prescribe MIFEPREX, so that the provider knows that she is undergoing a medical abortion.

[65] The Mifeprex labeling also was revised in June 2011 when the REMS was approved. In addition, as described above, FDA is today approving a supplemental NDA submitted by Danco that proposed modified labeling for Mifeprex. See Mifeprex labeling (Mar. 29, 2016) available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

The WARNINGS section of the Mifeprex labeling states, in part, the following:

[With respect to infection and sepsis:]

> As with other types of abortion, cases of serious bacterial infection, including very rare cases of fatal septic shock, have been reported following the use of MIFEPREX. Healthcare providers evaluating a patient who is undergoing a medical abortion should be alert to the possibility of this rare event. A sustained (> 4 hours) fever of 100.4°F or higher, severe abdominal pain, or pelvic tenderness in the days after a medical abortion may be an indication of infection.
>
> A high index of suspicion is needed to rule out sepsis (e.g., from *Clostridium sordellii*) if a patient reports abdominal pain or discomfort or general malaise (including weakness, nausea, vomiting or diarrhea) more than 24 hours after taking misoprostol. Very rarely, deaths have been reported in patients who presented without fever, with or without abdominal pain, but with leukocytosis with a marked left shift, tachycardia, hemoconcentration, and general malaise. No causal relationship between MIFEPREX and misoprostol use and an increased risk of infection or death has been established. *Clostridium sordellii* infections have also been reported very rarely following childbirth (vaginal delivery and caesarian section), and in other gynecologic and non-gynecologic conditions.

[With respect to uterine bleeding:]

> Uterine bleeding occurs in almost all patients during a medical abortion. Prolonged heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours) may be a sign of incomplete abortion or other complications and prompt medical or surgical intervention may be needed to prevent the development of hypovolemic shock. Counsel patients to seek immediate medical attention if they experience prolonged heavy vaginal bleeding following a medical abortion.
>
> Women should expect to experience vaginal bleeding or spotting for an average of 9 to 16 days. Women report experiencing heavy bleeding for a median duration of 2 days. Up to 8% of all subjects may experience some type of bleeding for 30 days or more. In general, the duration of bleeding and spotting increased as the duration of the pregnancy increased.
>
> Decreases in hemoglobin concentration, hematocrit, and red blood cell count may occur in women who bleed heavily.
>
> Excessive uterine bleeding usually requires treatment by uterotonics, vasoconstrictor drugs, surgical uterine evacuation, administration of saline infusions, and/or blood transfu¬sions. Based on data from several large clinical trials, vasoconstrictor drugs were used in 4.3% of all subjects, there was a decrease in hemoglobin of more than 2 g/dL in 5.5% of subjects, and blood transfusions were administered to $\leq 0.1\%$ of subjects. Because heavy bleeding requiring surgical uterine evacuation occurs in about 1% of patients, special care should be given to patients with hemostatic disorders, hypocoagulability, or severe anemia.

[With respect to ectopic pregnancy:]

> MIFEPREX is contraindicated in patients with a confirmed or suspected ectopic pregnancy because MIFEPREX is not effective for terminating ectopic pregnancies. Healthcare providers should remain alert to the possibility that a patient who is undergoing a medical abortion could have an undiagnosed ectopic pregnancy because some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. The presence of an ectopic pregnancy may have been missed even if the patient underwent ultrasonography prior to being prescribed MIFEPREX.
>
> Women who became pregnant with an IUD in place should be assessed for ectopic pregnancy.

The Agency has regularly completed a cumulative summary of U.S. postmarketing adverse events reported for the use of mifepristone for medical termination of pregnancy. From the approval date of Mifeprex (September 28, 2000) through October 31, 2012, we received 2,740 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy,[66] including 57 reports of severe infections[67] and 416 incidences of blood loss requiring transfusion. From November 1, 2012, through April 30, 2015, we received 984 reports of adverse events associated with the use of mifepristone in the United States to terminate pregnancy, including 9 reports of severe bacterial infections and 134 incidences of blood loss requiring transfusion.[68] As of April 30, 2015, 89 ectopic pregnancies associated with the use of mifepristone in the United States had been reported since the approval of Mifeprex. As of July 24, 2015, 17 U.S. deaths had been reported since the approval of Mifeprex. Deaths were associated with sepsis in 8 of the 17 reported fatalities (7 cases tested positive for *Clostridium sordellii*, and 1 case tested positive for *Clostridium perfringens*).[69] Seven of the eight fatal sepsis case reported vaginal misoprostol use;

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[66] This represents data from the FDA's previous adverse event reporting system, which was known as AERS.

[67] Severe infections generally involve death or hospitalization for at least 2-3 days, intravenous antibiotics for at least 24 hours and total antibiotic usage for at least 3 days, and any other physical or clinical findings, laboratory data or surgery that suggest a severe infection.

[68] This represents data from the current FDA Adverse Event Reporting System (FAERS), which was implemented in September 2012 and replaced AERS. FDA migrated all of the data from the previous reporting system (AERS) to FAERS. FDA validated and recoded product information as the reports from the AERS database were migrated to the FAERS database. In addition, the FAERS database features a new search functionality that is based on the date FDA initially received for the case; this facilitates more accurate follow-up for cases that have multiple reports and multiple receipt dates. For these reasons, there may be differences in the case counts between AERS and FAERS.

[69] We note your statements in your October 10, 2003, Response to Opposition Comments that the presence of retained products of conception can lead to the development of intrauterine or systemic infection and that Mifeprex might potentiate this possibility through negative effects on immune system function or normal protective mechanisms (Response to Opposition at 17). Regarding retained products of conception and the emergence of infections, based on autopsy and/or ultrasound reports, there were no retained products of conception in any of the eight deaths associated with infections (sepsis). With respect to your claim that Mifeprex might increase the likelihood of infection by adversely affecting immune system function, although

one case reported buccal misoprostol use. Seven of the nine remaining U.S. deaths involved two cases of ruptured ectopic pregnancy and one case each of the following: substance abuse/drug overdose; methadone overdose; suspected homicide; suicide; and a delayed onset of toxic shock-like syndrome. In the eighth case, the cause of death could not be established despite performance of an autopsy; tissue samples were negative for *C. sordellii*. In the ninth case, infection was ruled out and the final autopsy report listed pulmonary emphysema as the cause of death. [70]

We disagree with your assertion that adverse event reporting for Mifeprex is "spotty" and that, as a result, the database for post-approval adverse events for Mifeprex is incomplete (Response to Opposition at 18). You are correct that reporting to the Agency's MedWatch program is voluntary, and we acknowledge that there is always a possibility with any drug that some adverse events are not being reported. We believe, however, that the potential for underreporting of serious adverse events associated with the use of Mifeprex for medical abortion has been very low because of the restricted distribution of the product and because healthcare providers have agreed in writing to report any hospitalizations, transfusions, or other serious adverse events associated with the drug to the sponsor, which is required under FDA's regulations to report all adverse events, including serious adverse events, to the Agency (see 21 CFR 314.80, 314.81). As with all drugs, we will continue to closely monitor the postmarketing safety data on Mifeprex.

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published experimental data from animal models suggest that this is a theoretical possibility, the overall event rate of serious infections does not support this. If Mifeprex were adversely affecting immune system function, we would expect to see a much higher rate of serious infections from more common organisms, as well as a higher number of deaths in Europe (where mifepristone has been approved for over 24 years) and in the United States. Contrary to your statements, data from the medical literature and findings by the CDC suggest that the critical risk factor in the reported cases of sepsis is pregnancy itself (see Miech, RP, 2005, Pathophysiology of Mifepristone-Induced Septic Shock Due to *Clostridium sordellii*, Ann Pharmacother, 39:1483-1488). In May 2006, FDA, along with the CDC and the National Institute of Allergy and Infectious Diseases at the National Institutes of Health held a workshop on emerging clostridial disease. The issue of immunosuppression also was discussed at length during this public workshop. It was clear from the presentations at the workshop that *C. sordellii* causes rapid and serious clinical illness in settings other than medical abortion, including among pregnant women who have recently undergone spontaneous abortion or term delivery. The fact that cases of *C. sordellii* have been identified both in pregnant women who have undergone medical abortion and those who have not supports the idea that the physiology of pregnancy may be a more plausible risk factor for *C. sordellii* illness than having undergone a medical abortion with Mifeprex.

[70] FDA is aware of 11 additional deaths of women in foreign countries who used mifepristone for the termination of pregnancy. This included one death associated with sepsis (*Clostridium sordellii* identified in tissue samples) in a foreign clinical trial, and 10 deaths identified from post-marketing data. These 10 fatal cases were associated with the following: sepsis (Group A *Streptococcus pyogenes*); a ruptured gastric ulcer; severe hemorrhage; severe hemorrhage and possible sepsis; "multivisceral failure"; thrombotic thrombocytopenic purpura leading to intracranial hemorrhage; toxic shock syndrome (*Clostridium sordellii* was identified through uterine biopsy cultures); asthma attack with cardiac arrest; respiratory decompensation with secondary pulmonary infection 30 days after mifepristone in a patient on the lung transplant list with diabetes a jejunostomy feeding tube, and severe cystic fibrosis; *Clostridium septicum* sepsis (from a published literature report).

E. Withdrawal of the Approval for Mifeprex Based on Current Use Is Not Appropriate

You claim that Mifeprex abortion providers have disregarded the restrictions in the approved regimen "without any reaction from FDA, the Population Council, or Danco" (Petition at 71). You also claim that "common departures from the approved regimen" have included (1) offering the regimen to women with pregnancies beyond 7 weeks and (2) eliminating the second of the three prescribed visits to the health care provider (Petition at 72-74). You argue that we should withdraw approval of Mifeprex under § 314.530(a)(4) due to the failure of the Population Council and Danco to adhere to the postmarketing restrictions in the approval letter (Petition at 71).

In the Response to Opposition, you suggest that some providers have not met their obligations because many prescriber Web sites (1) advertise the Mifeprex regimen as being available for patients whose pregnancies have progressed beyond 49 days and (2) indicate that patients take misoprostol at home rather than at the provider's office (Response to Opposition at 19-20). Thus, you maintain that many prescribers have allowed patients to make false statements and that the applicant is obligated to stop sales to these prescribers (id. at 20). You claim that prescribers have disregarded the requirements imposed with the 2000 approval of Mifeprex to provide patients with the Medication Guide, obtain their signatures on the Patient Agreement, and give them the opportunity to read and discuss these documents (id. at 20-21). You state that because some prescribers, with the applicant's tacit approval, have permitted patients to sign the Patient Agreement while effectively directing them not to adhere to its requirements, the applicant cannot be described as meeting its obligations (id. at 21).

FDA is aware that medical practitioners may use modified regimens for administering Mifeprex and misoprostol. However, FDA does not believe that it is appropriate to initiate proceedings under 21 CFR 314.530 or section 505(e) of the FD&C Act to withdraw the approval of Mifeprex based on available information regarding the distribution of Mifeprex.

The Mifeprex approval letter included nine items that the applicant and/or prescriber were obligated to follow. As stated earlier in this response, Mifeprex has been subject to a REMS which incorporated these restrictions, including by appending a Prescriber's Agreement outlining required qualifications and guidelines prescribers must agree to follow. Specifically, the Prescriber's Agreement required each physician to attest to possessing certain necessary skills and abilities related to managing early pregnancy to ensure safe use of the drug.[71] The Prescriber's Agreement also contained responsibilities that prescribers must carry out.[72] The Prescriber's Agreement stated that prescribers must have read and understood the prescribing materials.[73]

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[71] Prescriber's Agreement, supra note 53, at 1.

[72] Id. at 1-2.

[73] Id. at 1.

The 2000 Prescriber's Agreement also required that the prescriber (1) provide each patient with a copy of the Medication Guide and the Patient Agreement, (2) fully explain the procedure to the patient, and (3) give the patient the opportunity to read and discuss the Medication Guide and Patient Agreement.[74] The Medication Guide and the Patient Agreement stated the approved dosage and administration of Mifeprex. FDA has no evidence, nor have you provided any evidence, that prescribers have not signed the Prescriber's Agreement, or that women either have not been given the opportunity to read and discuss the Patient Agreement or have not signed the Patient Agreement.

As noted above, restrictions on the distribution and use of Mifeprex substantially similar to those approved in 2000 remain in place today.

F. Safeguards Employed in Clinical Trials Are Not Necessarily Essential Conditions for Approval

You maintain that we effectively approved a drug regimen that we had not tested because the Mifeprex regimen approved in 2000 does not include important safeguards employed in the U.S. clinical trial (e.g., governing physician training, use of ultrasound, 4-hour post-misoprostol monitoring, physician privileges at facilities that provide emergency care) (Petition at 75-76). You argue that we should not have extrapolated conclusions about the safety and effectiveness of the Mifeprex regimen from data generated under trial conditions that do not mirror the approved regimen (id.).

We disagree with your assertions. Furthermore, your implication that the approved conditions of use for a drug product must mirror those used in the clinical trials supporting its approval is incorrect. As discussed above with respect to ultrasound dating and physician qualifications, safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval. Many clinical trial designs are more restrictive (e.g., additional laboratory and clinical monitoring, stricter inclusion and exclusion criteria, more visits) than will be necessary or recommended in postapproval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated. For example, in menopause hormonal therapy trials, specialists perform periodic endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product. During our review of the clinical data submitted in support of an NDA, we make an assessment of the procedures employed during the clinical trials and the conditions under which the drug was studied. This assessment is reflected in the approved labeling for the drug product.

Upon reviewing the data submitted in support of the Mifeprex NDA, we concluded in 2000 that restrictions requiring ultrasound dating of gestational age of the pregnancy and limiting access to Mifeprex to physicians trained in surgical abortions and capable of performing surgical intervention if complications arise subsequent to use of Mifeprex were not necessary to ensure its safe use (see discussion in section II.D above).

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[74] Id.

G. FDA Appropriately Concluded That Studies of Mifeprex in Pediatric Patients Were Unnecessary

You maintain that our 2000 approval of Mifeprex violated regulations requiring that new drugs be tested for safety and effectiveness in the pediatric population (Petition at 76). You state that although we stated in the September 28, 2000, approval letter that the application was subject to the Pediatric Rule (21 CFR 314.55), we waived the requirement without explanation (Petition at 78). You contend that the Mifeprex application was not in accordance with any of the three provisions under which an applicant may obtain a waiver under 21 CFR 314.55(c)(2) of the pediatric study requirement, for the following reasons:

- 21 CFR 314.55(c)(2)(i) does not apply because FDA maintained that Mifeprex represented a meaningful therapeutic benefit over existing treatments and because Mifeprex can be expected to be used in a substantial number of pediatric patients.

- 21 CFR 314.55(c)(2)(ii) does not apply because pediatric studies of Mifeprex would not have been either impossible or highly impractical because a large population of pediatric females becomes pregnant each year and the female population is evenly distributed throughout the country.

- 21 CFR 314.55(c)(2)(iii) does not apply because FDA stated that there was no reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen than older females (Petition at 79-82).

As an initial matter, we reject your contention that the Population Council did not provide evidence from any adequate and well-controlled adult studies of Mifeprex, and that therefore it was inappropriate to rely on the submitted adult studies under § 314.55(a) with respect to the use of Mifeprex in the pediatric population (Petition at 82). As discussed above, the Mifeprex approval was based on three adequate and well-controlled clinical trials.

Our conclusion that studies of Mifeprex in pediatric patients were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time.[75] We determined that there were sufficient data from studies of mifepristone. Therefore, the Mifeprex approval letter should have stated our conclusion that the pediatric study requirements were waived for pre-menarchal patients and that the pediatric study requirements were met for post-menarchal pediatric patients, rather than stating that we were waiving the requirements for all pediatric age groups.[76]

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[75] FDA was enjoined from enforcing 21 CFR § 314.55 under *Ass'n of Am. Physicians& Surgeons v. FDA*, 226 F. Supp. 204 (D.D.C. 2002). However, on December 3, 2003, the President signed into law the Pediatric Research Equity Act of 2003 (PREA 2003), Public Law 108-155, which gave FDA the statutory authority to require pediatric studies of drugs when such studies are needed to ensure the safe and effective use of drugs in children. PREA 2003 stated that any waivers or deferrals that were granted under the Pediatric Rule were considered to be granted under PREA 2003 (see Section 4 of Public Law 108-155).

[76] FDA's implementation of the Pediatric Rule was still at a relatively early stage in September 2000 and the Agency was not always precise regarding the language used in approval letters to distinguish between situations where studies were waived and where studies were not needed because the requirements were met.

It is still our scientific opinion, based on the medical literature and over 15 years of use in the United States, that there is no biological reason to expect menstruating females under age 18 — compared to women age 18 and older — to have a different physiological outcome with the Mifeprex regimen.[77]

H. The Mifeprex Approval Letter Included Appropriate Phase 4 Commitments

You state that although the Population Council agreed in 1996 to perform Phase 4 studies with six different objectives, the Mifeprex approval letter included only two Phase 4 study obligations (Petition at 85-86). You allege that the changes in its Phase 4 commitments were largely in response to the Population Council's unwillingness to explore the "ramifications" of the Mifeprex regimen (Petition at 87). You maintain that this alleged "curtailment" of Phase 4 study commitments was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law (Petition at 88).[78]

We disagree with your assertions. Our process for determining the appropriate Phase 4 studies for Mifeprex adequately addressed our concerns and reflected typical Agency-applicant interactions to reach consensus on appropriate postmarketing studies.[79] It is common for proposed Phase 4 commitments to evolve during the application review process. As you note (Petition at 85), in 1996, the Population Council committed to six postmarketing studies with the following objectives:

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[77] In the Mifeprex Approval Memorandum, the Office Director stated, "FDA agrees there is no biological reason to expect menstruating females under age 18 to have a different physiological outcome with the regimen. The Spitz data actually suggests a trend towards increased success of medical abortion with younger patients" (Mifeprex Approval Memorandum, supra note 16, at 7).

[78] We note that post-marketing studies are not required for approvals under 21 CFR 314.520.

[79] You also state that, "[a]s a general rule, the clinical trials required by FDA to support an NDA are adequate to establish short-term drug safety and effectiveness. The standard pre-approval clinical trials, however, are typically incapable of providing either the amount or type of data necessary to assess a drug's long-term effects" (Petition at 84). This argument is not relevant to Mifeprex, which is approved for medical termination of pregnancy. Mifeprex is not approved for long-term or chronic use, which is an important factor in assessing the need to study long-term effects of a drug. Long-term safety for a single-dose medication is generally not a concern. However, FDA routinely monitors postmarketing safety data for all approved drugs. Mifeprex is no exception. FDA's Office of Surveillance and Epidemiology continuously monitors available safety data from use of mifepristone for termination of pregnancy both within and outside of the United States and has not identified any long-term safety signals. The Mifeprex adverse events reported are consistent with product labeling and with what can be expected with spontaneous and surgical abortions. Furthermore, as explained in this response, since Mifeprex's approval, safety concerns and adverse events have been monitored through enhanced surveillance and reporting by certified prescribers, and we have required a REMS for Mifeprex including a Medication Guide, elements to assure safe use, an implementation system that requires the sponsor to assess the performance of certified distributors, and a timetable for submission of assessments of the REMS. We also continue to closely monitor the post-marketing safety of mifepristone for termination of pregnancy for any new or long-term signals.

(1) Monitor the adequacy of the distribution and credentialing system.

(2) Follow-up on the outcome of a representative sample of Mifeprex-treated women who have surgical abortion because of method failure.

(3) Assess the long-term effects of multiple use of the regimen.

(4) Ascertain the frequency with which women follow the complete treatment regimen and the outcome of those who do not.

(5) Study the safety and efficacy of the regimen in women under age 18, women over age 35, and women who smoke.

(6) Ascertain the effect of the regimen on children born after treatment failure.

As stated in the Mifeprex Approval Memorandum (at 7), during the final review of the Mifeprex NDA in 2000, items 1, 2, 4, and 5 above were revised and integrated into a single Phase 4 study to assess whether, for providers who did not have surgical intervention skills and referred patients for surgery, clinical outcomes were similar to those of patients under the care of physicians (such as those in the clinical trials) who possessed surgical skills. Based on a revised protocol, this Phase 4 study would monitor the adequacy of provider qualifications (item 1) and collect data on safety outcomes and method failures (item 2) and return of patients for their follow-up visits (item 4). Because patients would not be restricted to a specific age range or smoking status, information to address item 5 also would be obtained. In a second Phase 4 study, the applicant would examine the outcomes of ongoing pregnancies (i.e., method failures) through a surveillance, reporting, and tracking system (item 6). Thus, although the approval letter listed only two Phase 4 studies, those two studies incorporated all but one element of the six studies listed in the September 18, 1996, approvable letter concerning the Mifeprex NDA. (As discussed below, the remaining study was not included for logistical and practical reasons.)

As mentioned in section II.D.2 above, for the first Phase 4 study, which addressed items 1, 2, 4, and 5 above, the applicant reported in a submission in February 2008 that so few medical abortions are prescribed by physicians who do not have surgical intervention skills that it was not feasible to do a meaningful study to assess this specific issue. We agreed with the applicant regarding the non-feasibility of conducting a meaningful study and concluded that no differences between non-referrers or referrers in terms of clinical outcomes could be identified based on the data that had been submitted. In September 2008, we released the applicant from this postmarketing commitment.

For the second Phase 4 study, which addressed item 6 above, based on the reporting of ongoing pregnancies during the first 5 years of Mifeprex distribution, the applicant provided updates in January 2006 and November 2007. Danco reported that only one to two pregnancies per year were followed for final outcomes, and explained that the small number was due, in part, to the requirement that the patients consent to participation after seeking a pregnancy termination. In January 2008, because of the lack of an adequate number of enrolled women, and based on subsequent reports, we released the applicant from this postmarketing commitment.

In addition, as noted in the Mifeprex Approval Memorandum (at 7), we agreed with the Population Council both that it would not be feasible to identify and enroll sufficient numbers of repeat users of the drug and that the pharmacology of mifepristone does not suggest any carryover effect after one-time administration. Accordingly, we did not include item 3 as a Phase 4 commitment in the September 28, 2000, approval letter. However, we note that data from many other studies reported in the medical literature using mifepristone for, e.g., fibroids, uterine myoma, meningioma, psychiatric illnesses, and Cushing's disease, in much higher daily and lower daily doses for chronic use (months) have not raised any major safety issues.[80]

III. REQUEST FOR STAY AND REVOCATION OF APPROVAL

You request that we immediately stay the approval of Mifeprex, thereby halting all distribution and marketing of the drug pending final action on your Petition (Petition at 2). You cite 21 CFR 10.35 as the basis for your request for a stay (Petition at 1). In addition, you urge us to revoke the approval of Mifeprex because of the purported legal violations and safety concerns set forth in your Petition (Petition at 2).

As described above, we are denying your Petition. Therefore, your request for a stay pending final action on your Petition is moot.

For the reasons set forth in section II of this response, we conclude that you have not presented any evidence that the applicable grounds in 21 CFR 314.530 have been met with respect to Mifeprex. Furthermore, you have not provided any evidence that any of the applicable grounds in section 505(e) of the FD&C Act have been met for Mifeprex.[81] Therefore, you have not provided any evidence that would serve as a basis for seeking to withdraw the approval of Mifeprex.

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[80] See, e.g., Tristan, M, et al., 2012, Mifepristone for Uterine Fibroids (Review), Cochrane Library, 8:1-47; Esteve, JL, et al, 2013, Mifepristone Versus Placebo To Treat Uterine Myoma: A Double-Blind, Randomized Clinical Trial, Int J Womens Health, 5:361; Spitz, IM, et al., 2005, Management of Patients Receiving Long-Term Treatment With Mifepristone, Fertil Steril, 84:1719; Blasey, CM, TS Block, JK Belanoff, and RL Roe, 2011, Efficacy and Safety of Mifepristone for the Treatment of Psychotic Depression, J Clin Psychopharmacol, 31:436; Fleseriu, M, et al., 2012, Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome, J Clin Endocrinol Metab, 97:2039.

[81] You have not presented any clinical data or other information demonstrating that Mifeprex is unsafe for use under its approved conditions for use, either on the basis of evidence available to the Agency at the time of approval or when also considering evidence obtained subsequent to approval. In addition, you have not provided any new evidence that, when evaluated with the evidence available at the time of Mifeprex's approval, shows that there is a lack of substantial evidence that the drug will have its intended effect.

IV. CONCLUSION

We appreciate and share your concerns about the need to appropriately manage the risks associated with the use of Mifeprex. Our concerns about the potential complications associated with Mifeprex led to its approval in accordance with 21 CFR 314.520. It was deemed to have in effect a REMS in 2007, and it has had an approved REMS since 2011.[82]

For the reasons set forth above, your request that we immediately stay the approval of Mifeprex is moot, and we deny your request that we revoke approval of the Mifeprex NDA. In addition, we deny your request that we conduct an audit of all records of the French and U.S. clinical trials supporting the Mifeprex approval. As with all approved new drug products, we will continue to monitor the safety of Mifeprex and take any appropriate actions.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[82] As of today's approval of Danco's supplemental NDA, the Medication Guide is no longer part of the REMS. However, the Medication Guide will remain as part of approved patient labeling and will be required to be provided to the patient under current Medication Guide regulations.

Exhibit F

M I F E P R E X™
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.
- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the

event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.
- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this serial number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com

Exhibit G

PATIENT AGREEMENT

Mifeprex (mifepristone) Tablets

1. I have read the attached Medication Guide for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office.
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have the provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:

- return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
- return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the Medication Guide for mifepristone.

Provider's Signature: _____

Name of Provider print: _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the Medication Guide to the patient.

9/21/00

Exhibit H

NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 mg

Danco Laboratories, LLC PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

A. To provide information to patients about the benefits and risks of MIFEPREX before they make a decision whether to take the drug.

B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX and are able to assure patient access to appropriate medical facilities to manage any complications.

II. REMS ELEMENTS

A. Medication Guide

1. A Medication Guide will be dispensed with each MIFEPREX prescription in accordance with 21 CFR 208.24.

2. Please see the appended Medication Guide.

B. Elements to Assure Safe Use

1. Healthcare providers who prescribe MIFEPREX will be specially certified.

   Danco will ensure that healthcare providers who prescribe MIFEPREX are specially certified.

   a. To become specially certified, each prescriber must complete and fax to the MIFEPREX distributor the one-time Prescriber's Agreement, agreeing that they meet the qualifications and will follow the guidelines outlined in the Prescriber's Agreement.

   b. The following materials are part of the REMS and are appended:

      i. Prescriber's Agreement.

      ii. Patient Agreement.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 140 of 357

2. MIFEPREX will be dispensed only in certain health care settings, specifically clinics, medical offices, and hospitals.

   Danco will ensure that MIFEPREX will only be available to be dispensed in a clinic, medical office, or hospital, by or under the supervision of a specially certified prescriber. MIFEPREX will not be distributed to or dispensed through retail pharmacies.

3. MIFEPREX will only be dispensed to patients with documentation of safe use conditions.

   Danco will ensure that MIFEPREX will only be dispensed to patients with documentation of the following safe use conditions:

   a. The patient has completed and signed the Patient Agreement, and the Patient Agreement has been placed in the patient's medical record.

   b. The patient has been provided copies of the signed Patient Agreement and the Medication Guide.

C. Implementation System

The Implementation System will include the following:

1. Distributors who distribute MIFEPREX will be certified. To become certified, distributors must agree to:

   a. Ship drug only to site locations identified by specially certified prescribers in signed Prescriber's Agreements, and maintain secure and confidential records of shipments.

   b. Follow all distribution guidelines, including those for storage, tracking package serial numbers, proof of delivery, and controlled returns.

2. Danco will assess the performance of the certified distributors with regard to the following:

   a. Whether a secure, confidential and controlled distribution system is being maintained with regard to storage, handling, shipping, and return of MIFEPREX.

   b. Whether MIFEPREX is being shipped only to site locations identified by specially certified prescribers in the signed Prescriber's Agreement and only available to be dispensed to patients in a clinic, medical office, or hospital by or under the supervision of a specially certified prescriber.

Reference ID: 2957855

3. If Danco determines the distributors are not complying with these requirements, Danco will take steps to improve their compliance.

D. Timetable for Submission of Assessments

Danco will submit REMS assessments to the FDA one year from the date of the approval of the REMS and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the assessment reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco will submit each assessment so that it will be received by the FDA on or before the due date.

Reference ID: 2957855

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 142 of 357

MEDICATION GUIDE

Mifeprex® (MIF-eh-prex)
(mifepristone)

Read this information carefully before taking Mifeprex* and misoprostol. It will help you understand how the treatment works. This MEDICATION GUIDE does not take the place of talking with your health care provider (provider).

What is Mifeprex?

Mifeprex is used to end an early pregnancy. It blocks a hormone needed for your pregnancy to continue. It is not approved for ending later pregnancies. Early pregnancy means it is 49 days (7 weeks) or less since your last menstrual period began. When you use Mifeprex (Day 1), you also need to take another medicine misoprostol, 2 days after you take Mifeprex (Day 3), to end your pregnancy. But, about 5-8 out of 100 women taking Mifeprex will need a surgical procedure to end the pregnancy or to stop too much bleeding.

What is the most important information I should know about Mifeprex?

What symptoms should I be concerned with? Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth. Prompt medical attention is needed in these circumstances. Serious infection has resulted in death in a very small number of cases; in most of these cases misoprostol was used in the vagina. There is no information that use of Mifeprex and misoprostol caused these deaths. If you have any questions, concerns, or problems, or if you are worried about any side effects or symptoms, you should contact your provider. Your provider's telephone number is _____.

Be sure to contact your provider promptly if you have any of the following:

Heavy Bleeding. Contact your provider right away if you bleed enough to soak through two thick full-size sanitary pads per hour for two consecutive hours or if you are concerned about heavy bleeding. In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical abortion/D&C) to stop it.

Abdominal Pain or "Feeling Sick". If you have abdominal pain or discomfort, or you are "feeling sick", including weakness, nausea, vomiting or diarrhea, with or without fever, more than 24 hours after taking misoprostol, you should contact your provider without delay. These symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

Fever. In the days after treatment, if you have a fever of 100.4°F or higher that lasts for more than 4 hours, you should contact your provider right away. Fever may be a symptom of a serious infection or another problem (including an ectopic pregnancy).

Take this MEDICATION GUIDE with you. When you visit an emergency room or a provider who did not give you your Mifeprex, you should give them your MEDICATION GUIDE so that

they understand that you are having a medical abortion with Mifeprex.

What to do if you are still pregnant after Mifeprex with misoprostol treatment. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy. There is a chance that there may be birth defects if the pregnancy is not ended.

Talk with your provider. Before you take Mifeprex, you should read this MEDICATION GUIDE and sign a statement (PATIENT AGREEMENT). You and your provider should discuss the benefits and risks of your using Mifeprex.

Who should not take Mifeprex?

Some women should not take Mifeprex. Do not take it if:

- It has been more than 49 days (7 weeks) since your last menstrual period began.
- You have an IUD. It must be taken out before you take Mifeprex.
- Your provider has told you that you have a pregnancy outside the uterus (ectopic pregnancy).
- You have problems with your adrenal glands (chronic adrenal failure).
- You take a medicine to thin your blood.
- You have a bleeding problem.
- You take certain steroid medicines.
- You cannot return for the next 2 visits.
- You cannot easily get emergency medical help in the 2 weeks after you take Mifeprex.
- You are allergic to mifepristone, misoprostol, or medicines that contain misoprostol, such as Cytotec or Arthrotec.

Tell your provider about all your medical conditions to find out if you can take Mifeprex. Also, tell your provider if you smoke at least 10 cigarettes a day.

How should I take Mifeprex?

- **Day 1 at your provider's office:**
  - Read this MEDICATION GUIDE.
  - Discuss the benefits and risks of using Mifeprex to end your pregnancy.
  - If you decide Mifeprex is right for you, sign the PATIENT AGREEMENT.
  - After getting a physical exam, swallow 3 tablets of Mifeprex.
- **Day 3 at your provider's office:**
  - If you are still pregnant, take 2 misoprostol tablets.
  - Misoprostol may cause cramps, nausea, diarrhea, and other symptoms. Your provider may send you home with medicines for these symptoms.
- **About Day 14 at your provider's office:**
  - This follow-up visit is very important. You must return to the provider about 14 days after you have taken Mifeprex to be sure you are well and that you are not pregnant.
  - Your provider will check whether your pregnancy has completely ended. If it has not ended, there is a chance that there may be birth defects. If you are still pregnant, your provider will talk with you about the other choices you have, including a surgical procedure to end your pregnancy.

What should I avoid while taking Mifeprex and misoprostol?

Do not take any other prescription or non-prescription medicines (including herbal medicines or supplements) at any time during the treatment period without first asking your provider about them because they may interfere with the treatment. Ask your provider about what medicines you can take for pain.

If you are breastfeeding at the time you take Mifeprex and misoprostol, discuss with your provider if you should stop breastfeeding for a few days.

What are the possible and reasonably likely side effects of Mifeprex?

Cramping and bleeding are expected with this treatment. Usually, these symptoms mean that the treatment is working. But sometimes you can get cramping and bleeding and still be pregnant. This is why you must return to your provider on Day 3 and about Day 14. See "How should I take Mifeprex?" for more information on when to return to your provider. If you are not already bleeding after taking Mifeprex, you probably will begin to bleed once you take misoprostol, the medicine you take on Day 3. Bleeding or spotting can be expected for an average of 9–16 days and may last for up to 30 days. Your bleeding may be similar to, or greater than, a normal heavy period. You may see blood clots and tissue. This is an expected part of ending the pregnancy.

Other common symptoms of treatment include diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. These side effects lessen after Day 3 and are usually gone by Day 14. Your provider will tell you how to manage any pain or other side effects.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

When should I begin birth control?

You can become pregnant again right after your pregnancy ends. If you do not want to become pregnant again, start using birth control as soon as your pregnancy ends or before you start having sexual intercourse again.

* * *

Medicines are sometimes prescribed for purposes other than those listed in a MEDICATION GUIDE. For more information, ask your provider for the information about Mifeprex that is written for health care professionals. Ask your provider if you have any questions.

This MEDICATION GUIDE has been approved by the U.S. Food and Drug Administration.

Rev 3: 4/22/09
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

M I F E P R E X®
(Mifepristone) Tablets, 200 mg

PRESCRIBER'S AGREEMENT

We are pleased that you wish to become a provider of Mifeprex* (Mifepristone) Tablets, 200 mg, which is indicated for the medical termination of intrauterine pregnancy through 49 days from the first day of the patient's last menstrual period (see full prescribing information). Prescribing Information, Mifeprex Medication Guides and PATIENT AGREEMENT forms will be provided together with your order of Mifeprex.

Prior to establishing your account and receiving your first order, you must sign and return this letter to the distributor, indicating that you have met the qualifications outlined below and will observe the guidelines outlined below. If you oversee more than one office facility, you will need to list each facility on your order form prior to shipping the first order.

By signing the reverse side, you acknowledge receipt of the PRESCRIBER'S AGREEMENT and agree that you meet these qualifications and that you will follow these guidelines for use. You also understand that if you do not follow these guidelines, the distributor may discontinue distribution of the drug to you.

Under Federal law, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.

- Ability to diagnose ectopic pregnancies.

- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the prescribing information of Mifeprex. The prescribing information is attached to this letter, and is also available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to these qualifications, you must provide Mifeprex in a manner consistent with the following guidelines.

- Under Federal law, each patient must be provided with a Medication Guide. You must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and PATIENT AGREEMENT, give her an opportunity to read and discuss them, obtain her signature on the PATIENT AGREEMENT, and sign it yourself.

- The patient's follow-up visit at approximately 14 days is very important to confirm that a complete termination of pregnancy has occurred and that there have been no complications. You must notify Danco Laboratories in writing as discussed in the Package Insert under the heading DOSAGE AND ADMINISTRATION in the event of an on-going pregnancy which is not terminated subsequent to the conclusion of the treatment procedure.

- While serious adverse events associated with the use of Mifeprex are rare, you must report any hospitalization, transfusion or other serious event to Danco Laboratories, identifying the patient solely by package serial number to ensure patient confidentiality.

- Each package of Mifeprex has a serial number. As part of maintaining complete records for each patient, you must record this identification number in each patient's record.

Danco Laboratories, LLC
P.O. Box 4816
New York, NY 10185
1-877-4 Early Option (1-877-432-7596)
www.earlyoptionpill.com
*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

ACCOUNT SETUP FORM

MIFEPREX™ (Mifepristone) Tablets, 200 mg; NDC 64875-001-03

To set up your account:

1. Read the Prescriber's Agreement on the back of this Account Setup Form.
2. Complete and sign this form.
3. Fax the completed Account Setup Form to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned in and are usually shipped within 24 hours.
6. Unopened, unused product may be returned for a refund or exchange up to a year after the expiration date.

Billing information

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Shipping information (❑ Check if same as above)

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

Additional site locations

I will also be prescribing Mifeprex* at these additional locations:

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

Request additional materials

❑ Medication Guides ❑ Patient Agreements

❑ State Abortion Guidelines ❑ Patient Brochures

Establishing your account (required only with first order)

Each facility purchasing Mifeprex must be included on this form (see additional site locations box above) before the distributor can ship the product. Please read the Prescriber's Agreement on the reverse of this form and sign below.

By signing below, you acknowledge receipt of the Prescriber's Agreement and agree that you meet these qualifications and that you will follow these guidelines for use.

Print Name _____ Signature _____

Medical License # _____ Date _____

Fax this completed Account Setup Form to the authorized distributor. Fax: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*Mifeprex is a trademark of Danco Laboratories, LLC.

MIFEPREX™
(Mifepristone) Tablets, 200 mg

Reference ID: 2957855

Mifeprex® (Mifepristone) Tablets, 200 mg

PATIENT AGREEMENT

Mifeprex* (mifepristone) Tablets

1. I have read the attached MEDICATION GUIDE for using Mifeprex and misoprostol to end my pregnancy.
2. I discussed the information with my health care provider (provider).
3. My provider answered all my questions and told me about the risks and benefits of using Mifeprex and misoprostol to end my pregnancy.
4. I believe I am no more than 49 days (7 weeks) pregnant.
5. I understand that I will take Mifeprex in my provider's office (Day 1).
6. I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3).
7. My provider gave me advice on what to do if I develop heavy bleeding or need emergency care due to the treatment.
8. Bleeding and cramping do not mean that my pregnancy has ended. Therefore, I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
9. I know that, in some cases, the treatment will not work. This happens in about 5 to 8 women out of 100 who use this treatment.
10. I understand that if my pregnancy continues after any part of the treatment, there is a chance that there may be birth defects. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about my choices, which may include a surgical procedure to end my pregnancy.
11. I understand that if the medicines I take do not end my pregnancy and I decide to have a surgical procedure to end my pregnancy, or if I need a surgical procedure to stop bleeding, my provider will do the procedure or refer me to another provider who will. I have that provider's name, address and phone number.
12. I have my provider's name, address and phone number and know that I can call if I have any questions or concerns.
13. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
14. I will do the following:

- contact my provider right away if in the days after treatment I have a fever of 100.4°F or higher that lasts for more than 4 hours or severe abdominal pain.
- contact my provider right away if I have heavy bleeding (soaking through two thick full-size sanitary pads per hour for two consecutive hours).
- contact my provider right away if I have abdominal pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting or diarrhea, more than 24 hours after taking misoprostol.
- take the MEDICATION GUIDE with me when I visit an emergency room or a provider who did not give me Mifeprex, so that they will understand that I am having a medical abortion with Mifeprex.
- return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant.
- return to my provider's office about 14 days after beginning treatment to be sure that my pregnancy has ended and that I am well.

Patient Signature: _____

Patient Name (print): _____

Date: _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for mifepristone.

Provider's Signature: _____

Name of Provider (print): _____

Date: _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record. Give a copy of the MEDICATION GUIDE to the patient.

Rev 2: 7/19/05
*Mifeprex is a registered trademark of Danco Laboratories, LLC.

Reference ID: 2957855
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 149 of 357

Exhibit I

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-014

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated September 16, 2008, received September 17, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for MIFEPREX® (mifepristone) Tablets. We note that NDA 020687 is approved under the provisions of 21 CFR 314.520 (Subpart H).

This supplemental application provides for a proposed risk evaluation and mitigation strategy (REMS) for MIFEPREX (mifepristone) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified MIFEPREX (mifepristone) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We acknowledge receipt of your amendments dated December 9, 2008, November 8, 2010, and May 19 and 27, 2011.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for MIFEPREX (mifepristone) to ensure the benefits of the drug outweigh the risks of serious complications by requiring prescribers to certify that they are qualified to prescribe MIFEPREX (mifepristone) and are able to assure patient access to appropriate medical facilities to manage any complications.

Your proposed REMS, as amended and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

The REMS assessment plan will include the information submitted to FDA on May 27, 2011, and should include the following information:

a. Per section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.
b. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify future submissions containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR NDA 020687
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

As part of the approval under Subpart H, as required by 21 CFR 314.550, you must submit all promotional materials, including promotional labeling as well as advertisements, at least 30 days

before the intended time of initial distribution of the labeling or initial publication of the advertisement. Send one copy to the (b) (6) and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

ENCLOSURES:
REMS Document
REMS Materials

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

(b) (6)

06/08/2011

Exhibit J

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020687/S-020

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your Supplemental New Drug Application (sNDA) dated May 28, 2015, received May 29, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated July 17, 2015.

This "Prior Approval" supplemental new drug application proposes to provide for use through 70 days gestation, revise the labeled dose and dosing regimen and modify the REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for pre-menarcheal patients because the use of this product before menarche is not indicated, and we have determined that you have fulfilled the pediatric study requirement for post-menarcheal patients.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Mifeprex (mifepristone) Tablets was originally approved on June 8, 2011. The REMS consisted of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS included revisions to both the prescriber and patient agreement forms.

Other changes proposed in the efficacy supplement prompted additional revisions to the Mifeprex REMS materials. During review of this efficacy supplement, we also assessed the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure that the drug's benefits outweigh the risks.

After consultations between the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE), we have determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS. The REMS modifications submitted by you on March 29, 2016 are approved.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Mifeprex outweigh its risks. The

Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, submitted on July 17, 2015, and appended to this letter, is approved as amended. The modified REMS consists of elements to assure safe use (A, C and D), an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS remains the same as that approved on June 8, 2011.

The REMS assessment plan will include the information submitted to FDA on March 29, 2016.

The revised REMS assessment plan must include, but is not limited to, the following:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative).
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support any proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit any future supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 158 of 357

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 159 of 357

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 020687 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 020687/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 160 of 357

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate: (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6) .

Sincerely,

{See appended electronic signature page}

(b) (6)
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 162 of 357

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 K

Risk Evaluation and Mitigation Strategy (REMS) Memorandum
REMS Modification

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
(b) (6)
(b) (6)

NDA: 020687
PRODUCT: Mifeprex (mifepristone) oral tablets
APPLICANT: Danco Laboratories (Danco)
FROM: (b) (6)
DATE: March 29, 2016

This memorandum provides the (b) (6) ((b) (6) review of the proposed modifications to the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) addressed in the (b) (6) ((b) (6) REMS Modification Review and Addendum to REMS Modification Review. A REMS for Mifeprex was approved on June 8, 2011, to ensure the benefits of the drug outweighed the risks of serious complications. The Mifeprex REMS consists of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Mifeprex was approved for the medical termination of an intrauterine pregnancy through 49 days of gestation on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H). It was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the 2007 Food and Drug Administration Amendments Act. A formal REMS proposal was submitted by Danco and approved on June 8, 2011. The goals and elements of the approved Mifeprex REMS are briefly summarized in Table 1 below.

Table 1. Summary of Mifeprex REMS[1]

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
	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.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex is dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient Agreement form that is to be placed in the patient's medical record. A copy of the Patient Agreement form and Medication Guide must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

[1] Source: The (b) (6) REMS Modification Review (NDA 20867/S-020, dated March 29, 2016), Table 1.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 165 of 357

On May 29, 2015, Danco submitted an efficacy supplement (S-020) that proposed modifications to the Mifeprex Prescribing Information and REMS. In the S-020 submission, Danco seeks the following major changes (among others):

- [redacted] dosing regimen of Mifeprex and misoprostol
- Extension of maximum gestational age from 49 days to 70 days
- Replacement of the term "licensed physician" with "[redacted] in the REMS Prescriber's Agreement form
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement form
- Revisions to the Patient Agreement form reflecting changes to the Prescribing Information

The proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials and also updating of the REMS materials to current format. During review of this efficacy supplement, we also evaluated the current REMS program to determine whether each Mifeprex REMS element remains necessary to ensure the drug benefits outweigh the risks. The Agency considered the recent [redacted] REMS Assessment review completed October 13, 2015, safety data gathered since drug approval in 2000, and experience from current clinical practice to support additional modifications to the Mifeprex REMS.

After consultations between the [redacted] and [redacted] and considering the [redacted] REMS Modification Review and Addendum to the REMS Modification Review, [redacted] has determined that the approved REMS for Mifeprex should be modified as follows:

1. Revisions to the Prescriber's Agreement form in addition to those proposed by the Applicant
2. Removal of the Medication Guide as a REMS element
3. Removal of the Patient Agreement form as a Documentation of Safe Use Condition (ETASU D)
4. Updating of REMS goals to reflect the above changes

We concur with [redacted] recommendation that the Prescriber's Agreement form should include other modifications to reflect current REMS standards and materials and also to reflect changes to align with approval of the efficacy supplement S-020, such as the dose and dose regimen and upper limit of gestational age.

In addition, we agree with Danco's proposed removal of the phrase "Under Federal Law," because of the lack of precedent for requiring such text and clinical rationale for its inclusion. As approvals and REMS are governed by Federal law, the phrase "Under Federal law" is unnecessary. Regarding Danco's proposal to replace "licensed physician," we have determined that the replacement term should be "licensed healthcare providers who prescribe," to include other practitioners who prescribe; in addition, this phrase is consistent with language in the statute.

We concur with [redacted] recommendation that the Medication Guide is no longer necessary as an element of the REMS to ensure the benefits of Mifeprex outweigh its risks. The Medication Guide will continue to be part of the approved labeling that must be provided to a patient in accordance with 21 CFR part 208. Like other labeling, Medication Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

In addition, we concur with [redacted] recommendation that the signed Patient Agreement form is no longer necessary and should be removed as a condition of safe use (ETASU D). Recent professional guidelines for women seeking surgical and medical abortion services emphasize comprehensive counseling, education about the risks of different treatments, and obtaining and documenting informed consent.[2,3] The National Abortion

[2] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

Reference ID: 3909589

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 166 of 357

Federation (NAF) clinical practice guidelines include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[4] Approximately (b)(4)% of the use of Mifeprex in the U.S. is through Planned Parenthood Federation of America (PPFA)- and NAF-affiliated members, where patient counseling and informed consent is standard of care. The practice of treating women with Mifeprex is well-established by these organizations and their associated providers who choose to provide this care to women. In addition, the Medication Guide, which must be provided to the patient under 21 CFR part 208, contains the same risk information contained in the Patient Agreement form.

The safety profile of Mifeprex is well-characterized and its risks well-understood after more than 15 years of marketing. Serious adverse events are rare and the safety profile of Mifeprex has not substantially changed.[5] The removal of the Medication Guide as a REMS element and of the Patient Agreement form is not expected to adversely impact the ability of the REMS to ensure that the drug benefits outweigh its risks. The benefit-risk balance of Mifeprex remains favorable in the presence of the following:

- Retention of ETASUs A and C in the Mifeprex REMS: The Prescriber's Agreement form required for prescriber certification under ETASU A will continue to require 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 by or under the supervision of a certified prescriber. This ensures that Mifeprex can only be dispensed by or under the direct supervision of a certified prescriber.

- Communication of risks through patient labeling: The Medication Guide, which will be retained as part of labeling, contains the same risk information covered under the Patient Agreement form. Under 21CFR 208.24, prescribers who dispense Mifeprex are required to provide the Medication Guide to patients. The Prescriber's Agreement form also reminds the prescriber to provide the Medication Guide to the patient.

- Information from published articles on established clinical practices: This information, including clinical guidelines and publications, indicates that comprehensive patient counseling and informed consent prior to medical or surgical abortion treatment is standard of care when using Mifeprex.

We have also determined that the information in the efficacy supplement supports changes to the goals of the Mifeprex REMS. We concur with (b) (6) recommendation that the REMS goals should be modified from:

A. To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.
B. To minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications.

to:

The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.

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[3] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 11, 2016

[4] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 11, 2016.

[5] (b) (6) Mifeprex Post-marketing Safety Review, dated August 20, 2015.

Reference ID: 3909589

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 167 of 357

b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.

The above REMS modifications and changes in goals were discussed with the (b) (6) and concurrence with these changes was obtained.

The modified Mifeprex REMS should consist of ETASU A, in which healthcare providers who prescribe Mifeprex will be certified, and ETASU C, in which Mifeprex will be dispensed only in certain health care settings (specially clinics, medical offices, and hospitals) by or under the supervision of a certified prescriber. The Mifeprex REMS will also include an implementation system, and a timetable for continued submission of assessments of the REMS.

Addendum:

On March 28, 2016, Dr. Janet Woodcock, the Director, Center for Drug Evaluation and Research, asked (b) (6) and (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 (b) (4), (b) (6) the Director, OSE, and (b) (6), to the Directors of (b) (6) and (b) (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, as described in the (b) (6) Addendum to REMS Modification Review.

Reference ID: 3909589

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 168 of 357

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/s/

(b) (6)

03/29/2016

Signing for (b) (6), (b) (6)

Exhibit L

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

(b) (6)

REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (4) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Subject:	Proposed REMS Modifications
Drug Name(s):	Mifeprex® (mifepristone)
Therapeutic class:	Progesterone-receptor modulator
Dosage forms:	200 mg tablets
(b) (6) Review Division:	(b) (6)
Application Type/Number:	NDA 020687, Supp 20
Applicant/sponsor:	Danco Laboratories
(b) (6) (b) (6) #:	2015-1719

Reference ID: 3909587
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 171 of 357

Table of Contents

1. INTRODUCTION 3
1.1 BACKGROUND 3
1.2 BRIEF SUMMARY OF KEY REGULATORY HISTORY 4
2. MATERIALS REVIEWED 4
3. OVERVIEW OF RATIONALE FOR proposed REMS MODIFICATIONS 5
4. Sponsor proposed modifications and Rationale 5
4.1. REMS ELEMENTS 5
4.1.1. Certification of Prescribers - ETASU A 5
4.1.1.1. Prescriber's Agreement 5
5. (b) (6) Proposed Modifications and Rationale 6
5.1. REMS ELEMENTS 6
5.1.1. Medication Guide 6
5.1.2. Certification of Prescribers - ETASU A 6
5.1.2.1. Prescriber's Agreement 6
5.1.3. Drug dispensed only in certain health care settings - ETASU C 7
5.1.4. Documentation of Safe Use Conditions - ETASU D 7
5.1.4.1. Patient Agreement 7
5.2. REMS DOCUMENT 8
5.2.1. GOALS 8
5.2.2. Medication Guide 9
5.2.3. Certification of Prescribers - ETASU A 9
5.2.4. Drug dispensed only in certain health care settings - ETASU C 9
5.2.5. Documentation of Safe Use Conditions -ETASU D 9
5.2.6. Implementation System 9
5.2.7. Timetable for Submission of Assessments 9
5.3. Assessment Plan 9
6. CONCLUSION 10
7. RECOMMENDATIONS 11
8. Appendix 11

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 172 of 357

1. INTRODUCTION

This review provides the [redacted] evaluation of the modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex proposed in the efficacy supplement submitted by Danco Laboratories (Danco) on May 29, 2015, and provides [redacted] recommendations to the [redacted] The approved REMS consists of a Medication Guide (MG), elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The evaluation of modifications to the approved REMS utilized input received from the [redacted][1], REMS assessment data, and a postmarketing summary report by the [redacted]

1.1 BACKGROUND

Mifeprex is a synthetic steroid with antiprogestational effects. The currently approved dose is three 200 mg oral tablets which are to be taken under the supervision of a physician for the medical termination of intrauterine pregnancy through 49 days gestation. Mifeprex was approved September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (Subpart H).[2] Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007. A formal REMS proposal was submitted by Danco and approved on June 8, 2011with a MG, ETASU, an implementation system and a timetable for submission of assessments. The goals and elements of the REMS are briefly summarized in Table 1 below.

Table 1. Summary of Currently Approved Mifeprex REMS

REMS Goals	To provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug.

[1] [redacted]

[2] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 173 of 357

	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.
REMS Elements	Medication Guide
	ETASU A – Special certification of healthcare providers (HCPs) who prescribe Mifeprex: Completion of Prescriber's Agreement form and enrollment in the REMS program.
	ETASU C – Mifeprex dispensed only in certain healthcare settings: It is only available to be dispensed in clinics, medical offices or hospitals, by or under the supervision of a specially certified prescriber. Mifeprex will not be distributed to or dispensed through retail pharmacies.
	ETASU D – Safe-use conditions: Patients must complete and sign the Patient's Agreement form that is to be placed in the patient's medical record. A copy of the Patient's Agreement form and MG must be provided to the patient.
Implementation System	Distributors of Mifeprex must be certified and agree to ship Mifeprex only to locations identified by certified prescribers. Distributors must agree to maintain secure and confidential records, as well as, follow all distribution guidelines concerning storage, shipments and controlled returns.

1.2 Brief Summary of Key Regulatory History

A brief summary of the key regulatory history relevant to the Mifeprex REMS is listed below:

September 28, 2000: Mifeprex is approved with restricted distribution and postmarketing commitments under 21 CFR 314.520 (Subpart H).

September 27, 2007: FDAAA enacted and Mifeprex is deemed to have a REMS.

June 8, 2011: Mifeprex REMS is approved, NDA 020687/S-014

June 1, 2012: REMS Assessment Report, Year 1

June 2, 2015: REMS Assessment Report, Years 2-4

May 29, 2015: Danco submitted PAS- 020 efficacy supplement

January 15, 2016: A (b) (6) meeting was held to discuss proposed revisions to the REMS which included revising the REMS goal and removal of the MG and Patient Agreement form as elements of the REMS.

2. MATERIALS REVIEWED

2.1 SUBMISSIONS

- Danco Laboratories, Prior Approval Efficacy Supplement and REMS Modification, PAS-020, received May 29, 2015 (paper submission)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Mifeprex approval letter, dated September 28, 2000
- (b) (6) Mifeprex PAS-014 approval letter, dated June 8, 2011
- (b) (6) Final deemed REMS Review for Mifeprex:, dated June 3, 2011
- (b) (6) Review of Year 1 REMS Assessment Report: dated August 1, 2012
- (b) (6) Review of Year 4 REMS Assessment Report: dated October 13, 2015

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 174 of 357

- (b) (6) Mifeprex Post-marketing Safety Review: dated August 20, 2015
- Addendum to (b) (6) Review of Year 4 REMS Assessment Report: dated March 29, 2016
- (b) (6) draft Clinical Review for Mifeprex, NDA 020687, PAS 20: dated March 29, 2016.

3. OVERVIEW OF RATIONALE FOR PROPOSED REMS MODIFICATIONS

On May 29, 2015, Danco submitted an efficacy prior approval supplement-020 (PAS-020) and REMS modification. In PAS-020, Danco is seeking approval of certain changes, including:

- Dosing of 200 mg orally x 1, instead of 600 mg orally x 1
- Extension of maximum gestational age
- Inclusion of misoprostol in the indication statement
- Inclusion of information regarding Pediatric Research Equity Act (PREA) data
- Replacement of the term "physician" with " (b) (4) in the PI and the REMS Prescriber's Agreement
- Removal of the phrase "Under Federal Law" from the REMS Prescriber's Agreement
- Revisions to the Patient Agreement Form to reflect proposed changes in the PI

The Sponsor's proposed changes in the efficacy supplement prompted revisions to the Mifeprex REMS materials. During review of the efficacy supplement and proposed REMS Modifications, (b) (6) evaluated the current REMS program to determine whether other changes were appropriate. As part of this evaluation, the review team took into consideration the recent (b) (6) review of the Mifeprex REMS Assessment completed on October 13, 2015, the addendum to the October 13, 2015 review completed on March 29, 2016, safety data gathered over the past 16 years since approval, and information regarding current clinical practice.[5,6,8,9]

Based on the available data and information, (b) (6) continues to believe that a REMS is necessary to ensure the benefits outweigh the risks; however, we recommend that some elements be modified or removed. All of the modifications in this review were discussed with (b) (6) The recommended modifications and supporting rationale for each are further described in Sections 4 and 5 below.

4. SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

4.1. REMS ELEMENTS

4.1.1. CERTIFICATION OF PRESCRIBERS - ETASU A

4.1.1.1. PRESCRIBER'S AGREEMENT

Danco is proposing two modifications to the Prescriber's Agreement form. The first proposal is to remove the phrase "Under Federal law" from the document. This phrase appears twice in the Prescriber's Agreement:

(1) *Under Federal law*, Mifeprex must be provided by or under the supervision of a physician who meets the following qualifications…
(2) *Under Federal law*, each patient must be provided with a Medication Guide.

Reference ID: 3909587
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 175 of 357

The Sponsor is proposing that the phrase be deleted from the beginning of the above sentences to be consistent with current REMS language.

Reviewer Comment: The review team agrees with this revision. The review team has determined that there is no precedent in other REMS for using the phrase, nor is there any clinical rationale for including it. As approvals are governed by Federal law, the review team concludes that the phrase "Under Federal law" is unnecessary in the Prescriber's Agreement.

The second proposed modification from Danco is to replace the word "physician" with "(b) (4) The Prescriber's Agreement currently reads: "Under Federal law, Mifeprex must be provided by or under the supervision of a *physician* who meets the following qualifications…" The Sponsor is proposing that the agreement read: "Mifeprex must be provided by or under the supervision of a (b) (4) who meets the following qualifications…"

Reviewer Comment: The review team agrees that the term "physician" should be replaced, but with the phrase "healthcare provider who prescribes." '(b) (4) . Mifeprex is a prescription medication and "healthcare providers who prescribe" accurately describes not only physicians but other healthcare providers, for example, nurse practitioners, certified nurse midwives and physician assistants, who may prescribe medications. Additionally, the phrase "healthcare provider who prescribes" is consistent with the language that is included in the statute.[3]

5. (b) (6) PROPOSED MODIFICATIONS AND RATIONALE

5.1. REMS ELEMENTS

5.1.1. MEDICATION GUIDE

FDA has generally been maintaining MGs as FDA-approved labeling but removing them from REMS when inclusion in REMS is not necessary to ensure that the benefits of a drug outweigh the risks. The Mifeprex MG, though an important tool for patient education that will continue to be distributed to patients, does not need to be an element of the REMS to ensure the benefits outweigh the risks for Mifeprex. The MG will remain part of labeling and will still be required to be distributed to the patient as per 21 CFR part 208. This approach is consistent with ongoing efforts to streamline REMS by allowing for changes to a MG without the need for a REMS modification.

5.1.2. CERTIFICATION OF PRESCRIBERS - ETASU A

5.1.2.1. PRESCRIBER'S AGREEMENT

Per the current Mifeprex REMS, a Prescriber's Agreement is required to be completed, signed and faxed to the distributor to complete enrollment. The review team is recommending

[3] FDCA 505-1(f)(3)(A).

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 176 of 357

changing the name of the form from "Prescriber's Agreement" to "Prescriber Agreement Form" to be consistent with the terminology used in other similar REMS Programs. The term *"physician"* should be replaced, as proposed by the Sponsor. However the review team recommends the phrase "*healthcare provider who prescribes*" in lieu of the Sponsor proposed "(b) (4) to more closely reflect the statutory provision, and to align with this revision in the Mifeprex Prescribing Information (PI), which was based on information in the supplement.[4] Additional changes are intended to improve the flow of the document. See the appended, redlined document for further details.

Consistent with the labeling revisions in the efficacy supplement, the language in the Prescriber Enrollment Form about the gestational age should be changed to match the labeling being approved.

5.1.3. DRUG DISPENSED ONLY IN CERTAIN HEALTH CARE SETTINGS - ETASU C

No changes to ETASU C are proposed.

5.1.4. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

5.1.4.1. PATIENT AGREEMENT

Per the Mifeprex REMS, a Patient Agreement form is required to be signed and placed in the patient's medical record as documentation of safe use conditions for Mifeprex. The review team recommends removal of the Patient Agreement form from the Mifeprex REMS. This recommendation is based in part on the fact that the current Patient Agreement is duplicative of the informed consent and counseling processes that take place in the US, consistent with medical standard of care and current clinical practice guidelines for abortion providers.[5,6,7] For example, the National Abortion Federation (NAF) clinical practice guidelines state that "obtaining informed consent and assessing that the decision to have an abortion is made freely by the patient are essential parts of the abortion process." The NAF guidelines also include a standard stating that documentation must show that the patient affirms that she understands the procedure and its alternatives, the potential risks and benefits, and that her decision is voluntary.[6] The NAF is a professional association; a condition of membership requires periodic quality assurance site visits, and members must agree to adhere to the Clinical Policy Guidelines published by the NAF.[7] When healthcare providers at NAF affiliated facilities were surveyed, between 96 and 99% of healthcare providers indicated they provided patient counseling and obtained and documented informed consent.[8,9] The review team is aware that

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[4] (b) (6) draft Clinical Review for Mifeprex (NDA 020687) PAS 20. Dated: March 29, 2016

[5] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[6] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf on March 9, 2016.

[7] National Abortion Federation Membership information accessed on the internet at http://prochoice.org/health-care-professionals/naf-membership/ on March 9, 2016

[8] Gould H, Perrucci A, Barar R, Sinkford D, Foster D. Patient Education and Emotional Support Practices in Abortion Care Facilities in the United States. Women's Health Issues 2012; 22-4; 359-364

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 177 of 357

Planned Parenthood of America has informed consent forms describing the risks associated with medical abortions. The NAF affiliated members and Planned Parenthood of America facilities account for (b) (4)% of Mifeprex use.

The information in the Mifeprex REMS Patient Agreement form is duplicative of the informed consent process that is followed and documented by these providers, who also provide abortion counseling and education about adverse events. Additionally, the MG, which is required to be provided under 21 CFR 208, contains the same risk information addressed in the Patient Agreement form and will be provided at the time the medication is dispensed to the patient. Based on this information, the Patient Agreement form is not necessary to ensure the benefits outweigh the risks of Mifeprex.

Finally, the U.S. marketing history of Mifeprex spans over fifteen years. During this period of surveillance, the safety profile of Mifeprex has been well-characterized, and serious adverse events have rarely occurred. [10,11,12]

5.2. REMS DOCUMENT

The REMS document is being revised to reflect the changes described above as well as to reflect the Agency's current thinking on the language and flow in REMS documents. The changes to the different sections of the REMS document are described further below. For additional details, see the redlined and clean REMS document appended to this review.

5.2.1. GOALS

The review team is recommending modification of the Mifeprex REMS goals. Currently the goals are (A) to provide information to patients about the benefits and risks of Mifeprex before they make a decision whether to take the drug and (B) to minimize the risk of serious complications by requiring prescribers to certify that they are qualified to prescribe Mifeprex and are able to assure patient access to appropriate medical facilities to manage any complications. Since (b) (6) is recommending removal of the Patient Agreement from the REMS, (b) (6) recommends revising the REMS goals to reflect this change. The revised goal is to ensure that prescribers are aware of the risks of serious complications associated with the use of Mifeprex and that it can only be dispensed in certain health care settings. The goal would be modified to read:

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[9] O'Connell K, Jones HE, Simon M, Saporta V, Paul M, Lichtenberg ES. First trimester surgical abortion practices: a survey of National Abortion Federation members. Contraception 2009; 79:385-392

[10] (b) (6) ((b) (6) Mifeprex Post-marketing Safety Review: (b) (6), dated August 20, 2015

[11] ACOG. Medical management of first trimester abortion. ACOG Practice Bulletin #143. Obstetrics and Gynecology 2014; 123(3):676-692

[12] National Abortion Federation Clinical Policy Guidelines (for abortion care). Revised 2015 edition, 56 pages, accessed on the internet at http://prochoice.org/wp-content/uploads/2015_NAF_CPGs.pdf

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 178 of 357

"The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.
b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber."

5.2.2. MEDICATION GUIDE

(b) (6) recommends this element be removed from the REMS document. See Section 5.1.1 for rationale.

5.2.3. CERTIFICATION OF PRESCRIBERS - ETASU A

The language in the REMS document stating that certified prescribers must obtain a completed Patient Agreement form from the patient is recommended to be removed (see Section 5.1.2.1 for rationale). In addition, edits to align the REMS document with language in the revised PI are being made. Finally, we recommend that this section of the REMS document be revised and edited to reflect the Agency's current thinking on the most appropriate language and flow of REMS documents. However, the requirement for Prescriber Certification remains and the qualifications of a healthcare provider who prescribes Mifeprex have not changed and continue to be necessary to ensure the benefits outweigh the risks.

5.2.4. DRUG DISPENSED ONLY IN CERTAIN HEALTH CARE SETTINGS - ETASU C

This section of the REMS was edited to provide clarification on where Mifeprex will not be dispensed.

In addition, the REMS document was revised and edited to reflect (b) (6) current thinking on the language and flow of REMS documents. These changes are not intended to be substantive.

5.2.5. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

This element is being recommended for removal from the REMS document. See section 5.1.4.1 for rationale.

5.2.6. IMPLEMENTATION SYSTEM

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.2.7. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

This section of the REMS document is proposed to be revised and edited to reflect the Agency's current thinking on the language and flow of REMS documents.

5.3. ASSESSMENT PLAN

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 179 of 357

Currently, the REMS Assessment Plan requires Danco to submit the following adverse event information as part of the periodic REMS Assessment Report:

> 6. Copies of MedWatch forms for each of the following adverse events during the assessment period; and for each of the following adverse events, the cumulative number from the date of approval of Mifeprex up to the approval date of the REMS, the number for each reporting period, and the cumulative number since the approval date of Mifeprex:
>
> a. On-going pregnancies not terminated subsequent to the conclusion of the treatment procedure
> b. Women hospitalized due to complications
> c. Women requiring transfusion(s) of two or more units of packed cells or whole blood, or having a hemoglobin of 6 gm/dL or less or a hematocrit of 18% or less
> d. Serious infection, sepsis
> e. Death
> f. Other serious and unexpected adverse events
>
> 7. Per section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue.

This information is being submitted to the Agency through other pathways including spontaneous adverse event reporting and the annual report. Therefore, (b) (6) is recommending it be removed from the Assessment Plan.

The revised Assessment Plan is as follows:

REMS Assessment Plan

1. Number of prescribers enrolled (cumulative)
2. Number of new prescribers enrolled during reporting period
3. Number of prescribers ordering Mifeprex during reporting period
4. Number of healthcare providers who attempted to order Mifeprex who were not enrolled; describe actions taken (during reporting period and cumulative)
5. Number of women exposed to Mifeprex (during reporting period and cumulative)
6. Summary and analysis of any program deviations and corrective action taken
7. Based on the information reported, an assessment and analysis of whether the REMS is meeting its goals and whether modifications to the REMS are needed

6. CONCLUSION

A REMS for Mifeprex is necessary to ensure that the benefits outweigh the risks. The review team and Sponsor have proposed modifications that continue to ensure that the benefit outweighs the risk, while updating the REMS in light of current medical practice and to provide clarifying language in the REMS documents.

The modifications to the Mifeprex REMS include the sponsor's proposed modifications and additional changes recommended by the review team and include the following: revision of the REMS goals, removal of the MG (it will remain as part of labeling) and the Patient Agreement; and changes to the Prescriber Enrollment Form.

Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 180 of 357

7. RECOMMENDATIONS

(b) (6) recommends the changes in the attached, redlined REMS document and materials, which represent (b) (6) proposed changes to the REMS as a result of this REMS Modification Review.

8. APPENDIX

1. Prescriber Enrollment Form, redlined
2. Prescriber Enrollment Form, clean
3. REMS Document, redlined
4. REMS Document, clean

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Reference ID: 3909587

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 181 of 357

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/s/

(b) (6)

03/29/2016

(b) (6)

03/29/2016

Concur

Exhibit M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

(b) (6)

(b) (6)

ADDENDUM TO REMS MODIFICATION REVIEW

Date:	March 29, 2016
Reviewer:	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
(b) (6)	(b) (6) (b) (6)
Subject:	Proposed REMS Modifications
Drug Name(s):	Mifeprex® (mifepristone)
Therapeutic class:	Progesterone-receptor modulator
Dosage forms:	200 mg tablets
(b) (6) Review Division:	(b) (6)
Application Type/Number:	NDA 020687, Supp 20
Applicant/sponsor:	Danco Laboratories
(b) (6) (b) (6) #:	2015-1719

1.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 184 of 357

INTRODUCTION

This review is an addendum to the [redacted] March 29, 2016, REMS Modification Review regarding modifications to the risk evaluation and mitigation strategy (REMS) for Mifeprex, as proposed by Danco Laboratories in the amendment to the prior approval efficacy supplement 020 (PAS-20). See the March 29, 2016, REMS Modification Review for a description of the original submission and the existing REMS, and the materials informing our review.

In addition to those materials, we considered additional communications with the sponsor which included proposed changes to the REMS and REMS materials on March 21, 25, 27, 28 and 29th. We also considered a memorandum dated March 28, 2016 from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, requesting that [redacted] 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 [redacted] This review addresses the sponsor's proposed changes as well as the changes that are needed in the REMS to reflect the fact that the Patient Agreement Form will be retained as part of the REMS.

This addendum will only describe changes that were recommended and that were not covered in the original REMS Modification Review. The changes we have agreed to were proposed to the sponsor and were accepted.

As with the original REMS modification review, all of the modifications discussed in this review were discussed with [redacted] and they are in agreement.

2. [redacted] AND SPONSOR PROPOSED MODIFICATIONS AND RATIONALE

2.1. REMS ELEMENTS

2.1.1. DOCUMENTATION OF SAFE USE CONDITIONS - ETASU D

2.1.1.1. PATIENT AGREEMENT FORM

As discussed above, it has been determined that the Mifeprex REMS should continue to include a Patient Agreement Form as ETASU D in the REMS. Therefore, the *Patient Agreement Form* is being revised as part of this modification.

The content has been modified to reflect the changes to the Prescribing Information that are being approved as part of the approval of PAS 020. These changes include changing the dosing regimen, updating the percentage of patients for which the treatment will not be effective, revising where Mifeprex or misoprostol should be taken and revising the patient follow-up recommendations after taking Mifeprex.

The requirement for a patient to read the MG has been removed since we are recommending that the MG be removed as an element of the REMS.[1] However, the MG will remain part of labeling

[1] [redacted] REMS Modification Review for Mifeprex, dated March 29, 2016.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 185 of 357

and will still be required to be distributed to the patient as per 21 CFR part 208. In addition, certified HCPs will have agreed to provide a MG to the patient before providing Mifeprex.

Additionally, the reference to birth defects should be removed because the effects of Mifeprex on an ongoing pregnancy are unknown. Lastly, the attestation that the patient believes she is no more than a certain number of weeks pregnant should be removed. The Prescriber is responsible for accurately dating the pregnancy. Therefore, the patient should not be relied upon to date her own pregnancy.

2.2. REMS DOCUMENT

2.2.1. GOALS

As discussed in the REMS Modification Review dated March 29, 2016, the Mifeprex REMS goals should be modified. As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form, which is an ETASU D (documentation of safe use) requirement (see Section 4.1.1). Therefore, the goal of the REMS also should include objective c) below in underlined text.

> The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:
>
> a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.
> b) Ensuring that Mifeprex is only dispensed in certain health care settings under the supervision of a certified prescriber.
> c) Informing patients about the risk of serious complications associated with Mifeprex

(b) (4) The REMS goal should include the risks to be mitigated by the REMS. The phrase "risk of serious complications" was taken from the previously approved REMS document and continues to be applicable. (b) (6) recommends keeping the risks in the goal.

2.2.2. CERTIFICATION OF PRESCRIBERS - ETASU A

As discussed above, it has been determined that the Mifeprex REMS should continue to include the Patient Agreement Form. Therefore, ETASU A in the REMS document needs to be revised to reinsert information regarding this requirement. First, as was the case in the previously approved REMS document, certified prescribers must agree to review the Patient Agreement Form with the patient and answer any of her questions. Additionally, the prescriber must agree to sign the Patient Agreement Form and obtain the patient's signature on the form. Finally, the prescriber must agree to provide the patient with a copy of the Patient Agreement Form and insert a copy in the patient's chart. See redlined, attached REMS document.

In its March 21, 2016, submission, the Sponsor disagrees with changing the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form* because "enrollment" may be misconstrued by prescribers to mean they are being placed on a list or database. (b) (6) agrees

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 186 of 357

with the Sponsor's concern about using the term "Enrollment" in the title and proposes to change the name of the *Prescriber's Agreement* to the *Prescriber Agreement Form*. This has been reflected in the REMS document and the *Prescriber Agreement Form.*

The second proposed revision by the Sponsor applies to the qualifications of a certified prescriber. The REMS document currently states that prescribers must have the "ability to assess the duration of pregnancy accurately." Danco is proposing [redacted] (b) (4) have concluded that not all practitioners are able to accurately assess gestational age. This ability is necessary for the safe use of Mifeprex.

In its March 21, 2016, submission, the Sponsor additionally proposed to insert "a non-identifiable reference" into the following statement in the REMS document and the *Prescriber Agreement Form* because it would increase the Sponsor's ability to track these adverse events. In addition, they stated that it is current practice for certified HCPs to provide this information. Danco also proposed removing "solely" from the statement, as shown below:

> Report any deaths to Danco Laboratories, identifying the patient ~~solely~~ by a non-identifiable reference and the serial number from each package of Mifeprex.

(b) (6) agreed with the above revisions. Lastly, the Sponsor proposed the following revised language in the REMS document and the Prescriber Agreement Form:

> …explain the risks (b) (4) of the ~~procedure, its effects, and the risks associated with~~ Mifeprex treatment regimen.

(b) (6) rejected the addition of (b) (4) to the REMS document and Prescriber Agreement Form. A REMS should only focus on the risks of a drug. Therefore, (b) (6) proposed that the final language be as follows:

> …explain the risks of the Mifeprex treatment regimen.

Additional minor edits and revisions were suggested for this section of the REMS document and corresponding language within the *Prescriber Agreement Form*. These changes were not intended to be substantive.

2.2.3. DOCUMENTATION OF SAFE USE CONDITIONS -ETASU D

As discussed above, it has been determined that the Mifeprex REMS should retain the Patient Agreement Form. Therefore, (b) (6) has proposed to insert the following text into the Mifeprex REMS document:

> 3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.
>
> a. The patient must sign a *Patient Agreement Form* indicating that she has:
>
> i. Received, read and been provided a copy of the *Patient Agreement Form*.
>
> ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 187 of 357

2.2.4. IMPLEMENTATION SYSTEM

In its March 21, 2016, submission, the Sponsor proposed to [redacted] (b) (4)

a. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

b. Complete the healthcare provider certification process upon receipt of the *Prescriber Enrollment Form.*

c. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

[redacted] (b) (6) [redacted] (b) (4). These are separate actions the distributor undertakes. Therefore, they should be described in the REMS document. Furthermore, it is not guaranteed that when a healthcare provider submits the *Prescriber Agreement Form*, they are ordering Mifeprex. In this situation, it is important that HCPs be notified when they are certified and, therefore, able to order Mifeprex in the future.

Lastly, [redacted] (b) (6) proposed to move the adverse event reporting requirements from the assessment to the implementation system of the REMS and to remove the requirement to report certain specifically enumerated adverse events such as all hospitalizations due to complications and women requiring transfusions, but retain the requirement to report all deaths. The following language was inserted:

"Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under the FDA regulations."

3. CONCLUSION

The review team and Sponsor have proposed additional modifications that continue to ensure that the benefit outweighs the risk for Mifeprex. This addendum addresses modifications to the REMS including those proposed by the sponsor in its March 21, 25, 27, 28 and 29, 2016, submissions, and additional changes recommended by [redacted] (b) (6) The additional changes include the following: reinsertion of the Prescriber Agreement Form (ETASU D) with certain changes to other documents to reflect this, and modification of the REMS goal, REMS document and appended materials provided to the Sponsor on March 17, 2016.

As discussed above, several changes to the language in the REMS document were proposed by Danco. The [redacted] (b) (4) were rejected by [redacted] (b) (6) The Sponsor additionally expressed their desire to not change the name of the *Prescriber's Agreement* to the *Prescriber Enrollment Form,* as suggested by the review team. In consideration of this, [redacted] (b) (6) proposes to change the title to the *Prescriber Agreement Form.*

The above changes to the REMS document and materials are appropriate modifications to the Mifeprex REMS. They are necessary to ensure that that the risks of serious complications will be mitigated and that the benefits of Mifeprex will continue to outweigh the risks.

4. RECOMMENDATIONS

The proposed amended modification submitted by Danco on March 29, 2016 is acceptable and (b) (6) recommends approval of the REMS.

Appendix

1. Prescriber Enrollment Form, clean
2. Patient Agreement Form, clean
3. REMS Document, clean

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 189 of 357

Initial REMS approval: 06/2011
Most recent modification: 03/2016

NDA 020687 MIFEPREX® (mifepristone) Tablets, 200 mg

Antiprogestational Synthetic Steroid

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with Mifeprex

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe Mifeprex must be specially certified.

   a. To become specially certified to prescribe Mifeprex, healthcare providers must:

      i. Review the Prescribing Information for Mifeprex.

      ii. Complete the *Prescriber Agreement Form*. By signing the *Prescriber Agreement Form*, prescribers agree that:

         1) They have the following qualifications:

            a) Ability to assess the duration of pregnancy accurately

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 190 of 357

b) Ability to diagnose ectopic pregnancies
c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

2) They will follow the guidelines for use of Mifeprex (see b.i-v below).

b. As a condition of certification, healthcare providers must follow the guidelines for use of Mifeprex described below:

i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
iv. Place the signed *Patient Agreement Form* in the patient's medical record.
v. Record the serial number from each package of Mifeprex in each patient's record.
vi. Report any deaths to Danco Laboratories, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex.

c. Danco Laboratories must:

i. Ensure that healthcare providers who prescribe Mifeprex are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
ii. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form*
- *Patient Agreement Form*

2. Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Danco Laboratories must:

i. Ensure that Mifeprex is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that Mifeprex is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.

a. The patient must sign a *Patient Agreement Form* indicating that she has:
   i. Received, read and been provided a copy of the *Patient Agreement Form*.
   ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

B. Implementation System

1. Danco Laboratories must ensure that Mifeprex is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

   a. Ensuring that distributors who distribute Mifeprex comply with the program requirements for distributors. The distributors must:

      i. Put processes and procedures in place to:

         a. Complete the healthcare provider certification process upon receipt of the *Prescriber Agreement Form.*

         b. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

         c. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

         d. Not ship Mifeprex to prescribers who become de-certified from the Mifeprex Program.

         e. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who (1) attempt to order Mifeprex and are not yet certified, or (2) inquire about how to become certified.

      ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of Mifeprex.

      iii. Train all relevant staff on the Mifeprex REMS Program requirements.

      iv. Comply with audits by Danco Laboratories, FDA or a third party acting on behalf of Danco Laboratories or FDA to ensure that all processes and procedures are in place and are being followed for the Mifeprex REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

   b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of Mifeprex.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 192 of 357

2. Danco Laboratories must monitor distribution data to ensure compliance with the REMS Program.

3. Danco Laboratories must audit new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifeprex REMS Program. Danco Laboratories will take steps to address distributor compliance if noncompliance is identified.

4. Danco Laboratories must take reasonable steps to improve implementation of and compliance with the requirements of the Mifeprex REMS Program based on monitoring and assessment of the Mifeprex REMS Program.

5. Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

Danco Laboratories must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (06/08/2011) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco Laboratories must submit each assessment so that it will be received by the FDA on or before the due date.

APPEARS THIS WAY ON ORIGINAL

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 193 of 357

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To set up your account to receive Mifeprex, you must:
1. complete, 2. sign, and 3. fax page 2 of this form to the distributor.

If you will be ordering for more than one facility, you will need to list each facility on your order form before the first order will be shipped to the facility.

Prescriber Agreement: By signing page 2 of this form, you agree that you meet the qualifications below and will follow the guidelines for use. You also understand that if you do not follow the guidelines, the distributor may stop shipping Mifeprex to you.

Mifeprex must be provided by or under the supervision of a healthcare provider who prescribes and meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of Mifeprex. The Prescribing Information is available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of Mifeprex in each patient's record.
- Report deaths to Danco Laboratories, identifying the patient by a non-identifiable patient reference and the serial number from each package of Mifeprex.

ACCOUNT SETUP MIFEPREX® (Mifepristone) Tablets, 200 mg; NDC 64875-001-01

TO SET UP YOUR ACCOUNT:

1. Read the Prescriber Agreement on page 1 of this form.
2. Complete and sign this form.
3. Fax this page to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned or faxed and are usually shipped within 24 hours.

Mifeprex® (Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

BILLING INFORMATION

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

SHIPPING INFORMATION ☐ *Check if same as above*

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

ADDITIONAL SITE LOCATIONS *I will also be prescribing Mifeprex* at these additional locations:*

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

REQUEST ADDITIONAL MATERIALS

☐ **Medication Guides** ☐ **State Abortion Guides** ☐ **Patient Brochures** ☐ **Patient Agreement Form**

ESTABLISHING YOUR ACCOUNT *(required only with first order)*

Each facility purchasing Mifeprex must be included on this form (*see additional site locations box above*) before the distributor can ship the product to the facility.

By signing below, you agree that you meet the qualifications and that you will follow the guidelines for use on page 1 of the Prescriber Agreement.

Print Name _____ Signature _____

Medical License # _____ Date _____

FAX THIS COMPLETED FORM TO THE AUTHORIZED DISTRIBUTOR. FAX: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

PATIENT AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of Mifeprex*. Both you and the patient must sign this form.*

Patient Agreement:

1. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take Mifeprex on Day 1.
   b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex.
3. My healthcare provider has talked with me about the risks including:
   - heavy bleeding
   - infection
   - ectopic pregnancy (a pregnancy outside the womb)
4. I will contact the clinic/office right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - severe stomach area (abdominal) pain
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - stomach pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
5. My healthcare provider has told me that these symptoms could require emergency care. If I cannot reach the clinic or office right away my healthcare provider has told me who to call and what to do.
6. I should follow up with my healthcare provider about 7 to 14 days after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
7. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
8. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
9. I have the MEDICATION GUIDE for Mifeprex. I will take it with me if I visit an emergency room or a healthcare provider who did not give me Mifeprex so that they will understand that I am having a medical abortion with Mifeprex.
10. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for Mifeprex.

Provider's Signature: _____ **Name of Provider (print):** _____ **Date:** _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record.

03/2016

Reference ID: 3909588

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

DANCO

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

(b) (6)

03/29/2016

Concur

Exhibit N

Initial REMS approval: 06/2011
Most recent modification: 03/2016

NDA 020687 MIFEPREX® (mifepristone) Tablets, 200 mg

Antiprogestational Synthetic Steroid

Danco Laboratories, LLC
PO Box 4816
New York, NY 10185

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the Mifeprex REMS is to mitigate the risk of serious complications associated with Mifeprex by:

a) Requiring healthcare providers who prescribe Mifeprex to be certified in the Mifeprex REMS Program.

b) Ensuring that Mifeprex is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber.

c) Informing patients about the risk of serious complications associated with Mifeprex

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe Mifeprex must be specially certified.

   a. To become specially certified to prescribe Mifeprex, healthcare providers must:

      i. Review the Prescribing Information for Mifeprex.

      ii. Complete the *Prescriber Agreement Form*. By signing the *Prescriber Agreement Form*, prescribers agree that:

         1) They have the following qualifications:

            a) Ability to assess the duration of pregnancy accurately

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 199 of 357

b) Ability to diagnose ectopic pregnancies
c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

2) They will follow the guidelines for use of Mifeprex (see b.i-v below).

b. As a condition of certification, healthcare providers must follow the guidelines for use of Mifeprex described below:

i. Review the *Patient Agreement Form* with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
ii. Sign the *Patient Agreement Form* and obtain the Patient's signature on the *Form*
iii. Provide the patient with a copy of the *Patient Agreement Form* and Medication Guide.
iv. Place the signed *Patient Agreement Form* in the patient's medical record.
v. Record the serial number from each package of Mifeprex in each patient's record.
vi. Report any deaths to Danco Laboratories, identifying the patient by a non-identifiable reference and the serial number from each package of Mifeprex.

c. Danco Laboratories must:

i. Ensure that healthcare providers who prescribe Mifeprex are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements
ii. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Prescriber Agreement Form*
- *Patient Agreement Form*

2. Mifeprex must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

a. Danco Laboratories must:

i. Ensure that Mifeprex is available to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber.

ii. Ensure that Mifeprex is not distributed to or dispensed through retail pharmacies or other settings not described above.

3. Mifeprex must be dispensed to patients with evidence or other documentation of safe use conditions.

a. The patient must sign a *Patient Agreement Form* indicating that she has:
   i. Received, read and been provided a copy of the *Patient Agreement Form*.
   ii. Received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

B. Implementation System

1. Danco Laboratories must ensure that Mifeprex is only distributed to clinics, medical offices and hospitals by or under the supervision of a certified prescriber by:

   a. Ensuring that distributors who distribute Mifeprex comply with the program requirements for distributors. The distributors must:

      i. Put processes and procedures in place to:

         a. Complete the healthcare provider certification process upon receipt of the *Prescriber Agreement Form.*

         b. Notify healthcare providers when they have been certified by the Mifeprex REMS Program.

         c. Ship Mifeprex only to clinics, medical offices, and hospitals identified by certified prescribers in the signed *Prescriber Agreement Form*.

         d. Not ship Mifeprex to prescribers who become de-certified from the Mifeprex Program.

         e. Provide the Prescribing Information and *Prescriber Agreement Form* to healthcare providers who (1) attempt to order Mifeprex and are not yet certified, or (2) inquire about how to become certified.

      ii. Put processes and procedures in place to maintain a distribution system that is secure, confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, proof of delivery and controlled returns of Mifeprex.

      iii. Train all relevant staff on the Mifeprex REMS Program requirements.

      iv. Comply with audits by Danco Laboratories, FDA or a third party acting on behalf of Danco Laboratories or FDA to ensure that all processes and procedures are in place and are being followed for the Mifeprex REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

   b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of Mifeprex.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 201 of 357

2. Danco Laboratories must monitor distribution data to ensure compliance with the REMS Program.

3. Danco Laboratories must audit new distributors within 90 calendar days after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifeprex REMS Program. Danco Laboratories will take steps to address distributor compliance if noncompliance is identified.

4. Danco Laboratories must take reasonable steps to improve implementation of and compliance with the requirements of the Mifeprex REMS Program based on monitoring and assessment of the Mifeprex REMS Program.

5. Danco Laboratories must report to FDA any death associated with Mifeprex whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

Danco Laboratories must submit REMS assessments to FDA one year from the date of the initial approval of the REMS (06/08/2011) and every three years thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Danco Laboratories must submit each assessment so that it will be received by the FDA on or before the due date.

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To set up your account to receive Mifeprex, you must:
1. complete, 2. sign, and 3. fax page 2 of this form to the distributor.

If you will be ordering for more than one facility, you will need to list each facility on your order form before the first order will be shipped to the facility.

Prescriber Agreement: By signing page 2 of this form, you agree that you meet the qualifications below and will follow the guidelines for use. You also understand that if you do not follow the guidelines, the distributor may stop shipping Mifeprex to you.

Mifeprex must be provided by or under the supervision of a healthcare provider who prescribes and meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of Mifeprex. The Prescribing Information is available by calling our toll free number, 1-877-4 Early Option (1-877-432-7596), or logging on to our website, www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Review the Patient Agreement Form with the patient and fully explain the risks of the Mifeprex treatment regimen. Answer any questions the patient may have prior to receiving Mifeprex.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of Mifeprex in each patient's record.
- Report deaths to Danco Laboratories, identifying the patient by a non-identifiable patient reference and the serial number from each package of Mifeprex.

ACCOUNT SETUP MIFEPREX® (Mifepristone) Tablets, 200 mg; NDC 64875-001-01

TO SET UP YOUR ACCOUNT:

1. Read the Prescriber Agreement on page 1 of this form.
2. Complete and sign this form.
3. Fax this page to the Danco distributor at 1-866-227-3343. Your account information will be kept strictly confidential.
4. The distributor will call to finalize your account setup and take your initial order.
5. Subsequent orders may be phoned or faxed and are usually shipped within 24 hours.

Mifeprex® (Mifepristone) Tablets, 200 mg
THE ORIGINAL EARLY OPTION PILL

BILLING INFORMATION

Bill to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

SHIPPING INFORMATION ☐ *Check if same as above*

Ship to Name _____

Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Attention _____

ADDITIONAL SITE LOCATIONS *I will also be prescribing Mifeprex* at these additional locations:*

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

Name _____ Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____

(Any additional sites may be listed on an attached sheet of paper.)

REQUEST ADDITIONAL MATERIALS

☐ **Medication Guides** ☐ **State Abortion Guides** ☐ **Patient Brochures** ☐ **Patient Agreement Form**

ESTABLISHING YOUR ACCOUNT *(required only with first order)*

Each facility purchasing Mifeprex must be included on this form (*see additional site locations box above*) before the distributor can ship the product to the facility.

By signing below, you agree that you meet the qualifications and that you will follow the guidelines for use on page 1 of the Prescriber Agreement.

Print Name _____ Signature _____

Medical License # _____ Date _____

FAX THIS COMPLETED FORM TO THE AUTHORIZED DISTRIBUTOR. FAX: 1-866-227-3343

Please fax any questions to the above number or call 1-800-848-6142.

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

PATIENT AGREEMENT FORM

Mifeprex® (Mifepristone) Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of Mifeprex*. Both you and the patient must sign this form.*

Patient Agreement:

1. I have decided to take Mifeprex and misoprostol to end my pregnancy and will follow my provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   a. I will take Mifeprex on Day 1.
   b. My provider will either give me or prescribe for me the misoprostol tablets which I will take 24 to 48 hours after I take Mifeprex.
3. My healthcare provider has talked with me about the risks including:
   - heavy bleeding
   - infection
   - ectopic pregnancy (a pregnancy outside the womb)
4. I will contact the clinic/office right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - severe stomach area (abdominal) pain
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - stomach pain or discomfort, or I am "feeling sick", including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
5. My healthcare provider has told me that these symptoms could require emergency care. If I cannot reach the clinic or office right away my healthcare provider has told me who to call and what to do.
6. I should follow up with my healthcare provider about 7 to 14 days after I take Mifeprex to be sure that my pregnancy has ended and that I am well.
7. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with Mifeprex and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
8. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
9. I have the MEDICATION GUIDE for Mifeprex. I will take it with me if I visit an emergency room or a healthcare provider who did not give me Mifeprex so that they will understand that I am having a medical abortion with Mifeprex.
10. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name (print):** _____ **Date:** _____

The patient signed the PATIENT AGREEMENT in my presence after I counseled her and answered all her questions. I have given her the MEDICATION GUIDE for Mifeprex.

Provider's Signature: _____ **Name of Provider (print):** _____ **Date:** _____

After the patient and the provider sign this PATIENT AGREEMENT, give 1 copy to the patient before she leaves the office and put 1 copy in her medical record.

03/2016

Reference ID: 3909592

*MIFEPREX is a registered trademark of Danco Laboratories, LLC.

DANCO

Exhibit O

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

DATE: March 28, 2016

FROM: Janet Woodcock, MD
Director, Center for Drug Evaluation and Research

THRU: [redacted] (b) (6)

TO: [redacted] (b) (6)

RE: NDA 020687, Supp 20

The currently approved REMS for Mifeprex contains a Patient Agreement Form required to be signed by both the patient and the prescriber. During the review of the REMS in connection with supplement 20 to NDA 020687 submitted by the sponsor, [redacted] (b) (6) found that the information contained in the Patient Agreement Form is generally duplicative of information in the Medication Guide and of information and counseling provided to patients under standard informed consent practices for medical care and under professional practice guidelines. For the reasons further described in their reviews, the reviewers recommended that the Patient Agreement Form be removed from the REMS.

After being briefed on the planned changes to the NDA that the Center was considering, the Commissioner concluded that continuing the REMS requirement for a signed Patient Agreement Form would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care. He requested that the Patient Agreement Form be retained as an element of the REMS.

Therefore, I have asked [redacted] (b) (6) and [redacted] (b) (6) to continue to include a Patient Agreement Form in the REMS for Mifeprex.

Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 207 of 357

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

adding to for the record

Exhibit P

Donna J. Harrison, M.D.
Executive Director
American Association of Pro-Life Obstetricians and Gynecologists
P.O. Box 395
Eau Claire, MI 49111-0395

Quentin L. Van Meter, M.D., FCP
President
American College of Pediatricians
P.O. Box 357190
Gainesville, FL 32635-7190

December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

(1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:

- Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.

- Dosage and Administration:
  - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.

  - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
w ww.fda.gov

- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.

- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.

- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.
[2] 73 FR 16313 (Mar. 27, 2008).

(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:[3]

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.

- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.

- Reduced the number of office visits by the patient under the approved regimen from three to one.

- Replaced the term "physician" with the term "healthcare provider."

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:[4]

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.

- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

[3] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.
[4] See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.[5]

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.[6]

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

[5] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

[6] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone - as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

FDA has recognized that during the COVID-19[7] public health emergency (PHE),[8] certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement").

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[9]

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA's intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA's Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

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[7] The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19).

[8] Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx.

[9] *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns "she" and "her" in the Patient Agreement Form were replaced with "the patient." The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.[10] In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.[11] Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

[10] We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

[11] Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprex Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to limit Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion[12] regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.[13] Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprex (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.[14] The studies reviewed in support of the 2016 approval for Mifeprex (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.[15]

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.[16] As discussed

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[12] In this response, the terms "medical abortion" and "medication abortion" both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.
[13] See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.
[14] See 1999 Medical Officer's Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.
[15] See 2016 Clinical Review, supra n. 13, at 28-31.
[16] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,[17] a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.[18] However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data[19] and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: "the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days."[20] This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.[21] The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.[22]

You also state that the failure rate of the approved regimen (which you refer to as the "buccal misoprostol regimen") increases as the gestational age increases, especially at

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[17] Mentula MJ, Niinimake M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, Human Reproduction. 2011;26(4):927-932.
[18] Id. at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.
[19] See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).
[20] Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.
[21] Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United Sates, NEJM. 1998;338 (18):1241-1247.
[22] See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. Obstetrics and Gynecology 2020; 136(4); e31 to e47.

gestational ages greater than 49 days, relying on a 2015 meta-analysis,[23] and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the "ability" to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen's serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.[24]

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.[25] Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

[23] Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, Obstet. Gynecol 126 (1) July 2015 12-21).
[24] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf; see also https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[25] See 2016 Clinical Review, supra n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, supra n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);[26,27] one trial studied a regimen using vaginal misoprostol (Warringer);[28] a fourth study did not specify the route of misoprostol administered (Puri).[29] Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warriner reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the "standard care" group.[30] Our 2016 review also included a systematic review of six controlled clinical studies by Renner;[31] the authors concluded that the evidence "indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services." Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.[32] The authors concluded, based in part on two of the studies that we had reviewed in 2016,[33] that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:[34]

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

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[26] Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. Bull World Health Organ. 2015;93:249-258.

[27] Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. BJOG. 2015; 122: 510-517.

[28] Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. Lancet. 2011; 377: 1155-61.

[29] Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. Reproductive Health Matters. 2015; 22(44) 94-103.

[30] 2016 Clinical Review, supra n. 13, at 43.

[31] Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. BJOG 2013 Jan;120(1):23-31.

[32] Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). Cochran Database of Systematic Reviews. 2015, Issue 7.

[33] Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundleb S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include avurvedic physicians and nurses. International Perspectives on Sexual and Reproductive Health 2012;38(3)133-42)

[34] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."[35] Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.[36] In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."[37]

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

[35] ACOG Practice Bulletin No. 225, supra n. 22.
[36] American Institute of Ultrasound in Medicine. Accessed November 26, 2021. https://www.aium.org/officialStatements/70.
[37] FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See https://www.regulations.gov/document/FDA-2002-P-0364-0002.

contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."[38] Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form[39] with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."[40]

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

[38] Id.
[39] See https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390.
[40] ACOG Practice Bulletin Number 225 supra n. 22.

- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).

- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:

    - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).

    - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).

- Because providers may now "confirm" that a patient's drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.[41]

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.[42] Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, "[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[43] The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.[44] As reflected in ACOG's guidance, appropriate follow-

[41] See 2016 Clinical Review, supra n. 13, at 44 and 64-67.
[42] ACOG Practice Bulletin Number 225, supra n. 22.
[43] Id.
[44] Id.

up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.[45] We note that this is consistent with current ACOG recommendations, which state that "follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility."[46]

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)'s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document[47] appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.[48] In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.[49] For the years 2008 to 2010, data were collected retrospectively; for the years

[45] Baiju, N, Acharya, G, D'Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. BJOG; 126:1536-1544.
[46] ACOG Practice Bulletin Number 225, supra n. 22.
[47] World Health Organization, Safe Abortion: technical and policy guidance for health systems – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.
[48] Id. at Section 2.3 Post-abortion care and follow-up, at 52.
[49] Carlsson I, Breding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, BMC Women's Health 18:158.

2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between "at home" abortions (managed as an outpatient) and "at the hospital" abortions, in 2015 and found no statistically significant difference (8.2 percent "at home" versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the "at home" group (10.0 percent) and the "at the hospital" group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.[50]

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,[51] but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination "can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan." Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that "available data support … that there are a variety of follow-up modalities that can adequately identify the need for additional intervention."[52] We note that these findings are also consistent with ACOG guidelines, which state that "[r]outine in-person follow-up is not necessary after uncomplicated medication abortion" and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.[53] Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

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[50] 2016 Clinical Review, supra n. 13, at 51-57.
[51] See ACOG Practice Bulletin Number 225, supra note 22.
[52] 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.
[53] ACOG Practice Bulletin Number 225, supra note 22.

iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.[54] Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.[55]

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.[56] Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations[57] using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).[58] The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

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[54] See 2016 Clinical Review, supra n. 13, at 41 and 48.
[55] Id. at 38.
[56] Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, Contraception, 76:215-220).
[57] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447–50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333–6.
[58] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.[59] It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.[60] As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a "minimum 24-hour interval between" mifepristone and misoprostol (emphasis included in the labeling).[61] The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found "women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen" (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that "based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent)."[62] The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

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[59] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[60] 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. Contraception 2013;87(1):26-37.)
[61] See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.
[62] See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. Obstet Gynecol. 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.[63] Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home, Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).[64] However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.[65] This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

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[63] Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, Obstet Gynecol 112(6):1303-1310.

[64] ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

[65] See https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers.

In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study[66] and ACOG statements as evidence that medical abortions have greater risks and more need for emergency "operation" than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.[67] For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.[68] In addition, one of the required qualifications listed in the Prescriber Agreement Form is the "[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary."[69] Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

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[66] See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimaki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, Obstet. Gynecol. 114:795 (Oct. 2009)).

[67] See Mifeprex labeling, approved 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

[68] Id.

[69] Mifepristone REMS Program, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=390. Emphasis added.

You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.[70] As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

[70] Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.[71] Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers "violate FDA protocol," instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access[72] to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing "many Mifeprex prescribers violate FDA protocol, instructing their patients to lie," or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA's determination as to whether a REMS is necessary

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[71] See Historical Information on Mifepristone (Marketed as Mifeprex), available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue "Dear Health Care Provider" letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, "[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely."

[72] We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019.

to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.[73] In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.[74]

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,[75] as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

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[73] See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).
[74] Id.
[75] See supra n. 10.

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[76]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

[76] REMS@FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.

c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS[77] assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

[77] This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,[78] through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

[78] FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.[79] To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.[80] Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies[81]

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[79] See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

[80] In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

[81] Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. Obstet Gynecol 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

and dispensing mifepristone from pharmacies by mail.[82] Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,[83] and (2) prescribers using couriered delivery of medications.[84] Different studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization."[85]

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

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abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. PLoS ONE 13(1): e0191174. https://doi.org/10.1371/journal.pone.019117; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. Contracept X. 2020; 2: 100023.

[82] Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2021, ISSN 0010-7824, https://doi.org/10.1016/j.contraception.2021.09.008, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. JAMA Network Open. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. Aust N Z J Obstet Gynaecol 2018;58: 335-340.

[83] See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. Contraception 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. Contraception 2019; 100:173-177. See also Chong et al., infra n. 103 Kerestes et al., infra n. 105, and Aiken et al., infra n. 106.

[84] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.

[85] Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. BJOG 2019;126;609-618. Norten H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. BJOG 2021; https://doi.org/10.1111/1471-0528.16765; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. BMJ 2017;357:j2011 http://dx.doi.org/10.1136/bmj.j2011.

Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,[86] Rocca,[87] Wiebe[88]). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca[89] conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[90] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

[86] Grossman et al., supra n. 81.
[87] Rocca et al., supra n. 81.
[88] Wiebe et al., supra n. 81.
[89] Rocca et al., supra n. 81.
[90] Wiebe et al., supra n. 81.

None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)[91], in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),[92] timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)[93] evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,[94] Upadhyay,[95] Hyland[96]). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay[97] reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

[91] Grossman et al., supra n. 81.
[92] Wiebe et al., supra n. 81.
[93] Rocca et al., supra n. 81.
[94] Grossman et al, supra n. 82.
[95] Upadhyay et al., supra n. 82.
[96] Hyland et al., supra n. 82.
[97] Upadhyay et al., supra n. 82.

7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[98] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up." The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study[99] the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland[100] study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay[101] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

[98] Hyland et al., supra n. 82.
[99] Grossman et al., supra n. 82.
[100] Upadhyay et al., supra n. 82.
[101] Hyland et al., supra n. 82.

2018),[102] Chong (outcomes from May 2016 to September 2020)[103] and Anger (outcomes from March 2020 to September 2020).[104] A fourth study, Kerestes,[105] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)[106] reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,[107] complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).[108] Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,[109] approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,[110] which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")[111]

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[102] Raymond et al., supra n. 83.
[103] Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. Contraception 2021;104:43-48.
[104] Anger et al., supra n. 83.
[105] Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. Contraception 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.
[106] Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. BJOG 2021;128:1464–1474.
[107] Raymond, supra n. 83.
[108] The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.
[109] Chong et al., supra n. 103.
[110] Anger et al., supra n. 83.
[111] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. Contraception 2020;101:361-366)

have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.[112] There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the "test" group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was "hospitalized and/or blood transfusion" and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the "no-test" group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were "hospitalized and/or blood transfusion" and 12.5 percent had an unplanned clinical encounter.

Kerestes[113] included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity's TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)[114] reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators' analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger's comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

[112] We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.
[113] Kerestes et al., supra n. 105.
[114] Aiken et al., supra n. 106.

sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright[115] reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))[116] reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail though a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

[115] Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjsrh-2020-200976.
[116] Endler et al., Norten et al., and Aiken et al., supra n. 85.

pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that "[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls" and that "health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs" (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the "physician serves a patient's medical needs;"[117] in the context of medical abortion, this

[117] See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.[118]

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).[119] Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'*rarely*, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure." (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).[120] The rate of infections requiring hospitalization or

[118] See https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine.
[119] Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf. Accessed December 13, 2021 (CIOMS).
[120] Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),[121] and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).[122] Therefore, "rarely" accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: "In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C)." This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimaki, et al.[123] study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.[124] reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

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[121] Id. at 36 (defining the "rare" standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).
[122] Id. at 36 (defining the "uncommon" standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, supra n. 13, at 47 and 51.
[123] Niinimaki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. Obstet Gynecol. 2009;114(4):795-804.
[124] Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the Frist Trimester. Obstetrics & Gynecology 126;22-28.

Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimaki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an "at home" and "at the hospital" abortion.[125]

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman's unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA's implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency's conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),[126] certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

[125] Carlsson et al., supra n. 49.
[126] Section 505B of the FD&C Act (21 U.S.C. 355c).

subpopulations, unless that requirement is waived or deferred.[127] In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.[128] Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented. [129] This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should "inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses," and in the Medication Guide, which states "You can become pregnant again right after your pregnancy ends." Although you state that more than one out of every three abortions in the United Sates is a repeat abortion (Petition at 14),[130] we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).[131] Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.[132]

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

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[127] Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).
[128] 2016 Clinical Review, supra n. 13, at 74-76.
[129] Id. at 47.
[130] In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. J Womens Health.
[131] Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. PLoS One. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.
[132] 2016 Clinical Review, supra n. 13, at 47.

Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.[133]
We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[133] You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.

Exhibit Q

Center for Drug Evaluation and Research (CDER)

[redacted]

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	December 16, 2021

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 251 of 357

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 252 of 357

Table of Contents

EXECUTIVE SUMMARY 4

1. Introduction 5
2. Background 5
   - 2.1. PRODUCT AND REMS INFORMATION 5
   - 2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW 7
3. Rationale for Proposed REMS Modification 9
   - 3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS 10
   - 3.2. EVALUATION OF THE EVIDENCE 10
   - 3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A) 12
   - 3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D) 14
   - 3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C) 19
4. Discussion 36
5. Conclusions and Recommendations 41
6. References 42
7. Appendix 45

Reference ID: 4905882

EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 254 of 357

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 255 of 357

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 256 of 357

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

Reference ID: 4905882

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 258 of 357

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4) .
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 259 of 357

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 260 of 357

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 261 of 357

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

Reference ID: 4905882

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.

- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 263 of 357

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

Reference ID: 4905882

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- 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 documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

Reference ID: 4905882

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the (b) (6) March 29, 2016 review and a memorandum from the signatory authority in (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 266 of 357

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 267 of 357

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 268 of 357

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 269 of 357

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 270 of 357

Mifeprex tablets to the distributor. [redacted] non-certified healthcare provider dispensed [redacted] to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed [redacted] shipments representing [redacted] tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The [redacted] ([redacted]) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

[redacted]. Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized April 12, 2021.

[redacted] Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. [redacted] # 2007-525. Finalized December 16, 2021.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 271 of 357

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 272 of 357

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 273 of 357

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

Reference ID: 4905882

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 275 of 357

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

Reference ID: 4905882

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 277 of 357

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 278 of 357

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

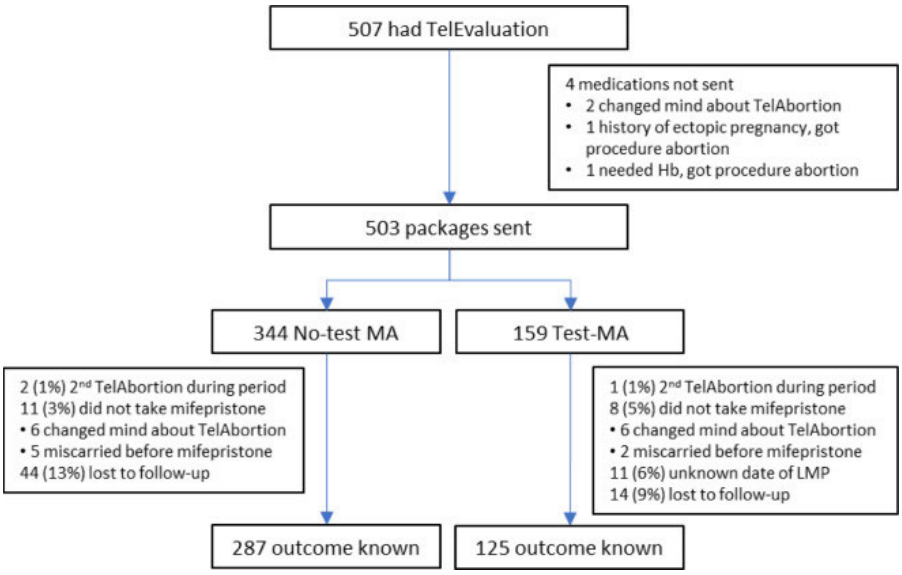
Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 279 of 357

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 280 of 357



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

Reference ID: 4905882

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 282 of 357

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

Reference ID: 4905882

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 284 of 357

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 285 of 357

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

Reference ID: 4905882

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Reference ID: 4905882

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 288 of 357

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 289 of 357

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 290 of 357

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (4) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

Reference ID: 4905882

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

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Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 292 of 357

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7. Appendix A

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Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 295 of 357

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

Reference ID: 4905882

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
Grossman D. Obstet Gynecol 2019;133 (3): 477-483

Reference ID: 4905882
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 297 of 357

Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Reference ID: 4905882

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

Reference ID: 4905882

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)
12/16/2021 10:22:50 AM

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12/16/2021 10:49:46 AM

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12/16/2021 10:59:01 AM

(b) (6)
12/16/2021 11:08:07 AM

Exhibit R

NDA 020687

REMS MODIFICATION NOTIFICATION

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

We refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for mifepristone was originally approved on June 8, 2011, and your single shared system REMS (SSS REMS) was approved on April 11, 2019. Your last SSS REMS modification was approved May 14, 2021. The SSS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks.

This determination is based on a review of published literature, safety information collected during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

Your approved REMS must be modified as follows:

Elements to Assure Safe Use: We have determined that the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") is no longer necessary to ensure the benefits of mifepristone outweigh the risks of serious complications associated with mifepristone that are listed in the labeling of the drug. Removal of the requirement for in-person dispensing will also minimize the burden on the healthcare delivery system of complying with the REMS.

Elements to Assure Safe Use: Pursuant to 505-1(f)(1), we have also determined that an additional element to assure safe use is necessary to mitigate the risk of serious

complications associated with mifepristone listed in the labeling of the drug. Modification of the Mifepristone REMS to allow dispensing of mifepristone by pharmacies requires the addition of certification of pharmacies that dispense the drug.

Your REMS must include elements to mitigate this risk, including at least the following:

- Healthcare providers have particular experience or training, or are specially certified

- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified

- The drug is dispensed to patients with evidence or other documentation of safe use conditions.

  The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above). Include an intervention plan to address any findings of non-compliance with the ETASU.

The proposed REMS must include a timetable for submission of assessments.
The proposed REMS modification submission should include a new proposed REMS document and appended REMS materials, as appropriate, that show the complete previously approved REMS with all proposed modifications highlighted and revised REMS materials.

In addition, the submission should also include an update to the REMS supporting document that includes a description of all proposed modifications and their potential impact on other REMS elements. Revisions to the REMS supporting document should be submitted with all changes marked and highlighted.

Because we have determined that a REMS modification as described above is necessary to minimize the burden on the health care delivery system of complying with the REMS, and to ensure that the benefits of the drug outweigh the risks, you must submit a proposed REMS modification within 120 days of the date of this letter.

Submit the proposed modified REMS as a Prior Approval supplement (PAS) to your NDA.

Because FDA is requiring the REMS modifications in accordance with section 505-1(g)(4)(B), you are not required to submit an adequate rationale to support the proposed modifications, as long as the proposals are consistent with the modifications described in this letter. If the proposed REMS modification supplement includes changes that differ from the modifications described in this letter, an adequate rationale is required for those additional proposed changes in accordance with section 505-1(g)(4)(A).

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR NDA 020687/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

Prominently identify subsequent submissions related to the proposed REMS modification with the following wording in bold capital letters at the top of the first page of the submission:

NDA 020687/S-000
PROPOSED REMS MODIFICATION-AMENDMENT

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

In addition to submitting the proposed modified REMS as described above, you can also submit the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, include the SPL file with your proposed REMS modification submission.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

If you have any questions, call (b) (6), at (b) (6).

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

12/16/2021 03:09:07 PM

Exhibit S

NDA 020687/S-025

SUPPLEMENT APPROVAL

Danco Laboratories, LLC
(b) (4), (b) (6)
P.O. Box 4816
New York, NY 10185

Dear (b) (4), (b) (6):

Please refer to your supplemental new drug application (sNDA) dated and received June 22, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mifeprex (mifepristone) Tablets, 200 mg.

This Prior Approval sNDA provides for modification to the approved single, shared system (SSS) risk evaluation and mitigation strategy (REMS) for mifepristone 200 mg tablets, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation, as well as corresponding labeling revisions to the prescribing information and the Medication Guide to align with the modification to the Mifepristone REMS Program. This SSS REMS is known as the Mifepristone REMS Program.

APPROVAL & LABELING

We have completed our review of the supplemental application, as amended. It is approved effective the date of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The Mifepristone REMS Program, of which Mifeprex is a member, was originally approved on April 11, 2019, and the most recent REMS modification was approved on May 14, 2021. The Mifepristone REMS Program consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of Mifeprex outweigh its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Notification letter dated December 16, 2021. In addition the following modifications were communicated during the course of the review:

- Revisions to the REMS goal to align with the updated REMS requirements.
- Replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- Additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms, Patient Agreement Form,* and *Pharmacy Agreement Forms*).

Your proposed modified REMS, received on June 22, 2022, amended and appended to this letter, is approved. The modified REMS consists of the elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The modification of the approved REMS must be fully implemented within 120 calendar days of this letter.

This shared system REMS, known as the Mifepristone REMS Program, currently includes those products listed on the FDA REMS website[3].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the approval of the modified SSS REMS (1/3/2023) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies

[3] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

i. Number of certified pharmacies
ii. Number and percentage of newly certified pharmacies
iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)

c. Wholesalers/Distributors
i. Number of authorized wholesalers/distributors
ii. Number and percentage of newly authorized wholesalers/distributors
iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
ii. The number of audits expected, and the number of audits performed
iii. The number and type of deficiencies noted
iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)
vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:
i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)
ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):
1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance

4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

Overall Assessment of REMS Effectiveness

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a

proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively,

updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 020687 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

> **NDA 020687 REMS ASSESSMENT**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 020687/S-000/**
> **PRIOR APPROVAL SUPPLEMENT**

PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 020687/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 020687

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov
.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call (b) (6)

Sincerely,

{See appended electronic signature page}

(b) (6)

Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - REMS Document
  - Prescriber Agreement
  - Patient Agreement Form
  - Pharmacy Agreement Form

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

(b) (6)

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Exhibit T

[redacted] and [redacted]

Center for Drug Evaluation and Research (CDER)

Application Type	NDA and ANDA
Application Number	NDA 020687 and ANDA 091178
Supplement Number, Date Received	NDA Supplement-025 and ANDA Supplement-004 received June 22, 2022 (sequences 18 and 87 respectively) and amended October 19, 2022 (sequences 22 and 91 respectively), November 30, 2022 (sequences 24 and 92 respectively), December 9, 2022 (sequences 25 and 93 respectively) and December 16, 2022 (sequences 26 and 95 respectively). This supplement is on a 180-Day clock.
Targeted Action Date	December 19, 2022
[redacted] #	2022-1169
Reviewer Names	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Review Completion Date	January 3, 2023
Subject	Review of proposed Major REMS Modification
Established Name	Mifepristone REMS
Name of Sponsor	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablet

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 319 of 357

TABLE OF CONTENTS

EXECUTIVE SUMMARY 3

1. Introduction 4
2. Background 4
   - 2.1. Product Information and REMS Information 4
   - 2.2. Regulatory History 6
3. Review of Proposed REMS Modification 8
   - 3.1. REMS Goal 8
   - 3.2. REMS Document 8
   - 3.3. REMS Requirements 9
     - 3.3.1. Addition and Removal of ETASU 9
     - 3.3.2. REMS Participant Requirements and Materials 9
       - 3.3.2.1. Prescriber Requirements 9
       - 3.3.2.2. Patient Requirements 11
       - 3.3.2.3. Pharmacy Requirements 12
       - 3.3.2.4. Distributor Requirements 15
     - 3.3.3. REMS Sponsor Requirements 15
       - 3.3.3.1. Sponsor Requirements to Support Prescriber Certification 15
       - 3.3.3.2. Sponsor Requirements to Support Pharmacy Certification 16
       - 3.3.3.3. Sponsor Implementation Requirements 16
   - 3.4. REMS Assessment Timetable 16
4. Supporting Document 17
5. REMS Assessment Plan 17
6. Discussion 19
7. Conclusions and Recommendations 21
8. References 21
9. Appendices 22

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 320 of 357

EXECUTIVE SUMMARY

This is a review of the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178. The Sponsors submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, and amended their submissions on October 19, 2022 (Danco), October 20, 2022 (GBP), November 30, 2022 (both), December 9, 2022 (both) and December 16, 2022 (both).

The Mifepristone REMS Program was originally approved on April 11, 2019, to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021.[a] The Mifepristone REMS Program consists of elements to assure safe use (ETASU) A, C and D, an implementation system, and a timetable for submission of assessments of the REMS.

The Sponsors submitted the proposed modification to the REMS in response to the Agency's REMS Modification Notification letters dated December 16, 2021, which required removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement") and the addition of certification of pharmacies that dispense the drug.

In addition, the following were addressed during the course of the review:

- revisions to the REMS goal to align with the updated REMS requirements.
- replacing serial number with recording of NDC and lot number of mifepristone dispensed.
- additional edits for clarification and consistency in the REMS Document and REMS materials (*Prescriber Agreement Forms*, *Patient Agreement Form*, and *Pharmacy Agreement Forms*).

The review team finds the proposed modification to the Mifepristone REMS Program last submitted on December 16, 2022, to be acceptable and recommends approval of the REMS modification. The proposed REMS modification includes changes to the REMS goal, additional REMS requirements for prescribers to incorporate dispensing from certified pharmacies and new REMS requirements for pharmacy certification.

The proposed goal of the modified REMS for mifepristone 200 mg is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

[a] The May 14, 2021 REMS modification approved the inclusion of gender neutral language in the Patient Agreement Form as well as corresponding minor changes to the REMS document to be consistent with the changes made to the Patient Agreement Form.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 321 of 357

The timetable for submission of assessments of the REMS was modified to one year from the date of the approval of the modified REMS and annually thereafter. The assessment plan was revised to align with the changes to the REMS and capture additional metrics for drug utilization and REMS operations.

The modified REMS includes ETASU A, B and D, an implementation system, and a timetable for submission of assessments of the REMS. Mifepristone will no longer be required to be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the "in-person dispensing requirement" for brevity) and will be able to be dispensed from certified pharmacies.

1. Introduction

This review evaluates the proposed modification to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program) submitted by Danco Laboratories, LLC (Danco) for new drug application (NDA) 020687 and by GenBioPro, Inc. (GBP) for abbreviated new drug application (ANDA) 091178.

The Sponsors initially submitted proposed modification to the Mifepristone REMS Program on June 22, 2022, in response to the Agency's REMS Modification Notification letters issued on December 16, 2021, to Danco and GBP, requiring the following modification to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks:

- removal of the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the "in-person dispensing requirement")
- addition of certification of pharmacies that dispense the drug

Per the Agency's December 16, 2021, REMS Modification Notification letters, the proposed REMS was required to include the following ETASU to mitigate the risk of serious complications associated with mifepristone, including at least the following:

- healthcare providers have particular experience or training, or are specially certified
- pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- the drug is dispensed to patients with evidence or other documentation of safe use conditions

The REMS was also required to include an implementation system and timetable for submission of assessments.

2. Background

2.1. Product Information and REMS Information

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000, with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 322 of 357

the risk of serious complications associated with mifepristone when used for medical abortion.[c] Mifeprex was deemed to have in effect an approved REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), and the Mifeprex REMS was approved on June 8, 2011.

On March 29, 2016, FDA approved an efficacy supplement for Mifeprex, which included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol, as well as a modification of the gestational age up to which Mifeprex has been shown to be safe and effective and a modification to the process for follow-up after administration of the drug. FDA also approved modification to the Mifeprex REMS that reflected the changes approved in the efficacy supplement.[1-5] On April 11, 2019, FDA approved ANDA 091178 and the Mifepristone REMS Program.[6-7] The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 091178. The goal of the approved Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b) Ensuring that mifepristone is only dispensed in certain healthcare settings by or under the supervision of a certified prescriber (under ETASU C).
c) Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

The Mifepristone REMS Program was last modified and approved in 2021 to revise the *Patient Agreement Form* to include gender-neutral language; however, the goal of the Mifepristone REMS Program has not changed since the initial approval in 2019.

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and agree to follow the guidelines for use of mifepristone. Under ETASU C, in the Mifepristone REMS Program as approved prior to today's action, mifepristone was required to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The approved Mifepristone REMS Program includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public health emergency (PHE) regarding the in-person dispensing requirement in the Mifepristone REMS Program. Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form*, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020, to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.[8]

[c] Mifepristone is also approved in approximately 80 other countries. https://gynuity.org/assets/resources/biblio_ref_lst_mife_en.pdf

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 323 of 357

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intended to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

2.2. Regulatory History

The following is a summary of the regulatory history relevant to this review:

- 04/11/2019: Approval of the Mifepristone REMS Program, a single, shared system REMS that includes NDA 020687 and ANDA 091178.
- 04/12/2021: The Agency issued a General Advice letter to both the NDA and ANDA Applicants, explaining that FDA intended to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form.
- 05/07/2021: The Agency stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with section 505-1 of the FD&C Act.
- 12/16/2021: The Agency completed its review of the Mifepristone REMS Program and determined, among other things, that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification.[9]
- 12/16/2021: REMS Modification Notification letters were sent to both Sponsors stating that the approved Mifepristone REMS Program must be modified to minimize the burden on the healthcare system of complying with the REMS and ensure that the benefits of the drug outweigh the risks.
- 04/08/2022: Final written responses to a Type A meeting request were provided to Danco, the point of contact for the Mifepristone REMS Program. The questions pertained to the 12/16/2021 REMS Modification Notification letter requirements.
- 04/13/2022: The Sponsors requested an extension to 6/30/2022, to submit a proposed REMS modification in response to the Agency's 12/16/2021 REMS Modification Notification letters.
- 04/15/2022: The Agency granted the Sponsors' request for an extension to submit a proposed REMS modification and conveyed that the modification must be submitted no later than 06/30/2022.[10]
- 06/22/2022: Danco and GBP submitted a proposed REMS modification to their respective applications in response to the 12/16/2021 REMS Modification Notification letters.
- 07/22/2022: An Information Request was sent to the Sponsors requesting clarification of the proposed prescriber and dispenser requirements and additional rationale to support their proposal.
- 08/26/2022: Sponsors submitted responses to 07/22/2022 Information Request.
- 09/19/2022: Teleconference was held between Agency and Sponsors where the Agency communicated the REMS requirements that are necessary to support the addition of pharmacy

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 324 of 357

certification. The Agency proposed focusing on the pharmacy settings where a closed system[d] REMS could be implemented using the existing email and facsimile based system, (b) (4) , as the best strategy for an approvable modification by the goal date.

- 09/22/2022: An Information Request was sent to Sponsors requesting confirmation that the Sponsors agree with the pharmacy distribution approach outlined in the 09/19/2022 teleconference so that the Agency's feedback could be appropriately tailored.
- 09/23/2022: The Sponsors confirmed via email that they were willing to pursue (b) (4) , as discussed in the 09/19/2022 teleconference. The Sponsors also requested a teleconference to discuss the current modification (b) (4) .
- 09/27/2022: Comments from the 09/19/2022 teleconference sent to Sponsors with additional comments and requests regarding what will be necessary for pharmacy certification.
- 09/29/2022: An Information request was sent to the Sponsors asking for agenda items, questions, and a request to walk through their proposed system for pharmacy certification, including dispensing through mail-order or specialty pharmacies, at the 10/06/2022 scheduled teleconference.
- 10/04/2022: Sponsors emailed that they will focus the 10/06/2022 teleconference on the 09/27/2022 Agency comments and their mail order and specialty pharmacy distribution model.
- 10/06/2022: Teleconference was held between Agency and Sponsors where Sponsors outlined their proposal for pharmacy certification, including dispensing through mail order and specialty pharmacies, as well as their concerns with certain requirements and general timelines.
- 10/19/2022: Danco submitted a REMS amendment to their pending sNDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/20/2022: GBP submitted a REMS amendment to their pending sANDA, which included a REMS document and REMS materials. They did not submit a REMS Supporting Document.
- 10/25/2022: Teleconference was held between Agency and Sponsors to discuss the *Patient Agreement Form* and timing related to shipping a mifepristone prescription from a certified pharmacy to the patient.
- 11/23/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document, submitted on 10/19/2022 (Danco) and 10/20/2022 (GBP).
- 11/30/2022: Danco and GBP submitted REMS amendments, which included the REMS Document, to their respective pending supplemental applications.
- 12/01/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document.
- 12/05/2022: An Information Request was sent to Sponsors with comments on their proposed REMS Document submitted on 11/30/2022 and discussed at the teleconference on 12/01/2022, and REMS materials submitted to their applications on 10/19/2022 and 10/20/2022.

[d] "Closed system" in this case refers to a system where prescribers, pharmacies, and distributors are certified or authorized in the REMS and the certification of the stakeholder must be verified prior to distribution or dispensing, as per the REMS.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 325 of 357

- 12/07/2022: Teleconference was held between Agency and Sponsors to discuss the REMS Document and REMS materials the Agency sent to the Sponsors on 12/05/22.
- 12/08/2022: Danco and GBP submitted REMS amendments, including the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form, Patient Agreement Form* and REMS Supporting Document, to their respective pending applications.
- 12/09/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS assessment plan.
- 12/14/2022: An Information Request was sent to Sponsors with the Agency's comments on the REMS Document, *Prescriber Agreement Form, Pharmacy Agreement Form*, and REMS Supporting Document.
- 12/15/2022: Two teleconferences were held between Agency and Sponsors to discuss the proposed REMS Document and REMS materials the Agency sent to the Sponsors on 12/14/22.
- 12/16/2022: Sponsors submitted a REMS amendment to their respective applications.

3. Review of Proposed REMS Modification

(b) (6) has discussed the Sponsors' proposed modification with the review team, which includes members of the (b) (6) and the (b) (6) ; hereafter referred to as the review team. This review includes their input and concurrence with the analysis and proposed changes to the Mifepristone REMS Program.

3.1. REMS Goal

The Sponsors proposed modification to the goal for the Mifepristone REMS Program to add that mifepristone can also be dispensed from certified pharmacies on prescriptions issued by certified prescribers. The proposed REMS goal is:

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

Reviewer Comment: *We agree with the Sponsors' proposal.*

3.2. REMS Document

The proposed REMS Document is not in the format as outlined in the 2017 Draft Guidance for Industry, Format and Content of a REMS Document.[11]

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 326 of 357

Reviewer Comment: *To avoid the misperception that this REMS modification is making major changes to the REMS document that go beyond our December 16, 2021, determination that the REMS must be modified to remove the in-person dispensing requirement and add pharmacy certification, CDER staff and management discussed whether to change the format of the REMS document to that described in the 2017 draft guidance.[11] After internal discussion, CDER staff and management aligned not to transition the REMS document at this time to the format described in the 2017 draft guidance.*

3.3. REMS Requirements

3.3.1. Addition and Removal of ETASU

The December 16, 2021, REMS Modification Notification letters specified that the ETASU must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure the benefits of the drug outweigh the risks by:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices and hospitals (i.e., the "in-person dispensing requirement"), and;
- Adding a requirement that pharmacies that dispense the drug be specially certified.

The Sponsors proposed changes to the REMS as reflected in the subsections below.

3.3.2. REMS Participant Requirements and Materials

3.3.2.1. Prescriber Requirements

Consistent with the approved Mifepristone REMS Program prescribers must be specially certified. To become specially certified to prescribe mifepristone, healthcare providers who prescribe must review the Prescribing Information for mifepristone and complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet certain qualifications and will follow the guidelines for use of mifepristone. The guidelines for use include ensuring i) that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained; ii) that the healthcare provider (HCP) and the patient sign the *Patient Agreement Form*, iii) the patient receives a copy of the *Patient Agreement Form* and Medication Guide, iv) the *Patient Agreement Form* is placed in the patient's medical record; v) that any patient deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient. The language on the guidelines for use was revised from the Mifepristone REMS Program approved in 2021 to clarify that, if the certified prescriber supervises the dispensing of mifepristone, they must ensure the guidelines for use of mifepristone are followed by those under their supervision. This clarification reflects the ongoing implementation of the approved Mifepristone REMS Program. For example, consistent with the approved REMS, the *Patient Agreement Form* does not require the certified prescriber's signature, but rather the signature of the healthcare provider counseling the patient on the risks of mifepristone. Additional changes were made globally to provide consistency and clarity of the requirements for certified prescribers and healthcare providers who complete tasks under the supervision of certified prescribers.

A certified prescriber may submit the *Prescriber Agreement Form* to an authorized distributor if the certified prescriber wishes to dispense or supervise the dispensing of mifepristone; this is consistent with the current requirements of the Mifepristone REMS Program. Additional requirements were

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 327 of 357

added to incorporate mifepristone dispensing by a certified pharmacy. If a healthcare provider wishes to prescribe mifepristone by sending a prescription to a certified pharmacy for dispensing, the healthcare provider must become certified by providing the pharmacy a *Prescriber Agreement Form* signed by the provider. A certified prescriber must also assess the appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy.

The NDC and lot number of the dispensed drug will be recorded in the patient's record when mifepristone is dispensed by or under the supervision of a certified prescriber, replacing the requirement that serial numbers from each package of mifepristone be recorded in the patient's record. If prescribers become aware of the death of a patient for whom the mifepristone was dispensed from a certified pharmacy, the prescribers will be required to obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy.

The following materials support prescriber requirements:

- *Prescriber Agreement Form* for Danco Laboratories, LLC
- *Prescriber Agreement Form* for GenBioPro, Inc.
- *Patient Agreement Form*

Reviewer Comment: *We agree with the Sponsors' proposal.*

Although certain activities (review of the Patient Agreement Form with patients and answering any questions about treatment, signing, providing a copy to the patient and retaining the Patient Agreement Form, providing a copy of the Medication Guide, and ensuring any deaths are reported to the Mifepristone Sponsor, recording the NDC and lot number from drug dispensed from the certified prescriber or those under their supervision) may be conducted by healthcare providers under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. We agree with the additional language to further clarify that the certified prescriber must ensure the guidelines for use of mifepristone are followed.

As proposed, certified prescribers may either, 1) continue to submit the Prescriber Agreement Form to an authorized distributor if the certified prescriber is dispensing or supervising the dispensing of the drug (as already required in the REMS), or 2) if the drug will be dispensed from a certified pharmacy, submit the Prescriber Agreement Form to the certified pharmacy that will dispense the drug (as proposed in the modification). Regarding #2, the pharmacy can only fill prescriptions written by a certified prescriber.

Based on our review of the proposed changes, the review team finds it acceptable for prescribers to submit their Prescriber Agreement Form directly to the certified pharmacy. Although certified prescribers still have the option of in-person dispensing of the drug, not all prescribers may want to stock mifepristone. Typically due to the number of drugs that are available and the expense associated with stocking prescription medications intended for outpatient use, most prescribers do not stock many medications, if they stock medications at all.

The proposal to submit a Prescriber Agreement Form to a certified pharmacy provides another option for dispensing mifepristone. The burden of providing the Prescriber Agreement Form prior to or when the prescription is provided to a certified pharmacy does not create unreasonable burden for prescribers. The burden of prescriber certification has been minimized to the extent possible. The Prescriber Agreement Form is designed to require minimal time to complete and requires that the prescriber submit it to the authorized distributor once, and if the prescriber chooses to use a certified pharmacy to dispense mifepristone, they will need to submit the form to the certified pharmacy.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 328 of 357

There is an additional requirement added for certified pharmacies and certified prescribers in the event that a patient will not receive their medication from the certified pharmacy within four calendar days of the pharmacy's receipt of the prescription (for example, if the medication is not in stock). In this circumstance, the pharmacy will be required to contact the certified prescriber to make them aware of the delay and will be required to obtain from the prescriber confirmation that it is appropriate to dispense mifepristone to the patient even though they will receive mifepristone more than four calendar days after the prescription was received by the certified pharmacy. This confirmation is intended to ensure timeliness of delivery in light of the labeled indication and gestational age. Additional details and rationale on the pharmacy requirements to dispense and ship drug in a timely manner are described in section 3.3.2.3.

If a certified prescriber becomes aware of a patient death that occurs subsequent to the use of mifepristone dispensed from a pharmacy, the certified prescriber must obtain the NDC and lot number of the package of mifepristone the patient received from the pharmacy. This information will be reported to the appropriate Mifepristone Sponsor in the same manner prescribers have done previously. This additional requirement to obtain the NDC and lot number from the pharmacy is needed to ensure consistent adverse event reporting when mifepristone is dispensed from a certified pharmacy.

Prescriber Agreement Form

The Sponsors' proposed changes to the *Prescriber Agreement Form* aligned with those described above. The proposed *Prescriber Agreement Form* explains the two methods of certification which are: 1) submitting the form to the authorized distributor and 2) submitting the form to the dispensing certified pharmacy. Further clarification was added that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification. The statement that certified prescribers are responsible for overseeing implementation and compliance with the REMS Program was also added. The following statement was added to the form: "I understand that the pharmacy may dispense mifepristone made by a different manufacturer than that stated on the Prescriber Agreement Form." The account set up information was removed and replaced with prescriber information response fields.

***Reviewer Comment**: We agree with the Sponsors' proposal. Changes in the above prescriber requirements were incorporated in the Prescriber Agreement Form.*

3.3.2.2. Patient Requirements

The *Patient Agreement Form* was updated to clarify that the signatures may be written or electronic, to reorganize the risk information about ectopic pregnancy, and to remove the statement that the Medication Guide will be taken to an emergency room or provided to a healthcare provider who did not prescribe mifepristone so that it is known that the patient had a medical abortion with mifepristone.

The following materials support patient requirements:

- *Patient Agreement Form*

***Reviewer Comment:** We agree with the Sponsors' proposal.*

The Patient Agreement Form continues to be an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 329 of 357

patient, to provide the patient with the Patient Agreement Form, and to have the healthcare provider and patient sign the Patient Agreement Form, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The form is signed by the patient and the provider and placed in the patient's medical record, and a copy is provided to the patient, to document the patient's acknowledgment of receiving the information from the prescriber. The Agency agrees that the further clarification that signatures can be written or electronic is appropriate for the continued use of the form.

The reference to ectopic pregnancy has been reorganized in the document since it is not a risk of the drug. The signs and symptoms of an untreated ectopic pregnancy that may persist after mifepristone use have been clarified in the section of the form that explains the signs and symptoms of potential problems that may occur after mifepristone use.

The review team agrees with removing the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion. Although this statement has been in the Medication Guide for a number of years, upon further consideration, the Agency has concluded that patients seeking emergency medical care are not likely to carry a Medication Guide with them, the Medication Guide is readily available online, and information about medical conditions and previous treatments can be obtained at the point of care.

3.3.2.3. Pharmacy Requirements

The Sponsors proposed that certified pharmacies, in addition to certified prescribers and HCPs under the supervision of certified prescribers, can dispense mifepristone. In order for a pharmacy to become certified, the pharmacy must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy. The Authorized Representative must certify that they have read and understood the Prescribing Information for mifepristone. Each location of the pharmacy must be able to receive *Prescriber Agreement Forms* by email and fax and be able to ship mifepristone using a shipping service that provides tracking information.

Additionally, each dispensing pharmacy location must put processes and procedures in place to fulfill the REMS requirements. Certified pharmacies must verify prescriber certification by confirming they have obtained a copy of the prescriber's signed *Prescriber Agreement Form* before dispensing. Certified pharmacies must dispense mifepristone such that it is received by the patient within four days from the day of prescription receipt by the pharmacy. If the pharmacy will not be able to deliver mifepristone to the patient within four days of receipt of the prescription, the pharmacy must contact the prescriber to confirm the appropriateness of dispensing mifepristone and document the certified prescriber's decision. The pharmacy must also record the NDC and lot number from each package of mifepristone dispensed in the patient's record, track and verify receipt of each shipment of mifepristone, dispense mifepristone in its original package, and only distribute, transfer, loan, or sell mifepristone to certified prescribers or between locations of the certified pharmacy. The pharmacy must also report any patient deaths to the prescriber, including the NDC and lot number from the package dispensed to the patient, and remind the prescriber of their obligation under the REMS to report patient deaths to the Sponsor that supplied the mifepristone; the certified pharmacy also must notify the Sponsor that supplied the mifepristone that the pharmacy submitted a report of a patient death to the prescriber and include the name and contact information for the prescriber as well as the NDC and lot number of the dispensed

Reference ID: 5103819

product. Record-keeping requirements of the pharmacy include records of *Prescriber Agreement Forms*, mifepristone dispensing and shipping, and all processes and procedures and compliance with those processes and procedures. Pharmacies must train all relevant staff and participate in compliance audits. Pharmacies must also maintain the identity of patients and providers as confidential, including limiting access to patient and provider identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes. The requirement that mifepristone not be dispensed from retail pharmacies was removed.

The following materials support pharmacy requirements:

- *Pharmacy Agreement Form* for Danco Laboratories, LLC
- *Pharmacy Agreement Form* for GenBioPro, Inc.

Reviewer Comment: *We agree with the Sponsors' proposal. The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, mifepristone can be dispensed from a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that the prescriber is certified prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the Patient Agreement Form is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review and our consideration of the distribution model implemented by the Sponsors during the periods when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients.*

The requirement to maintain confidentiality, including limiting access to patient and provider identity only to those personnel necessary for dispensing under the Mifepristone REMS Program or as necessary for payment and/or insurance purposes, is included to avoid unduly burdening patient access.

The Sponsors proposed inclusion of this requirement because of concerns that patients may be reluctant or unwilling to seek to obtain mifepristone from pharmacies if they are concerned that confidentiality of their medical information could be compromised, potentially exposing them to intimidation, threats, or acts of violence by individuals opposed to the use of mifepristone for medical abortion.[e] *Further, unwillingness on the part of prescribers to participate in the Mifepristone REMS Program on the basis of*

[e] See e.g., *2020 Violence and Disruption Statistics,* National Abortion Federation (Dec. 16, 2021), https://prochoice.org/national-abortion-federation-releases-2020-violence-disruption-statistics/; Amanda Musa, CNN, *Wyoming Authorities Search for a Suspect Believed to Have Set an Abortion Clinic on Fire*, CNN WIRE (June 10, 2022), https://abc17news.com/news/2022/06/10/wyoming-authorities-search-for-a-suspect-believed-to-have-set-an-abortion-clinic-on-fire/.

Reference ID: 5103819

similar confidentiality concerns may unduly burden patient access by limiting the number of prescribers who are willing to send prescriptions to certified pharmacies. Addition of this requirement protects patient access by requiring the pharmacy to put processes and procedures in place to limit access to confidential information to only those individuals who are essential for dispensing mifepristone under the Mifepristone REMS Program or as necessary for payment or insurance purposes. Inclusion of this requirement for certified pharmacies is consistent with the requirement in the current Mifepristone REMS Program, that distributors maintain secure and confidential records.

Reference to mifepristone not being available in retail pharmacies was removed from the REMS. There is no single definition of the term "retail pharmacy" and therefore the scope of the exclusion in the REMS was not well defined. Including a restriction in the Mifepristone REMS Program that retail pharmacies cannot participate in the REMS may unintentionally prohibit the participation of mail order and specialty pharmacies that could, under one or more definitions, also be considered a "retail pharmacy."

After reconsideration of the term, "retail," the Agency concluded that a more appropriate approach was to articulate the specific requirements that would be necessary for pharmacy certification. As modified, the REMS will not preclude the participation of any pharmacy that meets the certification requirements. However, we acknowledge that the provision in the REMS related to pharmacies' verification of prescriber enrollment will likely limit the types of pharmacies that will choose to certify in the REMS. The REMS requires that pharmacies dispense mifepristone only after verifying that the prescriber is certified. The REMS further requires that pharmacies be able to receive the Prescriber Agreement Forms by email and fax. (b) (4)

The pharmacy certification requirements include that the drug reach patients within four days of the certified pharmacy receiving the prescription. During the course of the review, the review team concluded that requiring medication delivery to the patient within four days of the pharmacy's receipt of a prescription is acceptable based on the labeled indication and literature,[13] while taking into account practical shipping considerations (e.g., shipping over weekends and holidays). For patients who will not receive the drug within four calendar days of the date the pharmacy receives the prescription, the pharmacy must notify the certified prescriber and the certified prescriber must determine if it is still appropriate for the certified pharmacy to dispense the drug. The pharmacy must document the certified prescriber's decision. A prescriber's confirmation that it is appropriate to dispense mifepristone when it will not be delivered to the patient within the allotted four days is intended to ensure timeliness of delivery in light of the labeled indication and gestational age.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 332 of 357

Pharmacy Agreement Form

The proposed *Pharmacy Agreement Form* is a new form and is the means by which a pharmacy becomes certified to dispense mifepristone. The form, which is submitted by an authorized representative on behalf of a pharmacy seeking certification, outlines all requirements proposed above. Clarification is included in the form that healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program, do not require pharmacy certification. Any new authorized representative must complete and submit the *Pharmacy Agreement Form*. Spaces for specific authorized representative information and pharmacy name and address are included. The completed form can be submitted by email or fax to the authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The Pharmacy Agreement Form aligns with the pharmacy requirements discussed above.*

3.3.2.4. Distributor Requirements

The Sponsors proposed that the distributors' processes and procedures in the approved Mifepristone REMS Program be updated to ensure that mifepristone is only shipped to clinics, medical offices and hospitals identified by certified prescribers and to certified pharmacies. Distributors will continue to complete the certification process for any *Prescriber Agreement Forms* they receive and also will complete the certification process for pharmacies upon receipt of a *Pharmacy Agreement Form*, including notifying pharmacies when they become certified. FDA was removed as a potential auditor for distributors.

Reviewer Comment: *We agree with the Sponsors' proposal. At this time, FDA does not audit distributors directly, it carries out inspections of Sponsors to monitor industry compliance with REMS requirements.*

3.3.3. REMS Sponsor Requirements

3.3.3.1. Sponsor Requirements to Support Prescriber Certification

The Sponsors proposed additions to this section of the REMS document, including that Sponsors will ensure prescribers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy, and that Sponsors will ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date. Sponsors will also ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*: (1) within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies, or (2) within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

Reviewer Comment: *We agree with the Sponsors' proposal. The requirement to confirm that the locations associated with the certified prescriber are current is parallel to the pharmacy requirement that the authorized representative's contact information is up to date. In determining the pharmacy requirement, which is necessary to ensure program compliance and is consistent with other approved REMS that include pharmacy certification, the Agency also concluded that a parallel requirement for certified prescribers should be added.*

With respect to recertification, it is important that active certified prescribers are informed of and agree to new REMS requirements to ensure the continued safe use of mifepristone. There is minimal burden to recertification and the timelines allow sufficient time to accomplish recertification.

Reference ID: 5103819

3.3.3.2. Sponsor Requirements to Support Pharmacy Certification

The Sponsors proposed the addition of Sponsor requirements to support pharmacy certification and compliance, including ensuring that pharmacies are certified in accordance with the requirements in the Mifepristone REMS Program, de-certifying pharmacies that do not maintain compliance with the certification requirements, and ensuring that pharmacy certification can be completed by email and fax to an authorized distributor. Annually, the authorized representative's name and contact information will be verified to ensure it corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, a new authorized representative must certify for the pharmacy. All reference to the requirement in the 2021 Mifepristone REMS Program that mifepristone to be dispensed to patients only in clinics, medical offices and hospitals by or under the supervision of a certified prescriber, and not from retail pharmacies, was removed.

Reviewer Comment: *We agree with the Sponsors' proposal. Changes are in line with the REMS Modification Notification letters sent December 16, 2021. Refer to section 3.3.2.3 Reviewer Comments on Pharmacy Certification for rationale for removing the statement that mifepristone is not distributed to or dispensed from retail pharmacies. Ensuring that the authorized representative's contact information is up to date is necessary to ensure that there is always a point person who is responsible for implementing the Mifepristone REMS Program in their pharmacy and can address any changes that are needed if pharmacy audits identify a need for improvement.*

3.3.3.3. Sponsor Implementation Requirements

The Sponsors proposed that they will ensure that adequate records are maintained to demonstrate that REMS requirements have been met (including but not limited to records of mifepristone distribution, certification of prescribers and pharmacies, and audits of pharmacies and distributors), and that the records must be readily available for FDA inspections. The distributor audit requirement was updated to audit new distributors within 90 calendar days of becoming authorized and annually thereafter (a one-time audit requirement was previously required). The Sponsors also proposed a pharmacy audit requirement whereby certified pharmacies that order mifepristone are audited within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter for pharmacies that ordered in the previous 12 months.

Reviewer's Comment: *We agree with the Sponsors' proposal.*

The number of pharmacies that will certify in the REMS is uncertain; therefore, to obtain a reliable sample size for the audits, the Sponsors will need to audit all certified pharmacies within 180 calendar days after the pharmacy places its first order and annually thereafter for pharmacies that have ordered mifepristone in the previous 12 months. Audits performed at 180 days should allow time for establishment and implementation of audit protocols and for the Sponsors to perform the audits. With the addition of more stakeholders (i.e., certified pharmacies), it is also necessary to audit distributors annually to ensure the REMS requirements are followed. The requirement to conduct audits annually may be revisited if assessment data shows that the REMS is meeting its goal.

3.4. REMS Assessment Timetable

The Sponsors proposed that assessments must be submitted one year from the approval of the modified REMS and annually thereafter, instead of every three years as per the previous requirement.

Reference ID: 5103819

***Reviewer's Comment**: We agree with the Sponsors' proposal. With the addition of new pharmacy stakeholders and removal of the in-person dispensing requirement, more frequent assessment after this REMS modification is needed to ensure REMS processes are being followed and that the REMS is meeting its goal. The requirement can be revisited at a later date if assessment data shows that the modified REMS is meeting its goal. The NDA applicant is required to submit assessment reports as outlined in the timetable for submission of assessments. These reports address requirements for the Mifepristone REMS Program. The Sponsors have indicated that some data will be submitted as separate reports when Sponsor-specific information is needed to address the assessment metrics.*

4. Supporting Document

The Sponsors' REMS Supporting Document was substantially updated to include information regarding the proposed modification under review. Background and rationale from the 12/16/21 REMS Modification Notification letters was included. An updated description of the REMS goal and the ETASU was also included to align with the changes in the REMS Document and provide further clarification. Further explanation of prescriber requirements and rationale for various pharmacy requirements was also included.

Regarding implementation of the modified REMS, the Sponsors additionally proposed that pharmacies that received and shipped mifepristone during the Agency's exercise of enforcement discretion during the COVID-19 PHE, that wish to continue to dispense mifepristone, will be required to comply with the pharmacy certification requirements within 120 days of approval of the modified REMS.

The communication strategy to alert current and future prescriber and pharmacy stakeholders was outlined. Distributors, certified prescribers that purchased mifepristone in the last twelve months, and various professional organizations will receive information about REMS changes within 120 days of modification approval. The Sponsors proposed to list pharmacies that agree to be publicly disclosed on their respective product websites but disclosure of this nature is not a requirement of the REMS. The Sponsors indicated that they anticipate certified pharmacies that do not agree to public disclosure will communicate with the certified prescribers they wish to work with.

The REMS Assessment Plan is discussed in the following section.

***Reviewer's Comment**: We agree with the Sponsors' proposal. The Supporting Document addresses all REMS requirements and provides sufficient clarification of implementation and maintenance of the REMS. The implementation requirements for pharmacies currently dispensing mifepristone under FDA's exercise of enforcement discretion during the COVID-19 PHE provide for continued use of these pharmacies without breaks in service. The communication strategy is also adequate given the efforts to reach both established certified prescribers and potentially new prescribers through professional organizations.*

The Sponsors' plan to communicate which pharmacies are certified to certified prescribers is adequate. For the reasons listed in section 3.3.2.3, confidentiality is a concern for REMS stakeholders. Disclosure of pharmacy certification status should be a choice made by individual certified pharmacies. The Sponsors have indicated that there will be some certified pharmacies that have agreed to publicly disclose their status, making this information available to certified prescribers who wish to use a pharmacy to dispense mifepristone.

5. REMS Assessment Plan

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 335 of 357

The REMS Assessment Plan is summarized in the REMS Supporting Document and will be included in the REMS Modification Approval letter.

The REMS Assessment Plan was revised to align with the modified REMS goal and objectives.

The goal of the Mifepristone REMS Program is to mitigate the risk of serious complications associated with mifepristone by:

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

b. Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.
    - This objective will be assessed using REMS Certification Statistics and REMS Compliance metrics.

c. Informing patients about the risk of serious complications associated with mifepristone.
    - This objective will be indirectly assessed using REMS Certification Statistics to avoid compromising patient and prescriber confidentiality. As part of the certification process, healthcare providers agree to:
        - Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained
        - Ensure that the *Patient Agreement Form* is signed by the healthcare provider and the patient
        - Ensure that the patient is provided with a copy of the *Patient Agreement Form* and the Medication Guide
        - Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record

The following revisions were made from the Mifepristone REMS Assessment Plan in the April 11, 2019, Supplement Approval letter:

The Assessment Plan Categories of 1) Program Implementation and Operations and 2) Overall Assessment of REMS Effectiveness were added.

REMS Certification Statistics metrics were added to capture certification numbers for program stakeholders to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. The total number of certified prescribers who certified with the wholesaler/distributor and the total number of certified prescribers who submitted a *Prescriber Agreement Form* to certified pharmacies were added to capture the additional method of prescriber certification. The number of newly certified prescribers and the number of active certified prescribers (i.e., those who ordered mifepristone or submitted a prescription during the reporting period) were added. Metrics were also added to capture the total number of certified, newly certified, and active certified pharmacies as well as the total number of authorized, newly authorized, and active authorized wholesaler/distributors.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 336 of 357

Drug Utilization Data metrics were added to obtain information on shipment and dispensing of mifepristone. Metrics were added to capture the total number of tablets shipped by the wholesaler/distributor and the number of prescriptions dispensed.

REMS Compliance Data metrics were added to assess the first objective of requiring healthcare providers who prescribe mifepristone to be certified and the second objective of ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers. These metrics capture program deviations and evaluate overall if the REMS is operating as intended. Metrics include certified pharmacies and wholesaler/distributor audit results and a summary of instances of non-compliance and actions taken to address non-compliance. Prescriber compliance metrics were added to assess if prescribers are decertified along with reasons why. Pharmacy compliance metrics were added to assess if prescriptions were dispensed that were written by non-certified prescribers or if mifepristone tablets were dispensed by non-certified pharmacies as well as the number of pharmacies that were decertified along with reasons why. Wholesaler/distributor metrics were added to assess if shipments were sent to non-certified prescribers and non-certified pharmacies and corrective actions taken. The audit plan and non-compliance plans will be submitted for FDA review within 60 days after the REMS modification approval.

The Sponsors were asked to develop an assessment of prescription delivery timelines to determine what percentage of prescriptions were delivered on time (within four calendar days) and what percentage were delivered late (more than four calendar days) along with the length of the delay and reasons for the delay (e.g., mifepristone is out of stock shipment issues, other). The protocol for this assessment will be submitted for FDA review within 60 days after the REMS modification approval.

The revised REMS Assessment Plan is in the Appendix.

Reviewer's Comment*: We agree with the Sponsors' proposed REMS Assessment Plan.*

6. Discussion

The Sponsors submitted changes to the REMS to remove the requirement that mifepristone be dispensed only in certain healthcare settings (i.e., the "in-person dispensing requirement") and to add that certified pharmacies can dispense the drug in order to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. The REMS goal was updated to this effect. Changes were required for prescriber requirements and Sponsors to support the change in ETASU, and new pharmacy requirements were introduced.

The qualifications to become a certified prescriber have not changed as a result of the modification to the Mifepristone REMS Program; however, clarification has been provided for certain prescriber requirements and new prescriber requirements have been added to support pharmacy dispensing. Although certain responsibilities may be conducted by staff under the supervision of a certified prescriber, the certified prescriber remains responsible for ensuring compliance with the requirements of the Mifepristone REMS Program. In order to clarify this, revisions were made throughout the prescriber requirements and REMS materials to reflect that the certified prescriber is responsible for ensuring that the prescriber requirements are met. Additionally, the review team finds it acceptable that certified prescribers who wish to use a certified pharmacy to dispense mifepristone submit their *Prescriber Agreement Form* to the dispensing certified pharmacy (b) (4) . The burden to prescriber and

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 337 of 357

pharmacy stakeholders of having certified prescribers submit the form directly to the certified pharmacy that will be dispensing the mifepristone is not unreasonable and has been minimized to the extent possible; it does not impact the safe use of the product. Prescriber requirements necessitated by the addition of some pharmacy requirements were added as well and include prescriber responsibilities in deciding whether or not mifepristone should be dispensed if the patient will receive the drug from the certified pharmacy more than four days after the pharmacy receives the prescription, and prescriber adverse event reporting requirements if a prescriber becomes aware of a patient death and the mifepristone was dispensed from a certified pharmacy. The addition of the latter requirements will ensure consistent adverse event data is relayed to the relevant Mifepristone Sponsor.

Changes were made to the *Patient Agreement Form.* Changes to the form were added to improve clarity of the safety messages. After further consideration, the patient's agreement to take the Medication Guide with them if they visit an emergency room or HCP who did not give them mifepristone so the emergency room or HCP will understand that the patient is having a medical abortion has been removed from the *Patient Agreement Form*. The Medication Guide is not typically carried by patients and this information can be obtained at the point of care. Changes align with updates to labeling submitted with this modification.[13, 14]

The Agency and Sponsors agreed during this modification to focus on certification of pharmacies that can receive *Prescriber Agreement Forms* via email or fax to complete the prescriber certification process. The proposed pharmacy certification requirements also support timely dispensing of mifepristone. If the mifepristone is shipped to the patient, the REMS requires that it must be delivered within four calendar days from the receipt of the prescription by the pharmacy; if the patient will receive the mifepristone more than four calendar days from pharmacy receipt of prescription, the REMS requires the pharmacist to confirm with the certified prescriber that it is still appropriate to dispense the drug to the patient. This allows prescribers to make treatment decisions based on individual patient situations. A requirement to maintain confidentiality was also added to avoid unduly burdening patient access since patients and prescribers may not utilize pharmacy dispensing if they believe their personal information is at risk. Ultimately, the addition of pharmacy distribution with the proposed requirements will offer another option for dispensing mifepristone, alleviating burden associated with the REMS.

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The Agency reviewed the REMS in 2021, and per the review team's conclusions, a REMS modification was necessary to remove the in-person dispensing requirement and add a requirement that pharmacies that dispense the drug be specially certified; the review team concluded that these changes could occur without compromising patient safety. There have been no new safety concerns identified relevant to the REMS ETASUs that the applicants proposed modifying in their June 22, 2022 submissions since the REMS Modification Notification letters dated 12/16/2021. It is still the position of the review team that the proposed modification is acceptable.

Because the modification proposed include changes to the ETASU of the Mifepristone REMS Program, the assessment plan and timetable of assessments were changed. The assessment plan will capture information on pharmacy dispensing and provide valuable insight as to whether the program is operating as intended Annual assessments are consistent with other approved REMS modifications for major modifications necessitating extensive assessment plan changes.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 338 of 357

As part of the REMS Assessment Plan, the REMS goal and objectives are assessed using Program Implementation and Operations Metrics, including REMS Certification Statistics and REMS Compliance Data. The metrics will provide information on the number of certified prescribers, certified pharmacies, and authorized wholesalers/distributors as well as if mifepristone is dispensed by non-certified prescribers or pharmacies. The Sponsors will use the indirect measure of healthcare provider certification to address the objective of informing patients of the risk of serious complications of mifepristone, due to concerns with prescriber and patient confidentiality. Although we typically assess whether patients are informed of the risks identified in a REMS through patient surveys and/or focus groups, we agree that the Sponsors' continued use of the indirect measure of healthcare provider certification adequately addresses the Mifepristone REMS Program objective of informing patients. In addition, because of these prescriber and patient confidentiality concerns, we believe it is unlikely that the Agency would be able to use the typical methods of assessment of patient knowledge and understanding of the risks and safe use of mifepristone.

7. Conclusions and Recommendations

The review team finds the proposed REMS modification for the Mifepristone REMS Program, as submitted on June 22, 2022, and amended on October 19, 2022 (Danco) and October 20, 2022 (GBP), November 30, 2022 (both), December 9 (both), and December 16 (both) acceptable. The REMS materials were amended to be consistent with the revised REMS document. The review team recommends approval of the Mifepristone REMS Program, received on June 22, 2022, and last amended on December 16, 2022, and appended to this review.

8. References

1. (b) (6) Clinical Review of SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909590.

2. (b) (6) Summary Review for Regulatory Action for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909594.

3. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909588.

4. (b) (6) REMS Review for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909587.

5. Approval Letter for SE-2 Efficacy Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 3909592.

6. (b) (6) REMS Review for mifepristone, NDA 020687. February 22, 2018. DARRTS Reference ID: 4224674.

7. Approval Letter for SE-20 REMS Supplement for mifepristone, NDA 020687. March 29, 2016. DARRTS Reference ID: 4418041.

8. *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 339 of 357

Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

9. (b) (6) REMS Modification Rationale Review for mifepristone, NDA 020687. December 16, 2021. DARRTS Reference ID: 4905882.

10. General Advice Letter for the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone, NDA 020687, April 15, 2022. DARRTS ID 4969358.

11. Format and Content of a REMS Document Guidance for Industry https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf. Accessed on December 18, 2022.

12. Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. Contraception 2022; 107:36-41. https://doi.org/10.1016/j.contraception.2021.09.008. This article was included in the literature review for the December 16, 2021 REMS Modification Rationale Review, while the article was still in press.

9. Appendices

REMS Document

Prescriber Agreement Form for Danco Laboratories, LLC

Prescriber Agreement Form for GenBioPro, Inc.

Patient Agreement Form

Pharmacy Agreement Form for Danco Laboratories, LLC

Pharmacy Agreement Form for GenBioPro, Inc.

Mifepristone REMS Assessment Plan

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 340 of 357

Initial Shared System REMS approval: 04/2019
Most Recent Modification: 01/2023

Mifepristone Tablets, 200 mg
Progestin Antagonist

RISK EVALUATION AND MITIGATION STRATEGY (REMS)
SINGLE SHARED SYSTEM FOR MIFEPRISTONE 200 MG

I. GOAL

The goal of the REMS for mifepristone is to mitigate the risk of serious complications associated with mifepristone by:

a) Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program.

b) Ensuring that mifepristone is only dispensed by or under the supervision of certified prescribers, or by certified pharmacies on prescriptions issued by certified prescribers.

c) Informing patients about the risk of serious complications associated with mifepristone.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe mifepristone must be specially certified.
   a. To become specially certified to prescribe mifepristone, healthcare providers must:
      i. Review the Prescribing Information for mifepristone.
      ii. Complete a *Prescriber Agreement Form*. By signing[1] a *Prescriber Agreement Form*, prescribers agree that:
         1) They have the following qualifications:
            a) Ability to assess the duration of pregnancy accurately
            b) Ability to diagnose ectopic pregnancies
            c) Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
         2) They will follow the guidelines for use of mifepristone (see b.i-vii below).
   b. As a condition of certification, prescribers must follow the guidelines for use of mifepristone described below:
      i. Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
      ii. Ensure that the healthcare provider and patient sign the *Patient Agreement Form.*

[1] In this REMS, the terms "sign" and "signature" include electronic signatures.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 341 of 357

iii. Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.

iv. Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.

v. Ensure that any deaths are reported to the Mifepristone Sponsor that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

vi. If mifepristone will be dispensed by a certified pharmacy:

1) Provide the certified pharmacy a signed *Prescriber Agreement Form*.

2) Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.

3) Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of the patient.

vii. The certified prescriber who dispenses mifepristone or who supervises the dispensing of mifepristone must:

1) Provide an authorized distributor with a signed *Prescriber Agreement Form*.

2) Ensure that the NDC and lot number from each package of mifepristone dispensed are recorded in the patient's record.

3) Ensure that healthcare providers under their supervision follow guidelines i.-v.

c. Mifepristone Sponsors must:

i. Ensure that healthcare providers who prescribe their mifepristone are specially certified in accordance with the requirements described above and de-certify healthcare providers who do not maintain compliance with certification requirements.

ii. Ensure prescribers previously certified in the Mifepristone REMS Program complete the new *Prescriber Agreement Form*:

1) Within 120 days after approval of this modification, for those previously certified prescribers submitting prescriptions to certified pharmacies.

2) Within one year after approval of this modification, if previously certified and ordering from an authorized distributor.

iii. Ensure that healthcare providers can complete the certification process by email or fax to an authorized distributor and/or certified pharmacy.

iv. Provide the Prescribing Information and their *Prescriber Agreement Form* to healthcare providers who inquire about how to become certified.

v. Ensure annually with each certified prescriber that their locations for receiving mifepristone are up to date.

The following materials are part of the Mifepristone REMS Program:

- *Prescriber Agreement Form for Danco Laboratories, LLC*
- *Prescriber Agreement Form for GenBioPro, Inc.*
- *Patient Agreement Form*

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 342 of 357

2. Pharmacies that dispense mifepristone must be specially certified

   a. To become specially certified to dispense mifepristone, pharmacies must:

      i. Be able to receive *Prescriber Agreement Forms* by email and fax.

      ii. Be able to ship mifepristone using a shipping service that provides tracking information.

      iii. Designate an authorized representative to carry out the certification process on behalf of the pharmacy.

      iv. Ensure the authorized representative oversees implementation and compliance with the Mifepristone REMS Program by doing the following:

         1) Review the Prescribing Information for mifepristone.

         2) Complete a *Pharmacy Agreement Form*. By signing a *Pharmacy Agreement Form*, the authorized representative agrees that the pharmacy will put processes and procedures in place to ensure the following requirements are completed:

            a) Verify that the prescriber is certified by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with the pharmacy.

            b) Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in c) below.

            c) Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.

            d) Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.

            e) Track and verify receipt of each shipment of mifepristone.

            f) Dispense mifepristone in its package as supplied by the Mifepristone Sponsor.

            g) Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to the Mifepristone Sponsor that provided the mifepristone. Notify the Mifepristone Sponsor that provided the dispensed mifepristone that the pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.

            h) Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.

            i) Maintain records of *Prescriber Agreement Forms*.

            j) Maintain records of dispensing and shipping.

            k) Maintain records of all processes and procedures including compliance with those processes and procedures.

            l) Maintain the identity of the patient and prescriber as confidential, including limiting access to patient and prescriber identity only to those personnel necessary to dispense mifepristone in accordance with the Mifepristone REMS Program requirements, or as necessary for payment and/or insurance purposes.

            m) Train all relevant staff on the Mifepristone REMS Program requirements.

Reference ID: 5103819
Case 1:23-cv-00077-CCE-LPA Document 73-1 Filed 06/02/23 Page 343 of 357

n) Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

b. Mifepristone Sponsors must:

i. Ensure that pharmacies are specially certified in accordance with the requirements described above and de-certify pharmacies that do not maintain compliance with certification requirements.

ii. Ensure that pharmacies can complete the certification process by email and fax to an authorized distributor.

i. Verify annually that the name and contact information for the pharmacy's authorized representative corresponds to that of the current designated authorized representative for the certified pharmacy, and if different, require the pharmacy to recertify with the new authorized representative.

The following materials are part of the Mifepristone REMS Program:

- *Pharmacy Agreement Form for Danco Laboratories, LLC*
- *Pharmacy Agreement Form for GenBioPro, Inc.*

3. Mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions as ensured by the certified prescriber in signing the *Prescriber Agreement Form*.

a. The patient must sign a *Patient Agreement Form* indicating that the patient has:

i. Received, read and been provided a copy of the *Patient Agreement Form*.

ii. Received counseling from the healthcare provider regarding the risk of serious complications associated with mifepristone.

B. Implementation System

1. Mifepristone Sponsors must ensure that their mifepristone is only distributed to certified prescribers and certified pharmacies by:

a. Ensuring that distributors who distribute their mifepristone comply with the program requirements for distributors.

i. The distributors must put processes and procedures in place to:

1) Complete the certification process upon receipt of a *Prescriber Agreement Form* or *Pharmacy Agreement Form*.

2) Notify healthcare providers and pharmacies when they have been certified by the Mifepristone REMS Program.

3) Ship mifepristone only to certified pharmacies or locations identified by certified prescribers.

4) Not ship mifepristone to pharmacies or prescribers who become de-certified from the Mifepristone REMS Program.

5) Provide the Prescribing Information and their Prescriber Agreement Form to healthcare providers who (1) attempt to order mifepristone and are not yet certified, or (2) inquire about how to become certified.

ii. Put processes and procedures in place to maintain a distribution system that is secure,

Reference ID: 5103819

confidential and follows all processes and procedures, including those for storage, handling, shipping, tracking package serial numbers, NDC and lot numbers, proof of delivery and controlled returns of mifepristone.

iii. Train all relevant staff on the Mifepristone REMS Program requirements.

iv. Comply with audits by Mifepristone Sponsors or a third party acting on behalf of Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed for the Mifepristone REMS Program. In addition, distributors must maintain appropriate documentation and make it available for audits.

b. Ensuring that distributors maintain secure and confidential distribution records of all shipments of mifepristone.

2. Mifepristone Sponsors must monitor their distribution data to ensure compliance with the Mifepristone REMS Program.

3. Mifepristone Sponsors must ensure that adequate records are maintained to demonstrate that the Mifepristone REMS Program requirements have been met, including, but not limited to records of mifepristone distribution; certification of prescribers and pharmacies; and audits of pharmacies and distributors. These records must be readily available for FDA inspections.

4. Mifepristone Sponsors must audit their new distributors within 90 calendar days and annually thereafter after the distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their distributor compliance if noncompliance is identified.

5. Mifepristone Sponsors must audit their certified pharmacies within 180 calendar days after the pharmacy places its first order of mifepristone, and annually thereafter audit certified pharmacies that have ordered mifepristone in the previous 12 months, to ensure that all processes and procedures are in place and functioning to support the requirements of the Mifepristone REMS Program. Mifepristone Sponsors will take steps to address their pharmacy compliance if noncompliance is identified.

6. Mifepristone Sponsors must take reasonable steps to improve implementation of and compliance with the requirements of the Mifepristone REMS Program based on monitoring and assessment of the Mifepristone REMS Program.

7. Mifepristone Sponsors must report to FDA any death associated with mifepristone whether or not considered drug-related, as soon as possible but no later than 15 calendar days from the initial receipt of the information by the Mifepristone Sponsor. This requirement does not affect the sponsors' other reporting and follow-up requirements under FDA regulations.

C. Timetable for Submission of Assessments

The NDA Sponsor must submit REMS assessments to FDA one year from the date of the approval of the modified REMS (1/3/2023) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 90 calendar days before the submission date for that assessment. The NDA Sponsor must submit each assessment so that it will be received by the FDA on or before the due date.

Reference ID: 5103819

MIFEPREX® (Mifepristone) Tablets, 200 mg

PRESCRIBER AGREEMENT FORM

Mifeprex* (Mifepristone) Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit Mifeprex prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit Mifeprex prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order Mifeprex for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where Mifeprex will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free), or by visiting www.earlyoptionpill.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received Mifeprex are reported to Danco Laboratories, LLC, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of Mifeprex that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If Mifeprex will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing Mifeprex when contacted by a certified pharmacy about patients who will receive Mifeprex more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of Mifeprex the patient received in the event the prescriber becomes aware of the death of a patient.
- If Mifeprex will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of Mifeprex are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]

Mifepristone Tablets, 200 mg, is indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy through 70 days gestation. Please see Prescribing Information and Medication Guide for complete safety information.

To ***become a certified prescriber***, you must:

- **If you submit mifepristone prescriptions for dispensing from certified pharmacies**:
  - Submit this form to each certified pharmacy to which you intend to submit mifepristone prescriptions. The form must be received by the certified pharmacy before any prescriptions are dispensed by that pharmacy.
- **If you order mifepristone for dispensing by you or healthcare providers under your supervision:**
  - Submit this form to the distributor. This form must be received by the distributor before the first order will be shipped to the healthcare setting.
  - Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

Prescriber Agreement: By signing this form, you agree that you meet the qualifications below and will follow the guidelines for use. You are responsible for overseeing implementation and compliance with the Mifepristone REMS Program. You also understand that if the guidelines below are not followed, the distributor may stop shipping mifepristone to the locations that you identify and certified pharmacies may stop accepting your mifepristone prescriptions.

Mifepristone must be provided by or under the supervision of a certified prescriber who meets the following qualifications:

- Ability to assess the duration of pregnancy accurately.
- Ability to diagnose ectopic pregnancies.
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others, and be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855—643-3463 toll-free), or by visiting www.MifeInfo.com.

In addition to meeting these qualifications, you also agree to follow these guidelines for use:

- Ensure that the *Patient Agreement Form* is reviewed with the patient and the risks of the mifepristone treatment regimen are fully explained. Ensure any questions the patient may have prior to receiving mifepristone are answered.
- Ensure the healthcare provider and patient sign the *Patient Agreement Form*.
- Ensure that the patient is provided with a copy of the *Patient Agreement Form* and Medication Guide.
- Ensure that the signed *Patient Agreement Form* is placed in the patient's medical record.
- Ensure that any deaths of patients who received mifepristone are reported to GenBioPro, Inc. that provided the mifepristone, identifying the patient by a non-identifiable reference and including the NDC and lot number from the package of mifepristone that was dispensed to the patient.

Ensure that healthcare providers under your supervision follow the guidelines listed above.

- If mifepristone will be dispensed through a certified pharmacy:
  - Assess appropriateness of dispensing mifepristone when contacted by a certified pharmacy about patients who will receive mifepristone more than 4 calendar days after the prescription was received by the certified pharmacy.
  - Obtain the NDC and lot number of the package of mifepristone the patient received in the event the prescriber becomes aware of the death of a patient.
- If mifepristone will be dispensed by you or by healthcare providers under your supervision:
  - Ensure the NDC and lot number from each package of mifepristone are recorded in the patient's record.

I understand that a certified pharmacy may dispense mifepristone made by a different manufacturer than that stated on this Prescriber Agreement Form.

Print Name: _____ Title: _____

Signature: _____ Date: _____

Medical License # _____ State _____

NPI # _____

Practice Setting Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]

PATIENT AGREEMENT FORM Mifepristone Tablets, 200 mg

Healthcare Providers: *Counsel the patient on the risks of mifepristone. Both you and the patient must provide a written or electronic signature on this form.*

Patient Agreement:

1. I have decided to take mifepristone and misoprostol to end my pregnancy and will follow my healthcare provider's advice about when to take each drug and what to do in an emergency.
2. I understand:
   - **a.** I will take mifepristone on Day 1.
   - **b.** I will take the misoprostol tablets 24 to 48 hours after I take mifepristone.
3. My healthcare provider has talked with me about the risks, including:
   - heavy bleeding
   - infection
4. I will contact the clinic/office/provider right away if in the days after treatment I have:
   - a fever of 100.4°F or higher that lasts for more than four hours
   - heavy bleeding (soaking through two thick full-size sanitary pads per hour for two hours in a row)
   - severe stomach area (abdominal) pain or discomfort, or I am “feeling sick,” including weakness, nausea, vomiting, or diarrhea, more than 24 hours after taking misoprostol
     — these symptoms may be a sign of a serious infection or another problem (including an ectopic pregnancy, a pregnancy outside the womb).

   My healthcare provider has told me that these symptoms listed above could require emergency care. If I cannot reach the clinic/office/provider right away, my healthcare provider has told me who to call and what to do.
5. I should follow up with my healthcare provider about 7 to 14 days after I take mifepristone to be sure that my pregnancy has ended and that I am well.
6. I know that, in some cases, the treatment will not work. This happens in about 2 to 7 out of 100 women who use this treatment. If my pregnancy continues after treatment with mifepristone and misoprostol, I will talk with my provider about a surgical procedure to end my pregnancy.
7. If I need a surgical procedure because the medicines did not end my pregnancy or to stop heavy bleeding, my healthcare provider has told me whether they will do the procedure or refer me to another healthcare provider who will.
8. I have the MEDICATION GUIDE for mifepristone.
9. My healthcare provider has answered all my questions.

Patient Signature: _____ **Patient Name** (print): _____ **Date**: _____

Provider Signature: _____ **Provider Name** (print): _____ **Date**: _____

Patient Agreement Forms may be provided, completed, signed, and transmitted in paper or electronically.

01/2023

MIFEPREX®(Mifepristone) Tablets, 200mg

PHARMACY AGREEMENT FORM

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense Mifeprex is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense Mifeprex is able to ship Mifeprex using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for Mifeprex. The Prescribing Information is available by calling 1-877-4 EARLY OPTION (1-877-432-7596 toll-free) or online at www.earlyoptionpill.com; and
- Each location of my pharmacy that will dispense Mifeprex will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting Mifeprex orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense Mifeprex such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing Mifeprex for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of Mifeprex dispensed.
  - Track and verify receipt of each shipment of Mifeprex.
  - Dispense mifepristone in its package as supplied by Danco Laboratories, LLC.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of Mifeprex dispensed to the patient, and remind the prescriber of their obligation to report the deaths to Danco Laboratories, LLC. Notify Danco that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, and all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of Mifeprex patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185
1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to Mifeprex@dancodistributor.com or fax to 1-866-227-3343.

DANCO
Support • Progress • Options

*MIFEPREX is a registered trademark of Danco Laboratories, LLC

P.O. Box 4816-New York, NY 10185

1-877-4-EARLY-OPTION (1-877-432-7596) www.earlyoptionpill.com

PHARMACY AGREEMENT FORM **Mifepristone Tablets, 200 mg**

Pharmacies must designate an authorized representative to carry out the certification process and oversee implementation and compliance with the Mifepristone REMS Program on behalf of the pharmacy.

Healthcare settings, such as medical offices, clinics, and hospitals, where mifepristone will be dispensed by or under the supervision of a certified prescriber in the Mifepristone REMS Program do not require pharmacy certification.

By signing this form, as the Authorized Representative I certify that:

- Each location of my pharmacy that will dispense mifepristone is able to receive *Prescriber Agreement Forms* by email and fax.
- Each location of my pharmacy that will dispense mifepristone is able to ship mifepristone using a shipping service that provides tracking information.
- I have read and understood the Prescribing Information for mifepristone. The Prescribing Information is available by calling 1-855-MIFE-INFO (1-855-643-3463 toll-free) or online at www.MifeInfo.com; and
- Each location of my pharmacy that will dispense mifepristone will put processes and procedures in place to ensure the following requirements are completed. I also understand that if my pharmacy does not complete these requirements, the distributor may stop accepting mifepristone orders.
  - Verify that the prescriber is certified in the Mifepristone REMS Program by confirming their completed *Prescriber Agreement Form* was received with the prescription or is on file with your pharmacy.
  - Dispense mifepristone such that it is delivered to the patient within 4 calendar days of the date the pharmacy receives the prescription, except as provided in the following bullet.
  - Confirm with the prescriber the appropriateness of dispensing mifepristone for patients who will receive the drug more than 4 calendar days after the date the pharmacy receives the prescription and document the prescriber's decision.
  - Record in the patient's record the NDC and lot number from each package of mifepristone dispensed.
  - Track and verify receipt of each shipment of mifepristone.
  - Dispense mifepristone in its package as supplied by GenBioPro, Inc.
  - Report any patient deaths to the prescriber, including the NDC and lot number from the package of mifepristone dispensed to the patient, and remind the prescriber of their obligation to report the deaths to GenBioPro, Inc. Notify GenBioPro that your pharmacy submitted a report of death to the prescriber, including the name and contact information for the prescriber and the NDC and lot number of the dispensed product.
  - Not distribute, transfer, loan or sell mifepristone except to certified prescribers or other locations of the pharmacy.
  - Maintain records of *Prescriber Agreement Forms*, dispensing and shipping, all processes and procedures including compliance with those processes and procedures.
  - Maintain the identity of mifepristone patients and prescribers as confidential and protected from disclosure except to the extent necessary for dispensing under this REMS or as necessary for payment and/or insurance purposes.
  - Train all relevant staff on the Mifepristone REMS Program requirements.
  - Comply with audits carried out by the Mifepristone Sponsors or a third party acting on behalf of the Mifepristone Sponsors to ensure that all processes and procedures are in place and are being followed.

Any new authorized representative must complete and submit the *Pharmacy Agreement Form*.

Authorized Representative Name: _____ Title: _____

Signature: _____ Date: _____

Email: _____ Phone: _____ Preferred __ email __ phone

Pharmacy Name: _____

Pharmacy Address: _____

Return completed form to **RxAgreements@GenBioPro.com** or fax to **1-877-239-8036.**

The REMS Assessment Plan must include but is not limited to the following items.

Program Implementation and Operations

1. REMS Certification Statistics
   a. Prescribers
      i. Number of certified prescribers who have certified with the Sponsor's distributor(s) and number who have submitted *Prescriber Agreement Forms* to Certified Pharmacies
      ii. Number and percentage of newly certified prescribers
      iii. Number and percentage of active certified prescribers (i.e., who ordered mifepristone or submitted a prescription during the reporting period)

   b. Pharmacies
      i. Number of certified pharmacies
      ii. Number and percentage of newly certified pharmacies
      iii. Number and percentage of active certified pharmacies (i.e., that dispensed mifepristone during the reporting period)
   c. Wholesalers/Distributors
      i. Number of authorized wholesalers/distributors
      ii. Number and percentage of newly authorized wholesalers/distributors
      iii. Number and percentage of active authorized wholesalers/distributors (i.e. that shipped mifepristone during the reporting period)

2. Utilization Data
   a. Total number of tablets shipped by wholesalers/distributors, stratified by Certified Prescriber or Certified Pharmacy location
   b. Number of prescriptions dispensed from pharmacies

3. REMS Compliance Data
   a. Audits: Summary of audit activities for each stakeholder (i.e., certified pharmacies and wholesalers/distributors) including but not limited to:
      i. A copy of the final audit plan for each stakeholder type (provide for the current reporting period)
      ii. The number of audits expected, and the number of audits performed
      iii. The number and type of deficiencies noted
      iv. For those with deficiencies noted, report the corrective and preventive actions (CAPAs) required, if any, to address the deficiencies, including the status (e.g., completed, not completed, in progress) (provide for the current reporting period)
      v. For any stakeholders that did not complete the CAPA within the timeframe specified in the audit plan, describe actions taken (provide for the current reporting period)

Reference ID: 5103819

vi. A summary report of all resulting changes to processes and procedures necessary to ensure compliance with the REMS requirements (provide for the current reporting period)

b. A summary report of non-compliance, associated corrective action plans (CAPAs), and the status of CAPAs including but not limited to:

i. A copy of the final non-compliance plans for Pharmacies and Distributors (provide for the current reporting period)

ii. For each instance of noncompliance below (iii-v), report the following information (provide for the current reporting period):

1. A unique, anonymized ID for the stakeholder(s) associated with the non-compliance event to enable tracking over time
2. The source of the non-compliance data (e.g., self-reported, audit, other)
3. A root cause analysis of the non-compliance
4. Actions to prevent future occurrences and outcomes of such actions

iii. Prescriber compliance

1. Number and percentage of certified prescribers who became decertified as a result of non- compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
2. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

iv. Pharmacy compliance

1. Number and percentage of prescriptions dispensed that were written by prescriber(s) who did not submit a Prescriber Agreement to the dispensing Certified Pharmacy
2. Number and percentage of mifepristone tablets dispensed by non-certified pharmacies
3. Number and percentage of pharmacies that became decertified as a result of non-compliance
   - Provide a summary of reasons for decertification (provide for the current reporting period)
4. An assessment of prescription delivery timelines, including percentage delivered more than four days after receipt of the prescription, duration and causes for delay. A proposal for this assessment will be submitted within 60 days of the approval of the REMS Modification.
5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

v. Wholesaler/distributor compliance

1. Number of healthcare providers who successfully ordered mifepristone who were not certified
2. Number of non-certified pharmacies that successfully ordered mifepristone
3. Number of shipments sent to non-certified prescriber receiving locations
4. Number of shipments sent to non-certified pharmacy receiving locations

Reference ID: 5103819

5. Summary and analysis of any program deviations and corrective actions taken (provide for the current reporting period)

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Reference ID: 5103819

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Exhibit B

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD,

Plaintiff,

v.

JOSHUA H. ~~STEIN, in his official capacity as Attorney General for the State of North Carolina; JEFF NIEMAN, in his official capacity as District Attorney for North Carolina 18th Prosecutorial District; KODY H. KINSLEY, in his official capacity as the North Carolina Secretary of Health and Human Services; MICHAUX R. KILPATRICK, MD, PhD, in her official capacity as President of the North Carolina Medical Board; and CHRISTINE M. KHANDELWAL, DO; DEVDUTTA G. SANGVAI, MD, MBA; JOHN W. RUSHER, MD, JD; WILLIAM M. BRAWLEY; W. HOWARD HALL, MD; SHARONA Y. JOHNSON, PhD, FNP-BC; JOSHUA D. MALCOLM, JD; MIGUEL A. PINEIRO, PA-C, MHPE; MELINDA H. PRIVETTE, MD, JD; ANURADHA RAO-PATEL, MD; and ROBERT RICH, JR., MD, in their official capacities as Board Members of the North Carolina Medical Board,~~STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*,

Case No.:
1:23-cv-~~77~~00077-WO-LPA

FIRST AMENDED
COMPLAINT

Defendants,

and

TIMOTHY K. MOORE and
PHILIP E. BERGER,

Intervenors.

INTRODUCTION

1. Under well-settled principles of preemption that preserve American federalism, a State cannot impose laws that conflict with and frustrate the objectives of federal law. When Congress enacted the Risk Evaluation and Mitigation Strategies ("REMS") provisions of the Federal Food, Drug, and Cosmetic Act ("FDCA"), its clear objective was to ensure that REMS drugs are regulated in a way that is commensurate with their risks while not imposing undue burdens on the healthcare system or patient access. The U.S. Food and Drug Administration ("FDA" or the "Agency") has acted pursuant to this authority to impose a precise set of controls on an FDA-approved drug, mifepristone. A State may not impose additional controls—including restrictions that FDA has specifically rejected—that upset the carefully balanced regulatory scheme established by federal law.

2. In the FDCA, Congress granted FDA exclusive authority to impose restrictions on the prescribing, dispensing, and administration of drugs that the Agency deems to pose particular risks but for which the importance of patient access justifies imposition of special controls. FDA imposes those controls by way of a REMS, which sometimes includes special Elements to Assure Safe Use ("ETASU"). *See* 21 U.S.C. § 355-1. In granting FDA (and only FDA) authority to impose drug-specific REMS and ETASU, Congress expressly charged the Agency with striking a balance between access to treatments and protection from identified risks, instructing FDA to impose only those restrictions necessary to ensure safety without imposing undue burdens on access or on the healthcare delivery system. *See id.* § 355-1(f).

3. In 2000, after several years of review of voluminous data, FDA concluded that mifepristone is safe and effective and approved the drug for use under the trade name Mifeprex. Specifically, FDA approved mifepristone for the medical termination of intrauterine pregnancy, in a two-drug regimen with misoprostol. Exercising its authority first under regulation and subsequently under its exclusive REMS

statutory authority, FDA has subjected Mifeprex to a carefully crafted set of regulatory controls that the Agency concluded were commensurate with the drug's risks while not unduly burdening patient access or the healthcare system. In doing so, FDA determined that any risk-mitigation benefits from additional restrictions would be outweighed by added burdens on patient access and the healthcare system.

4. During the more than two decades since FDA's approval of mifepristone as a safe and effective option for ending early pregnancy, medication abortion has been used by more than 5 million patients and now accounts for more than half of abortions nationwide. *See* Rachel K. Jones et al., Guttmacher Inst., *Medication Abortion Now Accounts for More than Half of All US Abortions* (updated Dec. 1, 2022), https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions. Over that time, substantial additional evidence of safe and effective use has accumulated.

5. As more data and evidence have emerged, the Agency has revised and fine-tuned the Mifepristone REMS numerous times as part of its ongoing obligation under the REMS

provisions of the FDCA. In its current form, the Mifepristone REMS requires providers to prescribe mifepristone under an FDA-approved Certified Prescriber Agreement, and to dispense mifepristone either directly or by issuing the prescription to a certified pharmacy. The Prescriber Agreement requires that providers be specially certified and possess certain qualifications~~.~~, and that they agree to report any patient deaths to the drug sponsor. The Mifepristone REMS also requires providers to ensure that medication abortion patients receive specific counseling and information, including a copy of the mifepristone Medication Guide, and that they consent by using an FDA-approved Patient Agreement Form. *See* FDA, Single Shared System for Mifepristone 200 MG, Risk Evaluation and Mitigation Strategy (REMS) (2023) ("2023 Mifepristone REMS~~") (2023),~~"), attached as Ex. A. The Mifepristone REMS does *not* require, because FDA has affirmatively determined it should not, that mifepristone be provided by physicians only~~,~~; that it be provided in person or in specially certified facilities~~, or~~; that it be preceded by in-person counseling, a 72-hour waiting period, an in-person examination by a physician, an ultrasound in all cases,

or a determination of blood type; that the physician schedule an in-person follow-up visit with the patient; or that the physician report all adverse events potentially associated with the drug.

6. Rejecting the regulatory framework imposed by Congress and FDA, North Carolina has imposed (and recently expanded) a complex web of requirements relating to the provision of mifepristone that apply to all patients and medical providers in the state, including Plaintiff. Unlike FDA's framework, North Carolina's requirements — including recent legislative amendments that are scheduled to take effect on July 1, 2023 — state that abortion medications may be provided only in person, only by a physician, and only ~~in a specially certified facility~~ after state-mandated in-person counseling, a 72-hour waiting period, ~~and (~~an in~~ certain circumstances)~~-person physician examination, an ultrasound~~.~~, and a determination of the patient's blood type. North Carolina also mandates that physicians use different patient consent forms than those required by FDA, schedule an in-person follow-up visit with every patient, and report any and all adverse events to the State and FDA within 3 days. *See* N.C. Gen. Stat. §§ 14-44,

14-45, 14-45.1, 90-21.82, 90-21.90; ~~10A N.C. Admin. Code Subchapter 14E.~~N.C. Sess. Law 2023-14 ("S.L. 2023-14"), Part I (changes effective July 1, 2023). North Carolina's restrictions conflict with federal law and upset the regulatory balance struck by FDA, creating an obstacle to the congressional objectives that FDA carried out in imposing the Mifepristone REMS.

7. Plaintiff is a physician who regularly provides care to patients of reproductive age and ability and who regularly prescribes mifepristone, as she is certified to do under the Mifepristone REMS. When prescribing mifepristone, Plaintiff complies with all of the Mifepristone REMS requirements, as she must to maintain her prescriber certification.

8. As a medical provider in North Carolina, Plaintiff is also subject to North Carolina's requirements relating to providing mifepristone. Under the North Carolina restrictions, instead of having the option of seeing patients ~~in an office setting (or~~ remotely via telehealth~~)~~ and ~~having the option of~~ either dispensing the medications or providing a prescription for a patient to fill from a pharmacy so that the patient may take the medication at the place of their choosing, as FDA

expressly authorizes, Plaintiff must ~~herself provide the mifepristone for medication abortion in person and be present when it is administered in a specially certified facility. And Plaintiff must navigate an arcane system of delays, compelled statements, and unnecessary burdens on her patients and her practice that are not part of the Medication Guide, FDA-approved Patient Agreement Form, or any other part of the Mifepristone REMS~~personally examine the patient; be physically present when the patient takes the mifepristone (which must be preceded by an ultrasound, a blood-type determination, state-mandated in person counseling, and a 72-hour waiting period); schedule and attempt to ensure that the patient returns for an in-person follow-up visit; and comply with the State's onerous and unnecessary reporting requirements.

9. These restrictions impose significant costs and burdens on both Plaintiff and her patients. As a North Carolina licensed physician, Plaintiff has a professional, legal, and ethical obligation to "use h[er] best judgment in the treatment and care of h[er] patient[s]" and to "exercise reasonable care and diligence in the application of h[er] knowledge and skill to [each] patient's case." *Hunt v. Bradshaw*, 88 S.E.2d 762, 765 (N.C. 1955); *see* N.C. Med. Bd., Position Statements, *The Licensee-Patient Relationship* 2.1.1:

(Mar. 2022) ("N.C. Med. Bd. Position Statement")[1] ("All licensees should exercise their best professional judgement when making patient care decisions" regardless of "the health care system or setting in which a licensee practices.").

10. The challenged restrictions impose unnecessary costs on Plaintiff and her practice and interfere with her ability to provide medical care to her patients according to her best medical judgment and in accordance with federal law. But for those restrictions, Plaintiff would be able to provide medication abortion care to a larger number of patients at lower cost. Further, medication abortion is inherently time-critical, and delaying such care can unnecessarily increase risk or even push patients outside the window for use of mifepristone, potentially forcing patients to have more involved and more expensive procedures (which will present heightened risks for some patients). Patients also must bear all of the risks and costs of pregnancy during the delays caused by the challenged restrictions.

[1] *Available at* https://www.ncmedboard.org/images/uploads/other_pdfs/Compendium_Final_03.25.2022.pdf.

11. As part of its congressionally mandated regulatory balancing, FDA specifically considered and rejected the idea that mifepristone must be provided in person by a physician in a particular type of facility. FDA also considered and rejected more stringent physician adverse-event reporting requirements. FDA instead concluded that mifepristone can be safely prescribed by any certified healthcare provider either in person or via telehealth, obtained by the patient directly from or under the supervision of the healthcare provider or from a certified pharmacy, and taken by the patient in her home or other place of her choosing. And FDA expressly concluded that requirements like those imposed by North Carolina are unnecessary to ensure patient safety and contrary to the regulatory balance that Congress and FDA sought to achieve.

12. For North Carolina to impose restrictions that go beyond those FDA deemed warranted as part of its regulatory balancing, including restrictions that FDA specifically rejected, frustrates the objectives of federal law. In light of FDA's heightened oversight and scrutiny of REMS drugs, as instructed by Congress in the REMS provisions of the FDCA,

there is no room for North Carolina to impose additional restrictions and specific conditions for use that FDA, in the exercise of its congressionally delegated REMS authority, concluded are unwarranted and inappropriate. Simply put, North Carolina cannot stand in the shoes of FDA to impose restrictions on medication access that FDA determined are not appropriate and that upset the careful balance FDA was directed by Congress to strike.

13. Plaintiff seeks a declaratory judgment that North Carolina's restrictions on mifepristone are preempted insofar as they are inconsistent with the federal REMS, and an injunction prohibiting Defendants from enforcing those restrictions or taking any other action to restrict the ability of a provider to provide, or a patient to access, mifepristone in accordance with federal law.

PARTIES

14. Plaintiff, Dr. Amy Bryant, is a North Carolina board-certified and licensed physician with a medical practice in Orange County, North Carolina. Dr. Bryant regularly provides medical care to patients of reproductive age and ability. In that capacity, she regularly counsels

patients about the option of mifepristone for medical termination of intrauterine pregnancy, in a regimen with misoprostol. She also provides care through telemedicine for other patients, and she would provide telehealth abortion care if she could do so free from the risk of enforcement action by Defendants. She is certified to prescribe mifepristone as required by the REMS, and she regularly prescribes and dispenses mifepristone in accordance with the REMS. Plaintiff brings this action in her personal capacity.

15. Defendant Joshua Stein is the Attorney General for the State of North Carolina. He is the chief law enforcement officer of the State with the power to enforce the North Carolina restrictions at issue. He is sued in his official capacity.

16. Defendant Jeff Nieman is the District Attorney for North Carolina's 18th Prosecutorial District. He is responsible for criminal prosecutions under relevant North Carolina law occurring within Prosecutorial District 18, including in Orange County. *See* N.C. Const. art. IV, § 18(1); N.C. Gen. Stat. §§ 7A-60, 7A-61. He is sued in his official capacity.

17. Defendant Kody H. Kinsley is the North Carolina Secretary of Health and Human Services, whose department is charged with (among other things) development of consent and physician declaration forms and printed and online materials required to be referenced in state-mandated pre-abortion counseling; licensing of hospitals and certification of clinics that provide abortion; denial, suspension, and revocation of facility certifications; and investigations of complaints relating to clinics that provide abortion. *See* N.C. Gen. Stat. §§ 90-21.83, 90-21.84; 10A N.C. Admin. Code 14E.0101, *et seq*.; S.L. 2023-14, sec. 1.2, §§ 90-21.83, 90-21.83A, 90-21.84. He is sued in his official capacity.

18. Defendant Michaux R. Kilpatrick, MD, PhD, is the President of the North Carolina Medical Board, an entity created by the North Carolina legislature and which establishes procedures and requirements for licensure as a physician in North Carolina. N.C. Gen. Stat. §§ 90-2, 90-9.1. The Medical Board has the power to sanction physicians, including placing them on probation and suspending or revoking their licenses, for "[p]roducing or attempting to produce an abortion contrary to law." *Id.* § 90-14(a)(2).);

S.L. 2023-14, sec. 1.2, § 90-21.88A. She is sued in her official capacity.

19. Defendant Christine M. Khandelwal, DO, is a member and President-Elect of the North Carolina Medical Board. She is sued in her official capacity.

20. Defendant Devdutta G. Sangvai, MD, MBA, is a member and Secretary and Treasurer of the North Carolina Medical Board. He is sued in his official capacity.

21. Defendant John W. Rusher, MD, JD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

22. Defendant William M. Brawley is a member of the North Carolina Medical Board. He is sued in his official capacity.

23. Defendant W. Howard Hall, MD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

24. Defendant Sharona Y. Johnson, PhD, FNP-BC, is a member of the North Carolina Medical Board. She is sued in her official capacity.

25. Defendant Joshua D. Malcolm, JD, is a member of the

North Carolina Medical Board. He is sued in his official capacity.

26. Defendant Miguel A. Pineiro, PA-C, MHPE, is a member of the North Carolina Medical Board. He is sued in his official capacity.

27. Defendant Melinda H. Privette, MD, JD, is a member of the North Carolina Medical Board. She is sued in her official capacity.

28. Defendant Anuradha Rao-Patel, MD, is a member of the North Carolina Medical Board. She is sued in her official capacity.

29. Defendant Robert Rich, Jr., MD, is a member of the North Carolina Medical Board. He is sued in his official capacity.

JURISDICTION AND VENUE

30. This Court has original subject matter jurisdiction over this action pursuant to 28 U.S.C. § 1331 because it arises under the Constitution and laws of the United States.

31. This Court has personal jurisdiction over Defendants because they are domiciled in North Carolina and enactment and enforcement of the state laws at issue occurred and

continues to occur within North Carolina.

32. Venue is proper within the Middle District of North Carolina under 28 U.S.C. § 1391(b)(2) because Plaintiff is located and practices medicine in this judicial district.

33. This Court has the authority to enter a declaratory judgment and provide injunctive relief pursuant to 28 U.S.C. §§ 2201 and 2202, Federal Rules of Civil Procedure 57 and 65, and this Court's inherent equitable powers.

34. Plaintiff has standing because the challenged provisions of North Carolina law directly operate against Plaintiff by regulating her conduct and subjecting her to a threat of enforcement when she prescribes mifepristone or advises patients regarding the use of mifepristone. As a North Carolina licensed physician, Plaintiff has a professional, legal, and ethical obligation to "use h[er] best judgment in the treatment and care of h[er] patient[s]" and to "exercise reasonable care and diligence in the application of h[er] knowledge and skill to [each] patient's case." *Hunt*, 88 S.E.2d at 765; *see* N.C. Med. Bd. Position Statement 2.1.1 ("All licensees should exercise their best professional judgement when making patient care decisions"

regardless of "the health care system or setting in which a licensee practices."). The challenged restrictions impose unnecessary costs on Plaintiff, her patients, and her practice and interfere with her ability to provide medical care to her patients according to her best medical judgment and in accordance with federal law. But for those restrictions, Plaintiff would be able to provide a wider range of mifepristone-related services to a larger number of patients at lower cost, including by providing flexible telehealth services to patients and by delegating some tasks related to medication abortion care to non-physician colleagues. Plaintiff would be subject to direct criminal, civil, and administrative penalties under North Carolina law if she were to violate its provisions.

35. Plaintiff's claims are ripe because the challenged North Carolina laws are currently in effect and enforceable and are presently impacting her ability to provide and offer medical advice regarding mifepristone to her patients according to her best medical judgment and in accordance with federal law.

FACTUAL ALLEGATIONS

A. Statutory and Regulatory Background

36. Under the FDCA, no drug manufacturer, or "sponsor," can introduce its drug into interstate commerce unless and until that sponsor first obtains marketing approval from FDA. 21 U.S.C. §§ 321(p), 331(d), 355(a).

37. To seek approval under the FDCA, a drug sponsor must undertake a lengthy development program that typically includes, as it did in this case, significant clinical trial data, as well as extensive engagement with FDA in meetings and through written and oral feedback. The drug sponsor then submits a new drug application ("NDA") seeking FDA's authorization to sell and market the drug.

38. FDA reviews NDAs to ensure that they include adequate safety data and substantial evidence of efficacy, among other things. FDA may not approve an NDA unless it determines that the data and information included in the NDA demonstrate that the drug is both safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b).

39. Because all drugs have the potential for adverse effects, demonstrating safety necessary for approval does not require showing that a drug has no potential adverse effects, but rather that the drug's benefits outweigh its risks. *See Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013).

40. Congress created REMS as a risk management tool, codifying FDA's authority with respect to drugs that are expected to provide substantial benefits, but which FDA determines also pose risks that would otherwise result in FDA denying an application to sell or market those drugs. *See* Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, § 901, 121 Stat. 823, 926 (enacting 21 U.S.C. § 355-1); 21 U.S.C. § 355-1(a)(2) (extending the REMS authority to already-approved drugs). Within a REMS, FDA may impose requirements, including requiring information for patients and imposing restrictions on prescribers and distribution, that go above and beyond those that FDA is able to require in the absence of a REMS.

41. In enacting the REMS provision, Congress required FDA to consider both the risks associated with the drugs and the burden of imposing various requirements, and to choose

the least restrictive set of requirements sufficient to ensure a positive benefit-risk profile, *i.e.*, ensuring safe use of the drug by managing identified safety risks while also maximizing patient access to the drug and minimizing burdens on the healthcare system. *See, e.g.*, 21 U.S.C. § 355-1(a)(1), (f)(2), (f)(5), (g)(2)(C), (g)(4)(B); *see also* FDA, No. FDA-2018-D-4628, Draft Guidance for Industry: REMS Assessment: Planning and Reporting at 13 (Jan. 2019) ("REMS Assessment Draft Guidance")[2] (REMS with ETASU "shall, considering the risk, not be unduly burdensome on patient access, and, to the extent practicable, minimize the burden on the health care delivery system").

42. Congress provided a series of tools that FDA can incorporate in a particular REMS to strike the right balance between ensuring safe use and avoiding undue burdens on patient access or the healthcare delivery system. For instance, a REMS may include a medication guide or patient package insert, *see* 21 U.S.C. § 355-1(e)(2); a communication

[2] *Available at* https://www.fda.gov/regulatory-information/search-fda-guidance-~~docu ments~~documents/rems-assessment-planning-and-reporting.

plan, including letters to healthcare providers, *see id.* § 355-1(e)(3); and/or packaging and disposal requirements, *see id.* § 355-1(e)(4).

43. In addition to these relatively more modest requirements, a REMS can also include ETASU that FDA determines are necessary for the drug to be approved. *See* 21 U.S.C. § 355-1(f)(1). These additional elements may require that healthcare providers who prescribe the drug have particular training or experience or be specially certified; that pharmacies, practitioners, or health care settings that dispense the drug be specially certified; that the drug be dispensed to patients only in certain health care settings; that the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results; or that patients be subject to monitoring or be enrolled in a registry. *Id.* § 355-1(f)(3).

44. Because ETASU requirements have the potential to unduly restrict access to drugs with meaningful therapeutic benefits, Congress imposed strict limitations on their use. Any ETASU imposed by FDA must be "commensurate with" a specific serious identified risk of the drug. 21 U.S.C.

§ 355-1(f)(2)(A). They must "not be unduly burdensome on patient access to the drug." *Id.* § 355-1(f)(2)(C). And they must be designed "to minimize the burden on the health care delivery system" of complying with the requirements. *Id.* § 355-1(f)(2)(D). In considering burdens on patient access, Congress directed FDA to give particular consideration to "(i) patients with serious or life-threatening diseases or conditions, (ii) patients who have difficulty accessing health care (such as patients in rural or medically underserved areas), and (iii) patients with functional limitations." *Id.* § 355-1(f)(2)(C)(i)-(iii).

45. When FDA imposes ETASU requirements, Congress requires the Agency to seek input from patients, physicians, pharmacists, and other healthcare providers about how to design those requirements so as not to be unduly burdensome on patient access to the drug and to minimize the burden on the healthcare delivery system. 21 U.S.C. § 355-1(f)(5)(A).

46. Congress also charged FDA with continued monitoring and periodic re-assessment of REMS and ETASU to ensure that they continue to reflect the least restrictive set of requirements necessary to ensure safety while protecting

patient access, in light of the Agency's evolving understanding of a particular drug's risks and benefits. Every REMS thus includes a timetable for periodic assessments of the effectiveness of the risk mitigation strategy. *See* 21 U.S.C. § 355-1(c)(1), (d). FDA must "periodically evaluate" ETASU requirements to assess whether they are necessary to assure safe use, are not unduly burdensome on patient access to the drug, and minimize the burden on the healthcare delivery system; and the Agency must "modify" those requirements "as appropriate" in light of those evaluations and input received from patients, physicians, pharmacists, and other healthcare providers. 21 U.S.C. § 355-1(f)(5)(B), (C). Further, Congress obligated FDA to institute a REMS review and initiate modification of a REMS if at any time the Agency determines that the REMS should be modified to "minimize the burden on the health care delivery system of complying with the strategy." *Id.* § 355-1(g)(4)(B).

47. FDA guidance states that the process of identifying and minimizing potential burdens on the healthcare system and barriers to patient access "should begin during the REMS design phase," when drug sponsors must demonstrate that they

have considered and attempted to minimize potential burdens and barriers; and should continue during the post-approval implementation phase, when sponsors are required, as part of their periodic REMS assessments, to use metrics, data sources, and analytical tools "to assess REMS burdens" and "barriers to patient access." REMS Assessment Draft Guidance at 13-15.

48. Because REMS with ETASU are the most restrictive approach available for ensuring safe use of approved drugs, they are imposed on a very limited number of drugs. Of the more than 20,000 prescription drugs FDA has approved,[3] FDA's website lists only 56 currently approved REMS with ETASU.[4]

B. FDA's Approval of Mifepristone and the Mifepristone REMS

49. Mifepristone is used in medication abortion in a regimen with misoprostol. Typically a patient first takes

[3] *See Fact Sheet: FDA at a Glance*, FDA.gov (Nov. 2021), https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance ("There are over 20,000 prescription drug products approved for marketing.").

[4] *See Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA.gov (2023), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

mifepristone, which works by blocking the hormone progesterone, without which the pregnancy cannot continue; followed by misoprostol 24 to 48 hours later, which causes uterine contractions similar to an early miscarriage. Medication abortion typically involves cramping, pain, and bleeding; more serious complications are extremely rare, "occurring in no more than a fraction of a percent of patients." Nat'l Acads. of Scis., Eng'g, & Med., The Safety and Quality of Abortion Care in the United States 55 (2018), *available at* http://nap.nationalacademies.org/24950. These risks "are both low and similar in magnitude to the reported risks of serious adverse effects of commonly used prescription and over-the-counter medications," such as pain relievers like aspirin and ibuprofen and common antibiotics. *Id.* at 58.

50. FDA initially approved mifepristone in 2000 under the trade name Mifeprex (an abbreviated new drug application for a generic version of mifepristone was approved in 2019). FDA-approved product labeling specified that mifepristone was approved for the medical termination of intrauterine pregnancy, in a regimen with misoprostol. Mifeprex

(mifepristone) Prescribing Information (2000) ("2000 Prescribing Information"), attached as Ex. B.

51. Since its initial approval in 2000, FDA has closely monitored mifepristone and has made updates to the mix of regulatory controls FDA has imposed on the drug— —including changes to the approved labeling, the risk mitigation plan, and the REMS— —in 2004, 2005, 2009, 2016, 2019, 2021, and 2023.[5] In so doing, FDA has approved lifting or otherwise modifying certain of the REMS elements and ETASU when it determined that a particular ETASU or other REMS element was unduly burdensome or no longer necessary to maintain a favorable benefit-risk profile for the drug.

52. Each REMS modification reflects FDA's exercise of its congressionally mandated responsibility to continue to consider scientific evidence regarding the safe and effective use of mifepristone as well as burdens on patient access and the health care delivery system, and to adjust and refine the

[5] *See Drugs@FDA: NDA 020687*, FDA.gov, https://www.accessdata.fda.gov/scripts/cder/daf/~~index.cfm~~index.cfm?event=overview.process&ApplNo=020687.

federal regulatory balance based on such consideration.

1. FDA's Initial Approval of Mifepristone in 2000

53. In initially considering whether to approve the Mifeprex NDA, FDA determined that medication abortion provides a meaningful therapeutic benefit to some patients. *See* 21 C.F.R. § 314.500; NDA 020687, Approval Letter from FDA to Sandra P. Arnold, Population Council at 1 (Sept. 28, 2000) ("Mifeprex Approval Letter"), attached as Ex. C (noting that the application was "approved under 21 CFR 314 Subpart H"); Memorandum from FDA to NDA 20-687 MIFEPREX (mifepristone) Population Council at 6 (Sept. 28, 2000) ("Mifeprex Approval Memorandum"), attached as Ex. D. It has never deviated from that determination. As FDA has recognized, "[p]regnancy can be a serious medical condition in some women" and is associated with numerous health risks, including preeclampsia and eclampsia; an increased risk of thromboembolic complications, including deep vein thrombophlebitis and pulmonary embolus; disseminated intravascular coagulopathy (a rare but serious complication); amniotic fluid embolism; life-threatening hemorrhage associated with placenta previa, placenta accreta, placental abruption, labor and delivery, or

surgical delivery; postpartum depression; and exacerbation or more difficult management of preexisting medical conditions (*e.g.*, diabetes, lupus, cardiac disease, hypertension). Letter from Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch. to Donna Harrison, M.D., *et al.*, Denying Citizen Petition Asking FDA to Revoke Approval of Mifeprex at 4 (Mar. 29, 2016), attached as Ex. E. FDA further observed that continued pregnancy carries a significant risk that a patient may require a major surgical procedure and anesthesia, as well as endure depression, anxiety, and other conditions. *Id.* at 4-5.

54. In reviewing the NDA for Mifeprex, FDA determined that distribution restrictions were necessary in order to approve Mifeprex. The approved NDA for Mifeprex thus included a risk mitigation plan that included distribution restrictions under the regulations that predated the 2007 REMS statute. *See* 21 C.F.R. § 314.520; Mifeprex Approval Letter at 2 (Ex. C); Mifeprex Approval Memorandum at 6, (Ex. D).

55. FDA's initial 2000 approval required that Mifeprex could only be "provided by or under the supervision of a

physician" who had signed a Prescriber Agreement Form. Mifeprex Approval Letter at 2 (Ex. C). The Prescriber Agreement Form specified the qualifications that FDA had determined were necessary for a physician to become certified to prescribe mifepristone, including the ability to (a) assess duration of pregnancy (although, as described in the Mifeprex 2000 Prescribing Information (Ex. B), an ultrasonographic scan need only be used if the duration of pregnancy is uncertain or if ectopic pregnancy is suspected); (b) diagnose ectopic pregnancies; (c) provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through others; and (d) assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. Mifeprex (Mifepristone) Tablets, 200 mg Prescriber's Agreement (2000~~), attached as Ex. F~~) ("2000 Prescriber Agreement~~").~~"), attached as Ex. F.

56. The Prescriber Agreement Form required the signatory to have read and understood the prescribing information and to follow guidelines for use, including: (a) providing the patient with a copy of the Patient Agreement Form and the

Medication Guide; (b) fully explaining the procedure to each patient; (c) answering any questions the patient had about the procedure; and (d) signing and obtaining the patient's signature on the Patient Agreement Form. ~~2000 Prescriber Agreement (Ex. F~~It also required the signatory to report "any hospitalization, transfusion, or other serious [adverse] event" to the drug's sponsor, 2000 Prescriber Agreement at 3 (Ex. F), which in turn was required to report it to FDA, 21 C.F.R. §§ 314.80, 314.81; Mifeprex Approval Letter (Ex. C).

57. According to FDA, the purpose of the Patient Agreement Form was to make sure that patients "understand the type of regimen they are about to commit to and its risks and benefits." Mifeprex Approval Memorandum at 3 (Ex. D). To that end, the form specified that the patient had been told about the risks and benefits of mifepristone and that she fully understood the treatment and its potential complications. It also included statements regarding the administration of mifepristone, *e.g.*, "I understand that I will take Mifeprex in my provider's office.~~"~~" and "I must return to my provider's office in about 2 weeks (about Day 14) after I take Mifeprex to be sure that my pregnancy has

ended and that I am well." Mifeprex (mifepristone) Tablets Patient Agreement (2000), attached as Ex. G.

58. The Prescriber Agreement Form and Patient Agreement Form remain part of the ETASU under the Mifepristone REMS today, with modifications including those described below.

2. FDA's Approval of the Mifepristone REMS in 2011

59. When Congress enacted the statutory REMS provision in 2007, it expressly deemed certain drugs (including mifepristone) that had in effect an approved risk mitigation plan under 21 C.F.R. Subpart H to have approved REMS in effect, and it required those drugs' sponsors to submit proposed REMS for approval under the new statute. *See* FDAAA § 909(b), 121 Stat. at 950-51; FDA, Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313 (Mar. 27, 2008).

60. In June 2011, FDA approved the first REMS for mifepristone under the FDAAA. The 2011 Mifepristone REMS carried forward the distribution restrictions FDA had previously imposed on mifepristone and included as ETASU the

restrictions previously imposed in the 2000 Mifeprex risk mitigation plan: Physicians were required to be "specially certified" by completing the Prescriber Agreement; mifepristone was to be dispensed "only in certain health care settings, specifically clinics, medical offices, and hospitals"; and it was to be dispensed only with documentation of safe use conditions, including obtaining the patient's signature on the Patient Agreement. Physicians were still required to report "serious" adverse events (in addition to the sponsor's ongoing adverse event reporting requirement). The 2011 REMS also specified as a REMS element that the Medication Guide be provided with each Mifeprex prescription. FDA, NDA 20-687 Mifeprex (mifepristone) Tablets, 200 mg, Risk Evaluation and Mitigation Strategy (REMS) at 1-2 (2011) ("2011 Mifepristone REMS"), attached as Ex. H~~.~~; *see also* NDA 020687/S-014, Supplement Approval Letter from FDA to Danco Labs., LLC at 1 (June 8, 2011), attached as Ex. I.

3. FDA's Modification of the Mifepristone REMS in 2016

61. In 2016, FDA "assessed the current REMS program to determine whether each Mifeprex REMS element remains

necessary to ensure that the drug's benefits outweigh the risks" in light of the extensive data and information about clinical practice collected since the original approval 16 years earlier. NDA 020687/S-020, Supplement Approval Letter from FDA to Danco Labs., LLC at 2 (Mar. 29, 2016), attached as Ex. J; *see also* FDA, NDA 020687/S-020, Risk Evaluation and Mitigation Strategy (REMS) Memorandum, REMS Modification at 2 (Mar. 29, 2016) ("2016 REMS Memorandum"), attached as Ex. K; FDA, NDA 020687/S-020, REMS Modification Review at 5, 10 (Mar. 29, 2016) ("2016 REMS Modification Review"), attached as Ex. L; FDA, NDA 020687/S-020, Addendum to REMS Modification Review § 3 (Mar. 29, 2016) ("2016 REMS Modification Review Addendum"), attached as Ex. M.

62. In light of its review, FDA approved several changes to the Mifepristone REMS that expanded the provision of medication abortion. *See* FDA, NDA 20-687 Mifeprex (mifepristone) Tablets, 200 mg, Risk Evaluation and Mitigation Strategy (REMS) (2016) ("2016 Mifepristone REMS"), attached as Ex. N. Among other things, the 2016 REMS allowed qualified healthcare providers other than physicians to become certified to prescribe mifepristone. *Compare* 2016

Mifepristone REMS, Prescriber Agreement Form (Ex. N) (stating that "Mifeprex must be provided by or under the supervision of *a healthcare provider* who prescribes and meets the following qualifications" (emphasis added)) *with* 2011 Mifepristone REMS, Prescriber's Agreement (Ex. H) (stating that "Mifeprex must be provided by or under the supervision of *a physician* who meets the following qualifications" (emphasis added)).

63. In addition, the 2016 modification revised the Patient Agreement to no longer state that the patient understood mifepristone would be *administered* in-person in the provider's office (while retaining the requirement that it be *dispensed* in-person in a clinic, medical office, or hospital). *Compare* 2016 Mifepristone REMS, Patient Agreement (Ex. N) (stating simply, "I understand . . . I will take Mifeprex on Day 1," with no location specified) *with* 2011 Mifepristone REMS, Patient Agreement (Ex. H) (stating, "I understand that I will take Mifeprex *in my provider's office*" (emphasis added)); *see also* 2016 Mifepristone REMS § II.A.2 (Ex. N) (continuing to specify locations where mifepristone could be dispensed); 2016 REMS Memorandum at 1-2 (Ex. K);

2016 REMS Modification Review at 5-7 (Ex. L); 2016 REMS Modification Review Addendum §§ 2.1.1.1, 2.2.1 (Ex. M). Consistent with its congressional mandate to assure safe use without burdening access, FDA concluded that in-person administration should not be required. *See* 2016 REMS Modification Review Addendum § 2.1.1.1 (Ex. M) (noting that the Patient Agreement was being modified to "revis[e] where Mifeprex . . . should be taken"). FDA also determined that in-person follow-up visits should not be required in all cases. *Compare* 2016 Mifepristone REMS, Patient Agreement (Ex. N) (stating, "I should follow up with my healthcare provider") *with* 2011 Mifepristone REMS, Patient Agreement (Ex. H) (stating, "I must return to my provider's office"); *see* Letter from Patrizia A. Cavazzoni, M.D., Dir., Ctr. For Drug Evaluation & Rsch. to Donna Harrison, M.D., *et al.*, Denying Citizen Petition at 13-14 (Dec. 16, 2021) ("AAPLOG Citizen Petition Denial Letter"), attached as Ex. P (noting FDA's conclusion that "appropriate follow-up . . . may be accomplished in multiple ways and not all require an in-clinic visit"). And FDA also determined that prescribers should no longer be required to report adverse events other

than death (although they could still report such events voluntarily, and the sponsor continued to be obligated to comply with post-approval reporting requirements). *See* 2016 Mifepristone REMS §§ II.A.1.b.vi, II.B.5 (Ex. N); 21 C.F.R. §§ 314.80, 314.81.

64. In considering the 2016 modifications, FDA also rejected certain REMS modifications the sponsor requested because FDA concluded those modifications would be inappropriate. For example, FDA did not approve the sponsor's application to remove the Patient Agreement Form requirement from the REMS because FDA determined that the form "would not interfere with access and would provide additional assurance that the patient is aware of the nature of the procedure, its risks, and the need for appropriate follow-up care." Memorandum from Janet Woodcock, M.D., Dir., Ctr. for Drug Evaluation & Rsch. regarding NDA 020687/S-020 (Mar. 28, 2016), attached as Ex. O.

4. FDA's Further Modification of the Mifepristone REMS in 2023

65. In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 public

health emergency regarding the REMS ETASU requiring that mifepristone be dispensed only in certain healthcare settings (*i.e.*, the in-person dispensing requirement). Joint Motion to Stay Case Pending Agency Review, *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw. May 7, 2021), Doc. 148 ("*Chelius* Stay Motion"); *see* ~~Letter from Patrizia A. Cavazzoni, M.D., Dir., Ctr. For Drug Evaluation & Rsch. to Donna Harrison, M.D., *et al.*, Denying Citizen Petition at 5 (Dec. 16, 2021) (~~"AAPLOG Citizen Petition Denial Letter~~"), attached as~~ at 5 (Ex. P~~.~~).

66. Also in 2021, FDA "undertook a full review of the Mifepristone REMS Program," reviewing multiple sources of information, including published literature, safety information submitted to the Agency during the COVID-19 public health emergency, FDA Adverse Event Reporting System reports, the REMS assessment reports for mifepristone submitted in April 2020, and information provided by the sponsors, advocacy groups, and individuals. AAPLOG Citizen Petition Denial Letter at 6 (Ex. P); *see Chelius* Stay Motion at 2 ("FDA is reviewing the elements of the REMS for Mifeprex and its approved generic . . . in accordance with the REMS assessment provisions of Section 505-1 of the [FDCA]."); *see*

also FDA, NDA 020687 & ANDA 91178, REMS Modification Rationale Review at 10, 19-36 (Dec. 16, 2021) ("REMS Modification Rationale Review"), attached as Ex. Q.

67. Following that review, on December 16, 2021, FDA sent REMS modification notification letters to the mifepristone drug sponsors. In those letters, FDA stated that "[i]n accordance with section 505-1(g)(4)(B) of the [FDCA], we have determined that your approved REMS for mifepristone must be modified to minimize the burden on the healthcare delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks." NDA 020687, REMS Modification Notification Letter from FDA to Danco Labs., LLC at 1 (Dec. 16, 2021), attached as Ex. R.

68. In particular, FDA required that the Mifepristone REMS be modified to (1) remove the in-person dispensing requirement and (2) add a requirement that pharmacies that dispense the drug be specially certified. *Id.* at 1-2. FDA explained that "[r]emoval of the requirement for in-person dispensing" was "necessary" to "minimize the burden on the healthcare delivery system of complying with the REMS," and that the requirement was "no longer necessary to ensure the

benefits of mifepristone outweigh the risks." *Id.* at 1-2; *see also* AAPLOG Citizen Petition Denial Letter at 6 (Ex. P) ("Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and . . . the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks.").

69. In January 2023, FDA approved a modification of the Mifepristone REMS that effectuated these changes. *See* 2023 Mifepristone REMS (Ex. A); *see also* NDA 020687/S-025, Supplement Approval Letter from FDA to Danco Labs., LLC (Jan. 3, 2023), attached as Ex. S. Consistent with FDA's 2021 directive, the 2023 modification removed the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (*i.e.*, the "in-person dispensing" requirement). It also added a certification requirement for pharmacies that dispense mifepristone in order to "ensure[] that pharmacies are aware of and agree to follow applicable REMS requirements, and [] that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers."

FDA, NDA 020687/S-025 and ANDA 091178/S-004, Review of proposed Major REMS Modification at 13 (Jan. 3, 2023) ("2023 REMS Modification Review"), attached as Ex. T; *see also id.* at 4, 9. The 2023 modification also updated the REMS goals to add that mifepristone can be dispensed "by or under the supervision of certified prescribers, *or* by certified pharmacies on prescriptions issued by certified prescribers." 2023 Mifepristone REMS at 1 (Ex. A) (emphasis added).

70. FDA left in place the REMS requirement of healthcare provider certification, while concluding that the "[t]he burden of prescriber certification has been minimized to the extent possible." 2023 REMS Modification Review at 10 (Ex. T); REMS Modification Rationale Review at 14 (Ex. Q). FDA also determined that the Patient Agreement Form remains "an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients." 2023 REMS Modification Review at 11 (Ex. T); REMS Modification Rationale Review at 18 (Ex. Q).

71. FDA did not substantively change the prescriber certification requirements, but it did add requirements

related to pharmacy certification to facilitate pharmacy dispensing. For example, for a pharmacy to become certified, the authorized representative must sign a "Pharmacy Agreement Form" attesting that they have read and understood the Prescribing Information and that each location of the pharmacy will be able to receive Prescriber Agreement Forms, ship mifepristone under certain conditions, and adopt processes and procedures to fulfill the REMS requirements. 2023 REMS Modification Review at 12-15 (Ex. T); *see also* 2023 Mifepristone REMS at 3-4 & Pharmacy Agreement Form (Ex. A); REMS Modification Rationale Review at 40-41 (Ex. Q).

72. FDA explained that the 2023 modifications "will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients." 2023 REMS Modification Review at 13 (Ex. T); *see also id.* at 19-20.

73. Thus, as it currently stands, FDA's Mifepristone REMS requires (among other things) that: (1) mifepristone can only be prescribed by or under the supervision of a certified provider, *i.e.*, a healthcare provider who has signed and

submitted a Prescriber Agreement Form; (2) mifepristone can be provided either directly by or under the supervision of a certified prescriber or through a certified pharmacy to which a certified prescriber has sent a prescription; and (3) the patient must sign a Patient Agreement Form, including an attestation that the prescribing healthcare provider has provided information as necessary to comply with the Mifepristone REMS and that the patient has received a copy of the Medication Guide.

74. This means that under federal law, a certified healthcare practitioner (who need not be a physician) can prescribe mifepristone to a patient (either in person or through telemedicine), and either she or someone under her supervision can dispense the medication to the patient or she can provide a prescription for the patient to obtain the medication from a certified pharmacy and take the medication at home or another place of her choosing. FDA has concluded that this specific package of regulatory requirements is, in the Agency's view, commensurate with the risks of mifepristone and sufficient to ensure its safe use while not unduly burdening patient access or the healthcare delivery

system. *See* 21 U.S.C. § 355-1(f)(2).

75. On January 22, 2023, President Biden issued a memorandum noting that FDA, "after an independent and comprehensive review of the risks and benefits" of mifepristone pursuant to the REMS statute, had taken "evidence-based action" to modify the Mifepristone REMS to ensure that "healthcare providers and patients can continue to use telehealth to prescribe and receive mifepristone by mail" and that "pharmacies can now choose to become certified to dispense mifepristone to patients." President Biden explained: "These changes seek to reduce the burden on the healthcare delivery system while ensuring the benefits of the medication outweigh the risks. These changes also help ensure that patients can access mifepristone similarly to how they would access other prescribed medications." Memorandum on Further Efforts to Protect Access to Reproductive Healthcare Services (Jan. 22, 2023), https://www.whitehouse.gov/briefing-room/presidential-actions/2023/01/22/memorandum-on-further-efforts-to-protect-access-to-reproductive-~~healthcare~~health care-services/. And the President decried efforts by some

state officials to "impose restrictions to limit access to this evidence-based, safe, and effective medication." *Id.*

C. North Carolina Law Imposes Unnecessary and Burdensome Requirements on Plaintiff's Prescribing of Mifepristone that Conflict with the FDA-Approved Regulatory Scheme

76. North Carolina's broad web of abortion laws imposes additional restrictions on the prescription and distribution of mifepristone that conflict with the regulatory balance struck by FDA's precisely calibrated REMS.

77. In North Carolina, medication abortion is legal only when performed in compliance with specific, onerous conditions and restrictions imposed by the State~~; otherwise it is a felony. *See* N.C. Gen. Stat. §§ 14-44, 14-45, 14-45.1. North Carolina law imposes, among others, the following restrictions on medication abortion, including abortions performed using mifepristone: North Carolina provides that an abortion, including a medication abortion with mifepristone, is lawful only "when the procedure is performed by a qualified physician . . . in a hospital or clinic certified by the Department of Health and Human Services to be a suitable facility for the performance of abortions." N.C. Gen. Stat § 14-45.1(a); *see also id.* § 14-45.1(g) (defining "qualified physician"). The State also specifically provides, with respect to medication abortion,~~. *See* N.C. Gen. Stat. §§ 14-44, 14-45, 14-45.1. On May 16, 2023, the North Carolina

legislature overrode the Governor's veto and passed Senate Bill 20 (which thus became Session Law 2023-14), amending North Carolina's laws with respect to surgical abortion and medication abortion with an effective date of July 1, 2023. Session Law 2023-14 carries forward or expands many of North Carolina's pre-existing restrictions on abortion, including restrictions that apply specifically to medication abortion. It also imposes onerous new restrictions on medication abortion.

~~77.~~78. Among other restrictions, currently operative North Carolina law provides that "[t]he physician prescribing, dispensing, or otherwise providing any drug or chemical for the purpose of inducing an abortion shall be physically present in the same room as the patient when the first drug or chemical is administered to the patient." N.C. Gen. Stat. § ~~*Id.* § 90-21.82(1)(a~~90-21.82(1)(a). Session Law 2023-14 maintains the requirement of in-person administration by a physician. *See* S.L. 2023-14, sec. 1.2, § 21.83A(b)(2)a;

id. sec. 1.3, § 14-44.1.[6] In addition, when the amendments in Session Law 2023-14 take effect, North Carolina law will require the physician prescribing, administering, or dispensing mifepristone to examine the patient in person

[6] In addition to requiring that mifepristone be provided in person by a physician, current North Carolina law strictly regulates the locations where such activities can take place. A physician can provide mifepristone only in a facility that the State deems "suitable," which means either a facility physically attached to or operated by a licensed hospital or a freestanding clinic certified by the State to provide abortion services. *See* N.C. Gen. Stat. § 14-45.1(a); 10A N.C. Admin. Code § 14E.0101(2). A hospital must meet numerous requirements to obtain and maintain state licensure, including facility requirements. *See generally* N.C. Gen. Stat. §§ 131E-75 *et seq.* A clinic not attached to or operated by a licensed hospital must likewise meet numerous facility requirements in order to be considered "a suitable facility for the performance of abortions," N.C. Gen. Stat. § 14-45.1(a), including (among other things) plan approval prior to construction, 10A N.C. Admin. Code §§ 14E.0104, .0105; regular facility inspections, *id.* § 14E.0111; N.C. Gen. Stat. § 14-45.1(a1); and specific building code requirements and specifications unnecessary for providing medication abortion, such as elevators, corridors, and doors large enough to accommodate a stretcher (N.C. Admin. Code §§ 14E.0203, .0204, .0205), ventilation and air supply requirements (*id.* § 14E.0206), and a "nourishment station with storage and preparation area for serving meals or in-between meal snacks" (*id.* § 14E.0207(14)). Under Session Law 2023-14, it appears that the facility requirement would not apply to medication abortion, while North Carolina law would still require that the physician be "physically present in the same room as the woman" when mifepristone is administered. S.L. 2023-14, sec. 1.2, § 21.83A(b)(2)a.

before providing the drug, schedule an in-person follow-up visit for the patient approximately seven to 14 days after providing the drug, and "make all reasonable efforts to ensure that the woman returns for the scheduled appointment." *Id.* sec. 1.2, §§ 90-21.83A(b)(4)(*l*), 90-21.83B, 90-21.93(b)(8)-(9).

~~78. In addition to requiring that mifepristone be provided in person by a physician, North Carolina strictly regulates the locations where such activities can take place. A physician can provide mifepristone only in a facility that the State deems "suitable," which means either a facility physically attached to or operated by a licensed hospital or a freestanding clinic certified by the State to provide abortion services. *See* N.C. Gen. Stat. § 14-45.1(a); 10A N.C. Admin. Code § 14E.0101(2). A hospital must meet numerous requirements to obtain and maintain state licensure, including facility requirements. *See generally* N.C. Gen. Stat. §§ 131E-75 *et seq.* A clinic not attached to or operated by a licensed hospital must likewise meet numerous facility requirements in order to be considered "a suitable facility for the performance of abortions," N.C. Gen. Stat. § 14-45.1(a), including (among other things) plan approval prior to construction, 10A N.C. Admin. Code §§ 14E.0104, .0105; regular facility inspections, *id.* § 14E.0111; N.C. Gen. Stat. § 14-45.1(a1); and specific building code requirements and specifications unnecessary for providing medication abortion, such as elevators, corridors, and doors~~

~~large enough to accommodate a stretcher (N.C. Admin. Code §§ 14E.0203, .0204, .0205), ventilation and air supply requirements (*id.* § 14E.0206), and a "nourishment station with storage and preparation area for serving meals or in-between meal snacks" (*id.* § 14E.0207(14)).~~

79. North Carolina law also imposes onerous counseling requirements that must be satisfied before ~~any abortion, including~~ a medication abortion with mifepristone. It requires that a physician or qualified professional provide specific, state-mandated information to the patient prior to the abortion, including statements that are inconsistent with FDA-approved patient labeling for mifepristone and Plaintiff's expert medical judgment and irrelevant to the patient's care, and then wait at least 72 hours before performing the abortion. *See* N.C. Gen. Stat. §§ 90-21.82, 90-21.90. ~~North Carolina law also requires that, for abortions performed in a clinic not attached to or operated by a licensed hospital, "[a]n ultrasound examination shall be performed and the results, including gestational age, placed in the patient's medical record for any patient who is scheduled for an abortion procedure." 10A N.C. Admin. Code § 14E.0305(d).~~The amendments in Session Law 2023-14 will make the counseling requirements even more onerous, including by requiring that the counseling be provided in person. *See* S.L. 2023-14, sec. 1.2, §§ 90-

21.83, 90-21.83A, 90-21.90. When those amendments take effect, North Carolina law will also mandate an ultrasound examination and a medically unnecessary blood-type determination (which may necessitate blood testing) for all medication abortion patients. *See id.* sec. 1.2, §§ 90-21.83A(b)(2)b, 90-21.83B(a)(2), 90-21.93(b)(6).[7]

80. Further, once Session Law 2023-14 takes effect, North Carolina will subject mifepristone prescribers to additional onerous and unreasonable reporting requirements that FDA has rejected. For example, the amendments made by S.L. 2023-14 require physicians to report "any specific complications" from mifepristone to the State within 15 days of the patient's last appointment, and to report any "adverse event" to the State —— and to FDA —— within three days. S.L. 2023-14, sec. 1.2, § 90-21.93(b)(10), (c). The law defines both "complication" and "adverse event" broadly to encompass any "physical or psychological" conditions that may have

[7] Under current North Carolina law, an ultrasound is required for abortions performed in a clinic not attached to or operated by a licensed hospital. 10A N.C. Admin. Code § 14E.0305(d).

arisen "as a primary or secondary result" of the abortion. *Id.* §§ 90-21.81(1b), (2a), 90-21.83(e)(2).

~~80.~~81. For those who fail to comply with these restrictions, North Carolina law threatens myriad and severe consequences, including criminal prosecution. A physician who "[p]roduce[s] or attempt[s] to produce an abortion contrary to law" is ~~further~~ subject to disciplinary action by the North Carolina Medical Board, including fines and suspension or revocation of the physician's medical license~~.~~ , N.C. Gen. Stat. § 90-14(a)(2~~). In addition, a physician who performs an abortion that does not fall within the narrow exception in §~~); S.L. 2023-14~~-45.~~, sec. 1~~(a) may be guilty of a felony~~.2, § 90-21.88A, as well as other potential enforcement action, *see* N.C. Gen. Stat.~~*id.*~~ §§ 14-44, 14-45, ~~and~~14-45.1; S.L. 2023-14, sec. 1.2, § 90-21.81B. And a physician who performs an abortion in knowing or reckless violation of ~~the~~those requirements ~~in § 90-21.82~~ may be subject to a civil action for damages and attorneys' fees. N.C. Gen. Stat. § ~~Failure to comply with the facility certification requirements also may subject a provider to administrative action, including denial, suspension, or revocation of certification. *See* 10A N.C. Admin. Code § 14E.0110.~~90-21.88; S.L. 2023-14,

sec. 1.2, § 90-21.88.[8]

~~81.~~82. As explained above, in imposing and administering the Mifepristone REMS and performing its congressionally mandated balancing to ensure safety while minimizing burdens on patient access and the healthcare system, FDA has made a deliberate choice not to impose restrictions on mifepristone that are the same as or highly similar to restrictions imposed by North Carolina. ~~In particular~~For example, FDA specifically considered, initially imposed, and ultimately rejected requirements that mifepristone be provided in person by physicians in a specific type of medical facility. FDA has concluded that such requirements are not necessary to ensure safety and would unduly burden patient access and the healthcare delivery system. Instead, FDA concluded that it is appropriate for certified physicians, other certified healthcare providers, and healthcare providers operating under their supervision to

[8] Failure to comply with the facility certification requirements also may subject a provider to administrative action, including denial, suspension, or revocation of certification. *See* 10A N.C. Admin. Code § 14E.0110.

prescribe mifepristone in any type of facility or by telehealth, after providing the specific counseling information that is listed in the FDA-approved Patient Agreement and Medication Guide and without any waiting period; and for patients to obtain mifepristone directly from a certified prescriber or a healthcare provider working under the supervision of a certified prescriber, or from a certified pharmacy upon prescription of a certified prescriber, and take the medication in a place of the patient's choosing. FDA also has required that pregnancy be assessed by ultrasound only if the duration of the pregnancy is uncertain or an ectopic pregnancy is suspected. ~~*See* ¶¶ 49-75~~And FDA has determined that in light of mifepristone's well-characterized safety profile, prescribers should not be subject to reporting requirements like those North Carolina is now seeking to impose. *See* ¶¶ 50-76, *supra*.

CAUSE OF ACTION

~~82.~~83. Plaintiff realleges and incorporates by reference each of the preceding paragraphs as though set forth fully herein.

~~83.~~84. Under the Supremacy Clause of the United States

Constitution, federal laws made under the authority of the United States are "the supreme Law of the Land," the "Laws of any State to the Contrary notwithstanding." U.S. Const. art. VI, cl. 2. Federal law thus preempts state law where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of federal law.

~~84.~~85. The restrictions imposed by North Carolina on the provision of mifepristone~~—~~ —— including the in-person ~~requirement,~~examination, administration, and follow-up requirements; the ~~specially certified facility requirement, the~~in-person counseling and 72-hour waiting period requirement~~,~~; the physician-only requirement~~, and~~; the ultrasound ~~requirement~~ and blood-type requirements; and the physician adverse event reporting requirements —— conflict with and stand as an obstacle to the accomplishment and execution of the full purposes of objectives of federal law, as reflected in the FDCA and FDA's Mifepristone REMS.

~~85.~~86. Congress has directed FDA, when imposing REMS, and in particular REMS with ETASU, to strike a precise and careful balance between managing the risks of a drug and ensuring patient access to the drug. FDA is required to

calibrate its restrictions to ensure patient safety while eschewing unnecessary restrictions that would unduly burden patient access or the healthcare delivery system. In exercising that authority with respect to mifepristone, FDA has crafted, and regularly revisited and revised, a precise set of regulatory controls that the Agency views as striking the appropriate balance between safety and patient access, and has included only those ETASU that the Agency has deemed to be commensurate with the drug's risks and not unduly burdensome on patients or healthcare providers. In so doing, FDA has concluded that restrictions of the type imposed by North Carolina are unnecessary, inappropriate, and unduly burdensome.

~~86.~~87. The REMS are not a minimum standard on which states are free to build. Rather, as Congress instructed, they reflect FDA's expert conclusion as to the appropriate level of regulatory control for drugs that are expected to provide substantial benefits, but which FDA determines also pose risks that would otherwise result in FDA denying an application to sell or market those drugs. By attempting to impose a different regulatory balance from the one crafted by

FDA under its REMS authorities, including by imposing restrictions on the provision of mifepristone that FDA itself has specifically rejected, North Carolina law frustrates Congress's objective of empowering FDA to ensure safety while minimizing burdens on patient access and on the healthcare delivery system; upsets the deliberate and fine-tuned regulatory balance contemplated by federal law; and thus stands as an obstacle to the accomplishment and execution of the full purposes and objectives of federal law.

~~87.~~88. Plaintiff is accordingly entitled to a declaratory judgment that North Carolina's restrictions on mifepristone are preempted insofar as they are inconsistent with the federal Mifepristone REMS. Plaintiff is also entitled to an injunction prohibiting Defendants from enforcing those restrictions to prevent Plaintiff from providing mifepristone in accordance with federal law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff respectfully prays for the following relief.

1. A declaration pursuant to 28 U.S.C. § 2201 that North Carolina's restrictions on the provision of mifepristone are in conflict with and preempted by federal law;

2. Injunctive relief enjoining Defendants from enforcing North Carolina's restrictions on providing mifepristone or taking any other action to restrict the ability of a provider to provide, or a patient to access, mifepristone in accordance with federal law;

3. An order awarding Plaintiff her costs, expenses, and attorneys' fees; and

4. Such other and further relief as the Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff demands trial by jury on all issues so triable.

Dated: ~~January 25~~June 2, 2023

Respectfully submitted,

/s/ Chelsea Corey

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CERTIFICATE OF SERVICE

I hereby certify that on June 2, 2023, the foregoing pleading was filed via the Court's CM/ECF System, which will effect service upon all registered counsel of record.

/s/ Chelsea Corey
Chelsea Corey
(NC Bar No. 48838)
Counsel for Plaintiff

Exhibit C

GENERAL ASSEMBLY OF NORTH CAROLINA
SESSION 2023

SESSION LAW 2023-14
SENATE BILL 20

AN ACT TO MAKE VARIOUS CHANGES TO HEALTH CARE LAWS AND TO APPROPRIATE FUNDS FOR HEALTH CARE PROGRAMS.

The General Assembly of North Carolina enacts:

PART I. ABORTION LAW REVISIONS

SECTION 1.1. G.S. 14-45.1 is repealed.

SECTION 1.2. Article 1I of Chapter 90 of the General Statutes reads as rewritten:

"Article 1I.

"~~Woman's Right to Know Act.~~Abortion Laws.

"**§ 90-21.80. Short title.**

This act may be cited as ~~the "Woman's Right to Know Act."~~"Abortion Laws."

"**§ 90-21.81. Definitions.**

The following definitions apply in this Article:

(1) Abortion. – A surgical abortion or a medical abortion, as those terms are defined in this section, respectively.

(1a) Abortion-inducing drug. – A medicine, drug, or any other substance prescribed or dispensed with the intent of terminating the clinically diagnosable pregnancy of a woman, with knowledge that the termination will, with reasonable likelihood, cause the death of the unborn child. This includes the off-label use of drugs such as mifepristone (Mifeprex), misoprostol (Cytotec), and methotrexate, approved by the United States Food and Drug Administration to induce abortions or known to have abortion-inducing properties, prescribed specifically with the intent of causing an abortion, whether or not there exists a diagnosed pregnancy at the time of prescription or dispensing, for the purposes of the woman taking the drugs at a later date to cause an abortion rather than contemporaneously with a clinically diagnosed pregnancy. This definition shall not include drugs that may be known to cause an abortion but are prescribed for other medical indications, such as chemotherapeutic agents and diagnostic drugs.

(1b) Adverse event. – Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

(1c) ~~Abortion. –~~ Surgical abortion. – The use or prescription of any ~~instrument, medicine, drug, or other substance~~ instrument or device intentionally to terminate the pregnancy of a woman known to be pregnant with an intention other than to do any of the following:

a. Increase the probability of a live birth.
b. Preserve the life or health of the child.
c. Remove a dead, unborn child who died as the result of (i) natural causes in utero, (ii) accidental trauma, or (iii) a criminal assault on the pregnant woman or her unborn child which causes the premature termination of the pregnancy.

d. Remove an ectopic pregnancy.

(2) Attempt to perform an abortion. – An act, or an omission of a statutorily required act, that, under the circumstances as the ~~actor~~ physician believes them to be, constitutes a substantial step in a course of conduct planned to culminate in the performance of an abortion in violation of this Article or Article 1K of this Chapter.

(2a) Complication. – Any physical or psychological conditions which, in the reasonable medical judgment of a licensed health care professional, arise as a primary or secondary result of an induced abortion, including:

a. Uterine perforation.
b. Cervical laceration.
c. Infection.
d. Bleeding or vaginal bleeding that qualifies as a Grade 2 or higher adverse event according to the Common Terminology Criteria for Adverse Events.
e. Pulmonary embolism.
f. Deep vein thrombosis.
g. Failure to actually terminate the pregnancy.
h. Incomplete abortion due to retained tissue.
i. Pelvic inflammatory disease.
j. Endometritis.
k. Missed ectopic pregnancy.
l. Cardiac arrest.
m. Respiratory arrest.
n. Renal failure.
o. Shock.
p. Amniotic fluid embolism.
q. Coma.
r. Free fluid in abdomen.
s. Allergic reactions to anesthesia and abortion-inducing drugs.
t. Psychological complications as described by the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

(3) Department. – The Department of Health and Human Services.

(4) Display a real-time view of the unborn child. – An ultrasound or any more scientifically advanced means of viewing the unborn child in real time.

(4a) Health care provider. – As defined in G.S. 90-410.

(4b) Hospital. – As defined in G.S. 131E-76.

(4c) Incest. – The criminally injurious conduct in the nature of the conduct described in G.S. 14-178.

(4d) Life-limiting anomaly. – The diagnosis by a qualified physician of a physical or genetic condition that (i) is defined as a life-limiting disorder by current medical evidence and (ii) is uniformly diagnosable.

(4e) Medical abortion. – The use of any medicine, drug, or other substance intentionally to terminate the pregnancy of a woman known to be pregnant with an intention other than to do any of the following:

a. Increase the probability of a live birth.
b. Preserve the life or health of the child.
c. Remove a dead, unborn child who died as a result of (i) natural causes in utero, (ii) accidental trauma, or (iii) a criminal assault of the pregnant woman or her unborn child which causes the premature termination of the pregnancy.

d. Remove an ectopic pregnancy.

(5) Medical emergency. – A condition which, in reasonable medical judgment, so complicates the medical condition of the pregnant woman as to necessitate the immediate abortion of her pregnancy to avert her death or for which a delay will create serious risk of substantial and irreversible physical impairment of a major bodily function, not including any psychological or emotional conditions. For purposes of this definition, no condition shall be deemed a medical emergency if based on a claim or diagnosis that the woman will engage in conduct which would result in her death or in substantial and irreversible physical impairment of a major bodily function.

(5a) Partial-birth abortion. – As defined in 18 U.S.C. § 1531(b)(1) as it exists on January 1, 2023.

(6) Physician. – An individual licensed to practice medicine in accordance with this Chapter.

(7) Probable gestational age. – What, in the judgment of the physician, will, with reasonable probability, be the gestational age of the unborn child at the time the abortion is planned to be performed.

(7a) Qualified physician. – Any of the following: (i) a physician who possesses, or is eligible to possess, board certification in obstetrics or gynecology, (ii) a physician who possesses sufficient training based on established medical standards in safe abortion care, abortion complications, and miscarriage management, or (iii) a physician who performs an abortion in a medical emergency as defined by this Article.

(8) Qualified professional. – An individual who is a registered nurse, nurse practitioner, or physician assistant licensed in accordance with Article 1 of this Chapter, or a qualified technician acting within the scope of the qualified technician's authority as provided by North Carolina law and under the supervision of a physician.

(9) Qualified technician. – A registered diagnostic medical sonographer who is certified in obstetrics and gynecology by the American Registry for Diagnostic Medical Sonography (ARDMS) or a nurse midwife or advanced practice nurse practitioner in obstetrics with certification in obstetrical ultrasonography.

(9a) Rape. – The criminally injurious conduct in the nature of the conduct described in G.S. 14-27.21, 14-27.22, 14-27.23, 14-27.24, and 14-27.25.

(10) ~~Stable Internet Web site. –~~ Website. – A ~~Web site~~ website that, to the extent reasonably practicable, is safeguarded from having its content altered other than by the Department.

(10a) Unborn child. – As defined in G.S. 14-23.1.

(11) Woman. – A female human, whether or not she is an adult.

"**§ 90-21.81A. Abortion.**

(a) Abortion. – It shall be unlawful after the twelfth week of a woman's pregnancy to advise, procure, or cause a miscarriage or abortion.

(b) Partial-Birth Abortion Prohibited. – It shall be unlawful for a qualified physician, any health care provider, or any person to perform a partial-birth abortion at any time.

"**§ 90-21.81B. When abortion is lawful.**

Notwithstanding any of the provisions of G.S. 14-44 and G.S. 14-45, and subject to the provisions of this Article, it shall not be unlawful to advise, procure, or cause a miscarriage or an abortion in the following circumstances:

(1) When a qualified physician determines there exists a medical emergency.

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 4 of 48

(2) During the first 12 weeks of a woman's pregnancy, when the procedure is performed by a qualified physician licensed to practice medicine in this State in a hospital, ambulatory surgical center, or clinic certified by the Department of Health and Human Services to be a suitable facility for the performance of abortions, in accordance with G.S. 90-21.82A or during the first 12 weeks of a woman's pregnancy when a medical abortion is procured.

(3) After the twelfth week and through the twentieth week of a woman's pregnancy, when the procedure is performed by a qualified physician in a suitable facility in accordance with G.S. 90-21.82A when the woman's pregnancy is a result of rape or incest.

(4) During the first 24 weeks of a woman's pregnancy, if a qualified physician determines there exists a life-limiting anomaly in accordance with this Article.

"**§ 90-21.81C. Abortion reporting, objection, and inspection requirements.**

(a) Procedure Information. – A qualified physician who advises, procures, or causes a miscarriage or abortion after the twelfth week of a woman's pregnancy shall record all of the following: (i) the method used by the qualified physician to determine the probable gestational age of the unborn child at the time the procedure is to be performed, (ii) the results of the methodology, including the measurements of the unborn child, and (iii) an ultrasound image of the unborn child that depicts the measurements. The qualified physician shall provide this information, including the ultrasound image, to the Department of Health and Human Services pursuant to subsection (c) of this section.

(b) Recording of Findings. – A qualified physician who procures or causes a miscarriage or abortion after the twelfth week of a woman's pregnancy shall record the findings and analysis on which the qualified physician based the determination that there existed a medical emergency, life-limiting anomaly, rape, or incest and shall provide that information to the Department of Health and Human Services pursuant to subsection (c) of this section. Materials generated by the physician or provided by the physician to the Department of Health and Human Services pursuant to this section shall not be public records under G.S. 132-1. The information provided under this subsection shall be for statistical purposes only, and the confidentiality of the patient and the physician shall be protected. It is the duty of the qualified physician to submit information to the Department of Health and Human Services that omits identifying information of the patient and complies with Health Insurance Portability and Accountability Act of 1996 (HIPAA).

(c) Reports. – The Department of Health and Human Services shall prescribe and collect on an annual basis, from hospitals, ambulatory surgical facilities, or licensed clinics where abortions are performed, statistical summary reports concerning the medical and demographic characteristics of the abortions provided for in this section, including the information described in subsection (b) of this section as it shall deem to be in the public interest. Hospitals, ambulatory surgical facilities, or licensed clinics where abortions are performed shall be responsible for providing these statistical summary reports to the Department of Health and Human Services. The reports shall be for statistical purposes only, and the confidentiality of the patient relationship shall be protected. Materials generated by the physician or provided by the physician to the Department of Health and Human Services pursuant to this section shall not be public records under G.S. 132-1.

(d) Fetal Death Reporting. – The requirements of G.S. 130A-114 are not applicable to abortions performed pursuant to this section.

(e) Medical Personnel Objection. – No physician, nurse, or any other health care provider who shall state an objection to abortion on moral, ethical, or religious grounds shall be required to perform or participate in medical procedures which result in an abortion. The refusal of a physician, nurse, or health care provider to perform or participate in these medical procedures shall not be a basis for damages for the refusal or for any disciplinary or any other recriminatory action against the physician, nurse, or health care provider.

(f) Requirement of Services. – Nothing in this section shall require a hospital, other health care institution, or other health care provider to perform an abortion or to provide abortion services.

(g) Clinic Inspection. – The Department of Health and Human Services shall annually inspect any clinic, including ambulatory surgical facilities and any suitable facility under G.S. 90-21.82A, where abortions are performed. The Department of Health and Human Services shall publish on the Department's website and on the State website established under this Article the results and findings of all inspections conducted on or after January 1, 2013, of suitable facilities, including ambulatory surgical facilities, where abortions are performed, including any statement of deficiencies and any notice of administrative action resulting from the inspection. No person who is less than 18 years of age shall be employed at any clinic, including ambulatory surgical facilities, where abortions are performed. The requirements of this subsection shall not apply to a hospital required to be licensed under Chapter 131E of the General Statutes.

"**§ 90-21.81D. Life-limiting anomaly procedure; informed consent.**

(a) Procedure; Informed Consent. – If a qualified physician has determined there exists a life-limiting anomaly in accordance with this Article, in order to procure or cause a miscarriage or abortion, the qualified physician who made that determination must (i) procure or cause the miscarriage or abortion during the first 24 weeks of a woman's pregnancy and (ii) explain in writing and orally or provide to the woman all of the following information:

(1) The basis of the determination that the diagnosis qualifies as life limiting.

(2) The risks associated with the life-limiting anomaly and any procedure or treatment, medical, surgical, or otherwise, to perform the abortion.

(3) While there exists a risk of stillbirth with life-limiting anomalies, life-limiting anomalies have resulted in live births of infants with unpredictable and variable lengths of life.

(4) The woman has been provided by the qualified physician with current information on the life-limiting anomaly, including the likelihood of survival and length of survival, if known, after birth based on current medical evidence. The qualified physician proposing the abortion will offer referrals to the woman for neonatal and perinatal palliative care consultations. Neonatal consultation will discuss options for medical stabilization, evaluation, and possible treatments to support the infant after birth. Perinatal palliative care will discuss a plan for comfort care interventions that include the possibility of home discharge on palliative care.

(5) The woman has been provided all information contained in G.S. 90-21.82 if the abortion is a surgical abortion or all information contained in G.S. 90-21.83A if the abortion is a medical abortion, and her informed consent has been obtained in accordance with those sections.

(6) The woman has been provided all information, in addition to the information provided under subdivision (5) of this subsection, regarding her options and the spectrum of care, including all of the following:

a. Continuation of the pregnancy.

b. Referrals offered to perinatal palliative comfort care service providers to discuss palliative care, neonatal specialists, and other appropriate specialists, as indicated by the particular life-limiting anomaly, and those service providers can discuss those options, including the stabilization of the infant in the labor and delivery room, transfer to the Neonatal Intensive Care Unit for further evaluation and treatment, and support for the mother and her family should they choose to continue the pregnancy.

(b) Affirmation. – All additional information provided to the woman under this section shall be signed and initialed by both the woman and the qualified physician.

(c) Report. – The qualified physician who performs an abortion due to the determination of a life-limiting anomaly under this section shall submit a report to the Department of Health and Human Services for statistical purposes. The report shall include, at a minimum, all of the following:

(1) Identification of the qualified physician who diagnosed the baby with a life-limiting anomaly.
(2) The probable gestational age of the unborn child.
(3) Identification of the qualified physician who performed the abortion.
(4) The pregnant woman's age and race.
(5) The number of previous pregnancies, number of live births, and number of previous abortions of the pregnant woman.

(d) Public Records. – Materials generated by the physician or provided by the physician to the Department of Health and Human Services pursuant to this section shall not be public records under G.S. 132-1.

"**§ 90-21.82. Informed consent to surgical abortion.**

(a) No surgical abortion shall be performed upon a woman in this State without her voluntary and informed ~~consent.~~ consent as described in this section.

(b) Except in the case of a medical emergency, consent to ~~an~~ a surgical abortion is voluntary and informed only if all of the following conditions are satisfied:

(1) At least 72 hours prior to the surgical abortion, a physician or qualified professional has orally informed the woman, ~~by telephone or~~ in person, of the information contained in the consent form.

(1a) The consent form shall include, at a minimum, all of the following:

a. The name of the physician who will perform the surgical abortion to ensure the safety of the procedure and prompt medical attention to any complications that may arise. The physician performing a surgical abortion shall be physically present during the performance of the entire abortion procedure. ~~The physician prescribing, dispensing, or otherwise providing any drug or chemical for the purpose of inducing an abortion shall be physically present in the same room as the patient when the first drug or chemical is administered to the patient.~~

b. The particular medical risks associated with the ~~particular~~ surgical abortion procedure to be employed, including, when medically accurate, the risks of infection, hemorrhage, cervical tear or uterine perforation, danger to subsequent pregnancies, including the ability to carry a child to full term, and any adverse psychological effects associated with the surgical abortion.

c. The probable gestational age of the unborn child at the time the surgical abortion is to be performed.

d. The medical risks associated with carrying the child to term.

e. The display of a real-time view of the unborn child and heart tone monitoring that enable the pregnant woman to view her unborn child or listen to the heartbeat of the unborn child are available to the woman. The physician performing the surgical abortion, qualified technician, or referring physician shall inform the woman that the printed materials and ~~Web site~~ website described in G.S. 90-21.83 and G.S. 90-21.84 contain phone numbers and addresses for facilities that offer the services free of charge. If requested by the woman, the

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 7 of 48

physician or qualified professional shall provide to the woman the list as compiled by the Department.

f. If the physician who is to perform the surgical abortion has no liability insurance for malpractice in the performance or attempted performance of ~~an~~ a surgical abortion, that information shall be communicated.

g. The location of the hospital that offers obstetrical or gynecological care located within 30 miles of the location where the surgical abortion is performed or induced and at which the physician performing or inducing the surgical abortion has clinical privileges. If the physician who will perform the surgical abortion has no local hospital admitting privileges, that information shall be communicated.

If the physician or qualified professional does not know the information required in sub-subdivisions a., f., or g. of this subdivision, the woman shall be advised that this information will be directly available from the physician who is to perform the surgical abortion. However, the fact that the physician or qualified professional does not know the information required in sub-subdivisions a., f., or g. shall not restart the 72-hour period. The information required by this subdivision shall be provided in English and in each language that is the primary language of at least two percent (2%) of the State's population. The information ~~may~~ shall be provided orally ~~either by telephone or~~ in person, by the physician or qualified professional, in which case the required information may be based on facts supplied by the woman to the physician and whatever other relevant information is reasonably available. The information required by this subdivision ~~may~~ shall not be provided by a tape recording but shall be provided during a consultation in which the physician is able to ask questions of the patient and the patient is able to ask questions of the physician. If, in the medical judgment of the physician, a physical examination, tests, or the availability of other information to the physician subsequently indicates a revision of the information previously supplied to the patient, then that revised information may be communicated to the patient at any time before the performance of the surgical abortion. Nothing in this section may be construed to preclude provision of required information in a language understood by the patient through a translator.

(1b) A consent form shall not be considered valid, and informed consent not obtained by the woman, unless all of the following conditions are satisfied:

a. The woman signs and initials each entry, list, description, or declaration required to be on the consent form described in sub-subdivisions a. through g. of subdivision (1a) of this subsection.

b. The woman signs and initials each entry, list, description, or declaration required to be on the acknowledgment of risks and consent statement described in sub-subdivisions a. through n. of subdivision (2) of this subsection.

c. The physician signs the qualified physician declaration described in subdivision (5) of this subsection.

d. The physician uses the consent form created by the Department for the purposes of this section.

(2) ~~The physician or qualified professional has informed the woman, either by telephone or in person, of each of the following~~ Prior to the surgical abortion, an acknowledgment of risks and consent statement must be signed and

initialed by the woman with a physical or electronic signature attesting she has received all of the following information at least 72 hours before the ~~abortion:~~surgical abortion. The acknowledgment of risks and consent statement shall include, at a minimum, all of the following:

a. That medical assistance benefits may be available for prenatal care, childbirth, and neonatal care.

b. That public assistance programs under Chapter 108A of the General Statutes may or may not be available as benefits under federal and State assistance programs.

c. That the father is liable to assist in the support of the child, even if the father has offered to pay for the abortion.

d. That the woman has other alternatives to abortion, including keeping the baby or placing the baby for adoption.

e. That the woman has ~~the right to review~~ been told about the printed materials described in G.S. 90-21.83, and that she has been told that these materials are available on a State-sponsored ~~Web site,~~ website, and she has been given the address of the State-sponsored ~~Web site.~~ website. The physician or a qualified professional shall orally inform the woman that the materials have been provided by the Department and that they describe the unborn child and list agencies that offer alternatives to abortion. If the woman chooses to view the materials other than on the ~~Web site,~~ website, the materials shall ~~either~~ be given to her at least 72 hours before the ~~abortion or be mailed to her at least 72 hours before the abortion by certified mail, restricted delivery to addressee.~~surgical abortion.

f. That the woman (i) is not being forced to have a surgical abortion, (ii) has a choice to not have the surgical abortion, and (iii) is free to withhold or withdraw her consent to the surgical abortion at any time before or during the surgical abortion without affecting her right to future care or treatment and without the loss of any State or federally funded benefits to which she might otherwise be entitled.

g. Attestation that the woman understands that the surgical abortion is intended to end her pregnancy.

h. Attestation that the woman understands the surgical abortion has specific risks and may result in specific complications.

i. Attestation that the woman has been given the opportunity to ask questions about her pregnancy, the development of her unborn child, and alternatives to surgical abortion.

j. Confirmation that the woman has been provided access to State-prepared, printed materials on informed consent for surgical abortion and the State-prepared and maintained website on informed consent for a surgical abortion.

k. If applicable, that the woman has been given the name and phone number of a qualified physician who has agreed to provide medical care and treatment in the event of complications associated with the surgical abortion procedure.

l. Attestation that the woman has received or been given sufficient information to give her informed consent to the surgical abortion.

m. That the woman has a private right of action to sue the qualified physician under the laws of this State if she feels she has been coerced

or misled prior to obtaining an abortion, and how to access State resources regarding her legal right to obtain relief.

n. A statement that she will be given a copy of the forms and materials with all signatures and initials required under this Article, and all other informed consent forms required by this State.

The information required by this subdivision shall be provided in English and in each language that is the primary language of at least two percent (2%) of the State's population. ~~The information required by this subdivision may be provided by a tape recording if provision is made to record or otherwise register specifically whether the woman does or does not choose to have the printed materials given or mailed to her. Nothing in this subdivision shall be construed to prohibit the physician or qualified professional from e-mailing a Web site link to the materials described in this subdivision or G.S. 90-21.83.~~

~~(3) The woman certifies in writing, before the abortion, that the information described in subdivisions (1) and (2) of this section has been furnished her and that she has been informed of her opportunity to review the information referred to in sub-subdivision (2)e. of this section. The original of this certification shall be maintained in the woman's medical records, and a copy shall be given to her.~~

~~(4) Before the performance of the abortion, the physician who will perform the abortion or the qualified technician must receive a copy of the written certification required by subdivision (3) of this section.~~

(5) The physician has signed a physician declaration form stating that prior to the surgical abortion procedure, the qualified physician has (i) explained in person the surgical abortion procedure to be used, (ii) provided all of the information required in this section, and (iii) answered all of the woman's questions regarding the surgical abortion.

"**§ 90-21.83. Printed information required.**

(a) Within 90 days after this Article becomes effective, the Department shall publish in English and in each language that is the primary language of at least two percent (2%) of the State's population and shall cause to be available on the ~~State Web site~~ website established under G.S. 90-21.84, the following printed materials in a manner that ensures that the information is comprehensible to a person of ordinary intelligence:

(1) Geographically indexed materials designed to inform a woman of public and private agencies and services available to assist her through pregnancy, upon childbirth, and while the child is dependent, including adoption agencies. The information shall include a comprehensive list of the agencies available, a description of the services they offer, including which agencies offer, at no cost to the woman, imaging that enables the woman to view the unborn child or heart tone monitoring that enables the woman to listen to the heartbeat of the unborn child, and a description of the manner, including telephone numbers, in which they might be contacted. In the alternative, in the discretion of the Department, the printed materials may contain a toll-free, 24-hour-a-day telephone number that may be called to obtain, orally or by tape recorded message tailored to the zip code entered by the caller, a list of these agencies in the locality of the caller and of the services they offer.

(2) Materials designed to inform the woman of the probable anatomical and physiological characteristics of the unborn child at two-week gestational increments from the time a woman can be known to be pregnant until full term, including pictures or drawings representing the development of the unborn child at two-week gestational increments. The pictures shall contain

the dimensions of the unborn child, information about brain and heart functions, the presence of external members and internal organs, and be realistic and appropriate for the stage of pregnancy depicted. The materials shall be objective, nonjudgmental, and designed to convey only accurate scientific information about the unborn child at the various gestational ages. The material shall contain objective information describing the methods of abortion procedures employed, the medical risks associated with each procedure, the possible adverse psychological effects of abortion, as well as the medical risks associated with carrying an unborn child to term.

(b) The materials referred to in subsection (a) of this section shall be printed in a typeface large enough to be clearly legible. The ~~Web site~~ website provided for in G.S. 90-21.84 shall be maintained at a minimum resolution of 70 DPI (dots per inch). All pictures appearing on the ~~Web site~~ website shall be a minimum of 200x300 pixels. All letters on the ~~Web site~~ website shall be a minimum of 12-point font. All information and pictures shall be accessible with an industry-standard browser requiring no additional plug-ins.

(c) The materials required under this section shall be available at no cost from the Department upon request and in appropriate numbers to any physician, person, health facility, hospital, or qualified professional. The Department shall create the consent forms described in this section to be used by qualified physicians for the purposes of obtaining informed consent for surgical and medical abortions.

(d) The Department shall cause to be available on the ~~State Web site~~ website a list of resources the woman may contact for assistance upon receiving information from the physician performing the ultrasound that the unborn child may have a disability or serious abnormality and shall do so in a manner prescribed by subsection (b) of this section.

"**§ 90-21.83A. Informed consent to medical abortion.**

(a) No medical abortion shall be performed upon a woman in this State without her voluntary and informed consent as described in this section.

(b) Except in the case of a medical emergency, consent to a medical abortion is voluntary and informed only if all of the following conditions are satisfied:

(1) At least 72 hours prior to the medical abortion, a qualified physician or qualified professional has orally informed the woman, in person, of the information contained in the consent form.

(2) The consent form shall include, at a minimum, all of the following:

a. The name of the physician who will prescribe, dispense, or otherwise provide the abortion-inducing drugs to ensure the safety of the procedure and prompt medical attention to any complications that may arise. The physician prescribing, dispensing, or otherwise providing any drug or chemical for the purpose of inducing an abortion shall be physically present in the same room as the woman when the first drug or chemical is administered to the woman.

b. The probable gestational age of the unborn child as determined by both patient history and by ultrasound results used to confirm gestational age.

c. A detailed description of the steps to complete the medical abortion.

d. A detailed list of the risks related to the specific abortion-inducing drug or drugs to be used, including hemorrhage, failure to remove all tissue of the unborn child which may require an additional procedure, sepsis, sterility, and possible continuation of the pregnancy.

e. The medical risks associated with carrying the child to term.

f. The display of a real-time view of the unborn child and heart tone monitoring that enable the pregnant woman to view her unborn child

or listen to the heartbeat of the unborn child are available to the woman. The physician performing the abortion, qualified technician, or referring physician shall inform the woman that the printed materials and website described in G.S. 90-21.83 and G.S. 90-21.84 contain phone numbers and addresses for facilities that offer the services free of charge. If requested by the woman, the physician or qualified professional shall provide to the woman the list as compiled by the Department.

g. Information about Rh incompatibility, including that if the woman has an Rh-negative blood type, she could receive an injection of Rh immunoglobulin at the time of the medical abortion to prevent Rh incompatibility in future pregnancies.

h. Information about the risks of complications from a medical abortion, including incomplete abortion, increase with advancing gestational age, and that infection and hemorrhage are the most common causes of deaths related to medical abortions.

i. Notice that the woman may see the remains of her unborn child in the process of completing the abortion.

j. Notice that the physician who is to perform the medical abortion has no liability insurance for malpractice in the performance or attempted performance of an abortion, if applicable.

k. The location of the hospital that offers obstetrical or gynecological care located within 30 miles of the location where the medical abortion is performed or induced and at which the physician performing or inducing the medical abortion has clinical privileges. If the physician who will perform the medical abortion has no local hospital admitting privileges, that information shall be communicated.

If the physician or qualified professional does not know the information required in sub-subdivision a., j., or k. of this subdivision, the woman shall be advised that this information will be directly available from the physician who is to perform the medical abortion. However, the fact that the physician or qualified professional does not know the information required in sub-subdivision a., j., or k. shall not restart the 72-hour period. The information required by this subdivision shall be provided in English and in each language that is the primary language of at least two percent (2%) of the State's population. The information shall be provided orally in person, by the physician or qualified professional, in which case the required information may be based on facts supplied by the woman to the physician and whatever other relevant information is reasonably available. The information required by this subdivision shall not be provided by a tape recording but shall be provided during a consultation in which the physician is able to ask questions of the patient and the patient is able to ask questions of the physician. If, in the medical judgment of the physician, a physical examination, tests, or the availability of other information to the physician subsequently indicates a revision of the information previously supplied to the patient, then that revised information may be communicated to the patient at any time before the performance of the medical abortion. Nothing in this section may be construed to preclude provision of required information in a language understood by the patient through a translator.

(3) A consent form shall not be considered valid, and informed consent not obtained from the woman, unless all of the following conditions are satisfied:

a. The woman signs and initials each entry, list, description, or declaration required to be on the consent form described in subdivision (2) of this subsection.

b. The woman signs and initials each entry, list, description, or declaration required to be on the acknowledgment of risks and consent statement described in subdivision (4) of this subsection.

c. The physician signs the qualified physician declaration described in subdivision (5) of this subsection.

d. The physician uses the consent form created by the Department for the purposes of this section.

(4) Prior to the medical abortion, an acknowledgment of risks and consent statement must be signed and initialed by the woman with a physical or electronic signature attesting she has received all of the following information at least 72 hours before the medical abortion. The acknowledgment of risks and consent statement shall include, at a minimum, all of the following:

a. That medical assistance benefits may be available for prenatal care, childbirth, and neonatal care.

b. That public assistance programs under Chapter 108A of the General Statutes may or may not be available as benefits under federal and State assistance programs.

c. That the father is liable to assist in the support of the child, even if the father has offered to pay for the abortion.

d. That the woman has other alternatives to abortion, including keeping the baby or placing the baby for adoption.

e. That the woman has been told about the printed materials described in G.S. 90-21.83, and that she has been told that these materials are available on a State-sponsored website, and she has been given the address of the State-sponsored website. The physician or a qualified professional shall orally inform the woman that the materials have been provided by the Department and that they describe the unborn child and list agencies that offer alternatives to abortion. If the woman chooses to view the materials other than on the website, the materials shall be given to her at least 72 hours before the medical abortion.

f. Attestation that the woman (i) is not being forced to have a medical abortion, (ii) has a choice to not have the medical abortion, and (iii) is free to withhold or withdraw her consent to the abortion-inducing drug regimen even after she has begun the abortion-inducing drug regimen.

g. Attestation that the woman understands that the medical abortion is intended to end her pregnancy.

h. Attestation that the woman understands the medical abortion regimen has specific risks and may result in specific complications.

i. Attestation that the woman has been given the opportunity to ask questions about her pregnancy, the development of her unborn child, and alternatives to medical abortion.

j. Confirmation that the woman has been provided access to State-prepared, printed materials on informed consent for abortion and the State-prepared and maintained website on informed consent for a medical abortion.

k. If applicable, that the woman has been given the name and phone number of a qualified physician who has agreed to provide medical

care and treatment in the event of complications associated with the abortion-inducing drug regimen.

l. Notice that the physician will schedule an in-person follow-up visit for the woman at approximately seven to 14 days after providing the abortion-inducing drug or drugs to confirm that the pregnancy is completely terminated and to assess the degree of bleeding and other complications.

m. That the woman has received or been given sufficient information to give her informed consent to the abortion-inducing drug regimen or procedure.

n. That the woman has a private right of action to sue the qualified physician under the laws of this State if she feels she has been coerced or misled prior to obtaining an abortion, and how to access State resources regarding her legal right to obtain relief.

o. A statement that she will be given a copy of the forms and materials with all signatures and initials required under this Article, and all other informed consent forms required by this State.

The information required by this subdivision shall be provided in English and in each language that is the primary language of at least two percent (2%) of the State's population.

(5) The physician has signed a physician declaration form stating that prior to the medical abortion procedure, the qualified physician has (i) explained in person the medical abortion procedure to be used, (ii) provided all of the information required in this section, and (iii) answered all of the woman's questions regarding the medical abortion.

"**§ 90-21.83B. Distribution of abortion-inducing drugs and duties of physician.**

(a) A physician prescribing, administering, or dispensing an abortion-inducing drug must examine the woman in person and, prior to providing an abortion-inducing drug, shall do all of the following:

(1) Independently verify that the pregnancy exists.

(2) Determine the woman's blood type; offer necessary medical services, treatment, and advice, based on the physician's reasonable medical judgment of any medical risks associated with the woman's blood type, including whether the woman's blood type is Rh negative; and be able to administer Rh immunoglobulin at the time of the abortion, if medically necessary.

(3) Provide any other medically indicated diagnostic tests, including iron or hemoglobin/hematocrit tests, to determine whether the woman has a heightened risk of complications.

(4) Screen the woman for coercion, abuse, comply with G.S. 90-21.91, and refer the woman to the appropriate health care provider for appropriate treatment, if medically necessary.

(5) Inform the patient that she may see the remains of her unborn child in the process of completing the abortion.

(6) Verify that the probable gestational age of the unborn child is no more than 70 days.

(7) Document in the woman's medical chart the probable gestation age and intrauterine location of the pregnancy, and whether the woman received treatment for an Rh negative condition or any other diagnostic tests.

(8) Comply with all provisions of this Article and laws of this State as applicable.

(b) The physician providing any abortion-inducing drug, or an agent of the physician, shall schedule a follow-up visit for the woman at approximately seven to 14 days after

administration of the abortion-inducing drug to confirm that the pregnancy is completely terminated and to assess the degree of bleeding. The physician shall make all reasonable efforts to ensure that the woman returns for the scheduled appointment. A brief description of the efforts made to comply with this subsection, including the date, time, and identification by name of the person making these efforts, shall be included in the woman's medical records.

"**§ 90-21.83C. Additional information provided to the pregnant woman.**

At least 72 hours prior to any medical or surgical abortion performed in accordance with this Article, the physician providing the abortion-inducing drug, performing the surgical abortion, or conducting any other appointment where an abortion is to be induced or performed shall provide the pregnant woman the physician's full name and specific information for the physician's hospital admitting privileges and whether the treatment or procedure to be performed is covered by the pregnant woman's insurance.

"**§ 90-21.84. Internet ~~Web site.~~website.**

The Department shall develop and maintain a stable Internet ~~Web site~~ website to provide the information described ~~under G.S. 90-21.83.~~ in this Article. No information regarding who accesses the ~~Web site~~ website shall be collected or maintained. The Department shall monitor the Web site on a regular basis to prevent and correct tampering.

"**§ 90-21.85. Display of real-time view requirement.**

(a) Notwithstanding G.S. 14-45.1, except in the case of a medical emergency, in order for the woman to make an informed decision, at least four hours before a woman having any part of an abortion performed or induced, and before the administration of any anesthesia or medication in preparation for the abortion on the woman, the physician who is to perform the abortion, or qualified technician working in conjunction with the physician, shall do each of the following:

(1) Perform an obstetric real-time view of the unborn child on the pregnant woman.

(2) Provide a simultaneous explanation of what the display is depicting, which shall include the presence, location, and dimensions of the unborn child within the uterus and the number of unborn children depicted. The individual performing the display shall offer the pregnant woman the opportunity to hear the fetal heart tone. The image and auscultation of fetal heart tone shall be of a quality consistent with the standard medical practice in the community. If the image indicates that fetal demise has occurred, a woman shall be informed of that fact.

(3) Display the images so that the pregnant woman may view them.

(4) Provide a medical description of the images, which shall include the dimensions of the embryo or fetus and the presence of external members and internal organs, if present and viewable.

(5) Obtain a written certification from the woman, before the abortion, that the requirements of this section have been complied with, which shall indicate whether or not she availed herself of the opportunity to view the image.

(6) Retain a copy of the written certification prescribed by subdivision (a)(5) of this section. The certification shall be placed in the medical file of the woman and shall be kept by the abortion provider for a period of not less than seven years. If the woman is a minor, then the certification shall be placed in the medical file of the minor and kept for at least seven years or for five years after the minor reaches the age of majority, whichever is greater.

If the woman has had an obstetric display of a real-time image of the unborn child within 72 hours before the abortion is to be performed, the certification of the physician or qualified technician who performed the procedure in compliance with this subsection shall be included in

the patient's records and the requirements under this subsection shall be deemed to have been met.

(a1) A pregnant woman has the right to view a real-time view image of the unborn child under this section and shall not be denied a real-time view of the unborn child due to a clinic policy or rule.

(b) Nothing in this section shall be construed to prevent a pregnant woman from averting her eyes from the displayed images or from refusing to hear the simultaneous explanation and medical description.

(c) In the event the person upon whom the abortion is to be performed is an unemancipated minor, as defined in G.S. 90-21.6(1), the information described in subdivisions (a)(2) and (a)(4) of this section shall be furnished and offered respectively to a person required to give parental consent under G.S. 90-21.7(a) and the unemancipated minor. The person required to give consent in accordance with G.S. 90-21.7(a), as appropriate, shall make the certification required by subdivision (a)(5) of this section. In the event the person upon whom the abortion is to be performed has been adjudicated mentally incompetent by a court of competent jurisdiction, the information shall be furnished and offered respectively to her spouse or a legal guardian if she is married or, if she is not married, to one parent or a legal guardian and the woman. The spouse, legal guardian, or parent, as appropriate, shall make the certification required by subdivision (a)(5) of this section. In the case of an abortion performed pursuant to a court order under G.S. 90-21.8(e) and (f), the information described in subdivisions (a)(2) and (a)(4) of this section shall be provided to the minor, and the certification required by subdivision (a)(5) of this section shall be made by the minor.

"**§ 90-21.86. Procedure in case of medical emergency.**

When a medical emergency compels the performance of an abortion, the physician shall inform the woman, before the abortion if possible, of the medical indications supporting the physician's judgment that an abortion is necessary to avert her death or that a 72-hour delay will create a serious risk of substantial and irreversible impairment of a major bodily function, not including psychological or emotional conditions. As soon as feasible, the physician shall document in writing the medical indications upon which the physician relied and shall cause the original of the writing to be maintained in the woman's medical records and a copy given to her.

"**§ 90-21.87. Informed consent for a minor.**

If the woman upon whom an abortion is to be performed is an unemancipated minor, the voluntary and informed written consent required under G.S. 90-21.82 or G.S. 90-21.83A shall be obtained from the minor and from the adult individual who gives consent pursuant to G.S. 90-21.7(a).

"**§ 90-21.88. Civil remedies.**

(a) Any person upon whom an abortion has been ~~performed~~ performed, her personal representative in the event of a wrongful death action in accordance with G.S. 28A-18-1, and any father of an unborn child that was the subject of an abortion may maintain an action for damages against the person who performed the abortion in knowing or reckless violation of this Article. Any person upon whom an abortion has been attempted may maintain an action for damages against the person who performed the abortion in willful violation of this Article.

(a1) Notwithstanding any other provision of law, (i) a woman upon whom the abortion has been attempted, induced, or performed or (ii) her parent or guardian, if she is a minor at the time of the attempted or completed abortion, may bring an action under this section within three years from the date of the alleged violation or from the date of the initial discovery of harm from an alleged violation. If at the time of the alleged violation the woman is a minor, then the minor shall have three years from the date the minor attains the age of majority to bring an action under this section.

(b) Injunctive relief against any person who has willfully violated this Article may be sought by and granted to (i) the woman upon whom an abortion was performed or attempted to

be performed in violation of this Article, (ii) any person who is the spouse, parent, sibling, or guardian of, or a current or former licensed health care provider of, the woman upon whom an abortion has been performed or attempted to be performed in violation of this Article, or (iii) the Attorney General. The injunction shall prevent the abortion provider from performing or inducing further abortions in this State in violation of this Article.

(c) If judgment is rendered in favor of the plaintiff in any action authorized under this section, the court shall also tax as part of the costs reasonable attorneys' fees in favor of the plaintiff against the defendant. If judgment is rendered in favor of the defendant and the court finds that the plaintiff's suit was frivolous or brought in bad faith, then the court shall tax as part of the costs reasonable attorneys' fees in favor of the defendant against the plaintiff.

"**§ 90-21.88A. Violation of this Article.**

A physician who violates any provision of this Article shall be subject to discipline by the North Carolina Medical Board under G.S. 90-14(a)(2) and any other applicable law or rule. Any licensed pharmacist who violates any provision of this Article shall be subject to discipline by the North Carolina Board of Pharmacy under Article 4A of this Chapter. Any other licensed health care provider who violates any provision of this Article shall be subject to discipline under their respective licensing agency or board. No pregnant woman seeking to obtain an abortion in accordance with this Article shall be subject to professional discipline for attempting to do so.

"**§ 90-21.89. Protection of privacy in court proceedings.**

In every proceeding or action brought under this Article, the court shall rule whether the anonymity of any woman upon whom an abortion has been performed or attempted shall be preserved from public disclosure if she does not give her consent to the disclosure. The court, upon motion or sua sponte, shall make the ruling and, upon determining that her anonymity should be preserved, shall issue orders to the parties, witnesses, and counsel and shall direct the sealing of the record and exclusion of individuals from courtrooms or hearing rooms to the extent necessary to safeguard her identity from public disclosure. Each order issued pursuant to this section shall be accompanied by specific written findings explaining (i) why the anonymity of the woman should be preserved from public disclosure, (ii) why the order is essential to that end, (iii) how the order is narrowly tailored to serve that interest, and (iv) why no reasonable less restrictive alternative exists. In the absence of written consent of the woman upon whom an abortion has been performed or attempted, anyone who brings an action under G.S. 90-21.88 (a) or (b) shall do so under a pseudonym. This section may not be construed to conceal the identity of the plaintiff or of witnesses from the defendant.

"**§ 90-21.90. Assurance of informed consent.**

(a) All information required to be provided under G.S. 90-21.82 and G.S. 90-21.83A to a woman considering abortion shall be presented to the woman individually ~~and, except for information that may be provided by telephone,~~ and in the physical presence of the woman and in a language the woman understands to ensure that the woman has adequate opportunity to ask questions and to ensure the woman is not the victim of a coerced abortion.

(b) Should a woman be unable to read the materials provided to the woman pursuant to this section, a physician or qualified professional shall read the materials to the woman in a language the woman understands before the abortion.

"**§ 90-21.91. Assurance that consent is freely given.**

If a physician acting pursuant to this Article has reason to believe that a woman is being coerced into having an abortion, the physician or qualified professional shall inform the woman that services are available for the woman and shall provide the woman with private access to a telephone and information about, but not limited to, each of the following services:

(1) Rape crisis centers.
(2) Shelters for victims of domestic violence.
(3) Restraining orders.
(4) Pregnancy care centers.

"**§ 90-21.92. Severability.**

If any one or more provision, section, subsection, sentence, clause, phrase, or word of this Article or the application thereof to any person or circumstance is found to be unconstitutional, the same is hereby declared to be severable, and the balance of this Article shall remain effective, notwithstanding such unconstitutionality. The General Assembly hereby declares that it would have passed this Article, and each provision, section, subsection, sentence, clause, phrase, or word thereof, irrespective of the fact that any one or more provision, section, subsection, sentence, clause, phrase, or word be declared unconstitutional.

"**§ 90-21.93. Reporting requirements.**

(a) Report. – After a surgical or medical abortion is performed, the physician or health care provider that conducted the surgical or medical abortion shall complete and transmit a report to the Department in compliance with the requirements of this section. The report shall be completed by either the hospital, clinic, or health care provider in which the surgical or medical abortion was completed and signed by the physician who dispensed, administered, prescribed, or otherwise provided the abortion-inducing drug or performed the procedure or treatment to the woman. Any physician or health care provider shall make reasonable efforts to include all of the required information in this section in the report without violating the privacy of the woman. The report shall be transmitted to the Department within 15 days after either the (i) date of the follow-up appointment following a medical abortion, (ii) date of the last patient encounter for treatment directly related to a surgical abortion, or (iii) end of the month in which the last scheduled appointment occurred, whichever is later. A report completed under this section for a minor shall be sent to the Department and the Division of Social Services within three days of the surgical or medical abortion.

(b) Contents. – Each report completed in accordance with this section shall contain, at a minimum, all of the following:

(1) Identifying information of the (i) physician who provided the abortion-inducing drug or performed the surgical abortion and (ii) referring physician, agency, or service, if applicable.

(2) The location, date, and type of the surgical abortion, or the location of where any abortion-inducing drug was administered or dispensed, including any health care provider facility, at the home of the pregnant woman, or other location.

(3) The woman's county, state, and country of residence; age; and race.

(4) The woman's number of live births, previous pregnancies, and number of previous abortions.

(5) The woman's preexisting medical conditions, which could complicate her pregnancy.

(6) The probable gestational age of the unborn child, as determined by both patient history and ultrasound, and the date of the ultrasound used to estimate gestational age.

(7) The abortion-inducing drugs used, and the date in which the abortion-inducing drugs were dispensed, administered, and used.

(8) Whether the woman returned for the scheduled follow-up appointment or examination to determine the completion of the abortion procedure and to assess bleeding, the results of the follow-up appointment or examination, and the date of any follow-up appointment or examination of the abortion procedure.

(9) The reasonable efforts of the physician to encourage the woman to attend the follow-up appointment or examination if the woman did not attend.

(10) Any specific complications the woman suffered from the abortion procedure.

(11) The amount of money billed to cover the treatment for specific complications, including whether the treatment was billed to Medicaid, private insurance, private pay, or any other method, including ICD-10 diagnosis codes reported, any other codes reported, any charges for hospitals, emergency departments, physicians, prescriptions or other drugs, laboratory tests, and any other costs for treatment.

(c) Adverse Event from Abortion-Inducing Drug Report. – If a woman has an adverse event related to the administration, dispensing, or prescription of an abortion-inducing drug for the purpose of inducing an abortion, the physician who provided the abortion-inducing drug or the physician who diagnosed or treated the woman for the adverse event shall provide a written report of the adverse event within three days of the adverse event to the Food and Drug Administration through the MedWatch Reporting System and to the Department.

(d) Adverse Event or Complication from Abortion Procedure Report. – If a woman has an adverse event or complication related to a surgical abortion or abortion procedure, the physician or health care provider who performed the surgical abortion or abortion procedure or the physician who diagnosed or treated the woman for the adverse event or complication shall make a report of the adverse event or complication, including the diagnosis or treatment that was provided. A report under this subsection shall be transmitted to the Department within 15 days of the end of the month that the adverse event or complication occurred.

(e) Additional Report Contents. – In addition to the information in subsection (b) of this section, a report made under subsection (c) or (d) of this section shall contain all of the following information:

(1) The date the woman presented for treatment of the adverse event or complication.

(2) The specific complication that led to the treatment, including any physical or psychological conditions, which, in the reasonable medical judgment of a physician or health care provider, arose as a primary or secondary result of an induced abortion.

(3) Whether the woman obtained abortion-inducing drugs as a mail order or from an internet website, and, if so, information identifying the name of the source, website or URL address, and telemedicine provider.

(f) Departmental Reports. – The Department shall prepare a comprehensive annual statistical report based upon the data gathered from reports under this Article. The report shall be made available to the public in a downloadable format. On or before October 1, 2023, and each October 1 thereafter, the Department shall submit the report to the Joint Legislative Oversight Committee on Health and Human Services. The Department shall also submit data and the annual report to the Centers for Disease Control and Prevention for inclusion in the annual Vital Statistics Report. Original copies of reports shall be made available to the North Carolina Medical Board, the North Carolina Board of Pharmacy, State law enforcement offices, and the Division of Social Services for official use.

(g) Identifying Information. – A report completed under this section shall not contain the woman's name, any common identifiers of the woman, or any other information that would make it possible to identify the woman subject to a report under this section, including the woman's social security number or drivers license identification number. The Department and any State agency or any contractor thereof shall not maintain statistical information that may reveal the identity of a woman obtaining or seeking to obtain a surgical or medical abortion. Absent a court order, the Department and any State agency or any contractor thereof shall not compare data concerning surgical or medical abortions or resulting complications maintained in an electronic or other information system file or format with data in any other format or information system in an effort to identify a woman obtaining or seeking to obtain a drug-induced abortion.

(h) Communication of Information. – The Department shall communicate the reporting requirements of this Article to all medical professional organizations, licensed physicians, hospitals, emergency departments, clinics certified to perform abortion services under this Article, other clinics and facilities that provide health care services, and any other health care facility in this State."

SECTION 1.3. Article 11 of Chapter 14 of the General Statutes is amended by adding a new section to read:

"**§ 14-44.1. Providing or advertising abortion-inducing drugs to pregnant woman.**

(a) Offense. – All of the following are unlawful:

(1) For any individual within the State, including a physician, an employee or contractor of a physician's office or clinic, or other abortion provider, or organization within the State, including a physician's office or clinic or other abortion provider, to mail, provide, or supply an abortion-inducing drug directly to a pregnant woman in violation of G.S. 90-21.83A(b)(2)a. Lack of knowledge or intent that the abortion-inducing drug will be administered outside the physical presence of a physician shall not be a defense to a violation of this subdivision.

(2) For any manufacturer or supplier of an abortion-inducing drug to ship or cause to be shipped any abortion-inducing drug directly to a pregnant woman in violation of G.S. 90-21.83A(b)(2)a. Lack of knowledge or intent that the abortion-inducing drug will be administered outside the physical presence of a physician shall not be a defense to a violation of this subdivision.

(3) For any individual or organization to purchase or otherwise procure an advertisement, host or maintain an internet website, or provide an internet service purposefully directed to a pregnant woman who is a resident of this State when the individual or organization knows that the purpose of the advertisement, website, or internet service is solely to promote the sale of an abortion-inducing drug to be administered to a woman in violation of G.S. 90-21.83A(b)(2)a.

(b) Punishment. – An individual or organization who violates this section commits an infraction as defined in G.S. 14-3.1 and is subject to a fine of five thousand dollars ($5,000) per violation.

(c) Definitions. – The following definitions apply in this section:

(1) Abortion-inducing drug. – As defined in G.S. 90-21.81(1a).

(2) Organization. – As defined in G.S. 15A-773(c)."

SECTION 1.4.(a) G.S. 90-21.120 reads as rewritten:

"**§ 90-21.120. Definitions.**

The following definitions apply in this Article:

(1) Abortion. – As defined in ~~G.S. 90-21.81(1).~~G.S. 90-21.81.

(2) Attempt to perform an abortion. – As defined in ~~G.S. 90-21.81(2).~~G.S. 90-21.81.

(3) Woman. – As defined in ~~G.S. 90-21.81(11).~~G.S. 90-21.81."

SECTION 1.4.(b) G.S. 90-21.121 reads as rewritten:

"**§ 90-21.121. ~~Sex-selective abortion~~ Eugenic abortions prohibited.**

(a) Notwithstanding any of the provisions of ~~G.S. 14-45.1,~~ G.S. 90-21.81B, no person shall perform or attempt to perform an abortion upon a pregnant woman ~~in this State with knowledge, or an objective reason to know,~~ if the person has knowledge that ~~a significant factor in~~ the pregnant woman is seeking the ~~abortion is related to the~~ abortion, in whole or in part, because of any of the following:

(1) The actual or presumed race or racial makeup of the unborn child.

(2) The sex of the unborn child.

(3) The presence or presumed presence of Down syndrome.

…."

SECTION 1.4.(c) G.S. 90-21.6 reads as rewritten:

"**§ 90-21.6. Definitions.**

For the purposes of Part 2 only of this Article, unless the context clearly requires otherwise:

(1) Abortion. – As defined in G.S. 90-21.81.

(1a) ~~"Unemancipated minor" or "minor" means any~~ Unemancipated minor or minor. – Any person under the age of 18 who has not been married or has not been emancipated pursuant to Article 35 of Chapter 7B of the General Statutes.

~~(2) "Abortion" means the use or prescription of any instrument, medicine, drug, or any other substance or device with intent to terminate the pregnancy of a woman known to be pregnant, for reasons other than to save the life or preserve the health of an unborn child, to remove a dead unborn child, or to deliver an unborn child prematurely, by accepted medical procedures in order to preserve the health of both the mother and the unborn child.~~"

SECTION 1.5.(a) Section 1.3 of this Part becomes effective July 1, 2023, and applies to offenses committed on or after that date. The remainder of this Part becomes effective on July 1, 2023.

SECTION 1.5.(b) Prosecutions for offenses committed before the effective date of this Part are not abated or affected by this Part, and the statutes that would be applicable but for this Part remain applicable to those prosecutions.

PART II. SUITABLE FACILITIES FOR THE PERFORMANCE OF SURGICAL ABORTIONS

SECTION 2.1. Article 1I of Chapter 90 of the General Statutes is amended by adding a new section to read:

"**§ 90-21.82A. Suitable facilities for the performance of surgical abortions.**

(a) The following definitions apply in this section:

(1) Abortion clinic. – As defined in G.S. 131E-153.1.

(2) Ambulatory surgical facility. – As defined in G.S. 131E-176.

(3) Hospital. – As defined in G.S. 131E-176.

(b) During the first 12 weeks of pregnancy, a physician licensed to practice medicine under this Chapter may perform a surgical abortion in a hospital, an ambulatory surgical facility, or an abortion clinic; provided, however, that (i) the clinic has been licensed by the Department of Health and Human Services to be a suitable facility for the performance of abortions and (ii) the licensed physician performs the abortion in accordance with this Article and Article 1K of this Chapter.

(c) After the twelfth week of pregnancy, a physician licensed to practice medicine under this Chapter may not perform a surgical abortion as permitted under North Carolina law in any facility other than a hospital."

SECTION 2.2. Article 6 of Chapter 131E of the General Statutes is amended by adding a new Part to read:

"Part 4A. Abortion Clinic Licensure.

"**§ 131E-153. Title; purpose.**

(a) This Part shall be known as the "Abortion Clinic Licensure Act."

(b) The purpose of this Part is to provide for the development, establishment, and enforcement of basic standards:

(1) For the care and treatment of individuals in abortion clinics; and

(2) For the maintenance and operation of abortion clinics so as to ensure safe and adequate treatment of such individuals in abortion clinics.

"**§ 131E-153.1. Definitions.**

The following definitions apply in this Part, unless otherwise specified:

(1) Abortion clinic. – A freestanding facility, that is neither physically attached nor operated by a hospital, for the performance of abortions during the first 12 weeks of pregnancy.

(2) Commission. – The North Carolina Medical Care Commission.

(3) Operating room. – A room used for the performance of surgical procedures requiring one or more incisions and that is required to comply with all applicable licensure codes and standards for an operating room.

"**§ 131E-153.2. Licensure requirement.**

(a) No person shall operate an abortion clinic without a license obtained from the Department.

(b) Applications shall be available from the Department, and each application filed with the Department shall contain all necessary and reasonable information that the Department may by rule require. A license shall be granted to the applicant upon a determination by the Department that the applicant has complied with the provisions of this Part and the rules adopted by the Commission under this Part. The Department shall charge the applicant a nonrefundable annual base license fee in the amount of eight hundred fifty dollars ($850.00) plus a nonrefundable annual per-operating room fee in the amount of seventy-five dollars ($75.00).

(c) A license to operate an abortion clinic shall be annually renewed upon the filing and the Department's approval of a renewal application. The renewal application shall be available from the Department and shall contain all necessary and reasonable information that the Department may by rule require.

(d) Each license shall be issued only for the premises and persons named in the application and shall not be transferable or assignable except with the written approval of the Department.

(e) Licenses shall be posted in a conspicuous place on the licensed premises.

"**§ 131E-153.3. Fair billing and collections practices for abortion clinics.**

All abortion clinics licensed under this Part shall be subject to the fair billing and collections practices set out in G.S. 131E-91.

"**§ 131E-153.4. Adverse action on a license.**

(a) Subject to subsection (b) of this section, the Department is authorized to deny a new or renewal application for a license and to amend, recall, suspend, or revoke an existing license upon a determination that there has been a substantial failure to comply with the provisions of this Part or the rules adopted under this Part.

(b) Chapter 150B of the General Statutes, the Administrative Procedure Act, shall govern all administrative action and judicial review in cases where the Department has taken the action described in subsection (a) of this section.

"**§ 131E-153.5. Rules and enforcement.**

(a) The Commission is authorized to adopt, amend, and repeal all rules necessary for the implementation of this Part. These rules shall be no stricter than those issued by the Commission under G.S. 131E-79 of the Ambulatory Surgical Facility Licensure Act.

(b) The Department shall enforce the rules adopted or amended by the Commission with respect to abortion clinics.

"**§ 131E-153.6. Inspections.**

(a) The Department shall make or cause to be made inspections of abortion clinics as necessary. The Department is authorized to delegate to a State officer, agent, board, bureau, or division of State government the authority to make inspections according to the rules adopted by the Commission. The Department may revoke this delegated authority in its discretion.

(b) Notwithstanding the provisions of G.S. 8-53 or any other provision of law relating to the confidentiality of communications between physician and patient, the representatives of the

Department who make these inspections may review any writing or other record in any recording medium that pertains to the admission, discharge, medication, treatment, medical condition, or history of persons who are or have been patients of the facility being inspected unless that patient objects, in writing, to review of that patient's records. Physicians, psychologists, psychiatrists, nurses, and anyone else involved in giving treatment at or through a facility who may be interviewed by representatives of the Department may disclose to these representatives information related to an inquiry, notwithstanding the existence of the physician-patient privilege in G.S. 8-53 or any other rule of law; provided, however, that the patient has not made written objection to this disclosure. The facility, its employees, and any person interviewed during these inspections shall be immune from liability for damages resulting from the disclosure of any information to the Department. Any confidential or privileged information received from review of records or interviews shall be kept confidential by the Department and not disclosed without written authorization of the patient or legal representative, or unless disclosure is ordered by a court of competent jurisdiction. The Department shall institute appropriate policies and procedures to ensure that this information is not disclosed without authorization or court order. The Department shall not disclose the name of anyone who has furnished information concerning a facility without the consent of that person. Neither the names of persons furnishing information nor any confidential or privileged information obtained from records or interviews shall be considered "public records" within the meaning of G.S. 132-1. Prior to releasing any information or allowing any inspections referred to in this section, the patient must be advised in writing by the facility that the patient has the right to object, in writing, to this release of information or review of the records and that by objecting, in writing, the patient may prohibit the inspection or release of the records.

"**§ 131E-153.7. Penalties.**

A person who owns in whole or in part or operates an abortion clinic without a license is guilty of a Class 3 misdemeanor and upon conviction will be subject only to a fine of not more than fifty dollars ($50.00) for the first offense and not more than five hundred dollars ($500.00) for each subsequent offense. Each day of continuing violation after conviction is considered a separate offense.

"**§ 131E-153.8. Injunction.**

(a) Notwithstanding the existence or pursuit of any other remedy, the Department may, in the manner provided by law, maintain an action in the name of the State for injunction or other process against any person or governmental unit to restrain or prevent the establishment, conduct, management, or operation of an abortion clinic without a license.

(b) If any person shall hinder the proper performance of duty of the Secretary or a representative in carrying out the provisions of this Part, the Secretary may institute an action in the superior court of the county in which the hindrance occurred for injunctive relief against the continued hindrance, irrespective of all other remedies at law.

(c) Actions under this section shall be in accordance with Article 37 of Chapter 1 of the General Statutes and Rule 65 of the Rules of Civil Procedure."

SECTION 2.3. G.S. 131E-272 reads as rewritten:

"**§ 131E-272. Initial licensure fees for new facilities.**

The following fees are initial licensure fees for new facilities and are applicable as follows:

Facility Type	**Number of Beds**	**Initial License Fee**	**Initial Bed Fee**
Adult Care Licensure	More than 6	$400.00	$19.00
	6 or Fewer	$350.00	$ -
Acute and Home Care			
General Acute Hospitals	1-49	$550.00	$19.00
	50-99	$750.00	$19.00
	100-199	$950.00	$19.00

	200-399	$1150.00	$19.00
	400-699	$1550.00	$19.00
	700+	$1950.00	$19.00
Other Hospitals		$1050.00	$19.00
Home Care	-	$560.00	$ -
Ambulatory Surgical Ctrs.	-	$900.00	$85.00
Hospice (Free Standing)	-	$450.00	$ -
Abortion Clinics	-	~~$750.00~~$850.00	$ -
Cardiac Rehab. Centers	-	$425.00	$ -
Nursing Home & L&C			
Nursing Homes		$470.00	$19.00
All Others		$ -	$19.00
Mental Health Facilities			
Nonresidential		$265.00	$ -
Non ICF/IID	6 or fewer	$350.00	$ -
ICF/IID only	6 or fewer	$900.00	$ -
Non ICF/IID	More than 6	$525.00	$19.00
ICF/IID only	More than 6	$850.00	$19.00."

SECTION 2.4. No later than October 1, 2023, the Department of Health and Human Services shall adopt the rules necessary to administer this Part.

SECTION 2.5. Section 2.4 of this Part becomes effective July 1, 2023. The remainder of this Part becomes effective on October 1, 2023.

PART III. BORN-ALIVE ABORTION SURVIVORS PROTECTION

SECTION 3.(a) Chapter 90 of the General Statutes is amended by adding a new Article to read:

"Article 1M.

"Born-Alive Abortion Survivors Protection Act.

"**§ 90-21.140. Definitions.**

As used in this Article, the following definitions apply:

(1) Abortion. – As defined in G.S. 90-21.81.

(2) Attempt to perform an abortion. – As defined in G.S. 90-21.81.

(3) Born alive. – With respect to a member of the species Homo sapiens, this term means the complete expulsion or extraction from his or her mother of that member, at any stage of development, who after such expulsion or extraction breathes or has a beating heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, regardless of whether the umbilical cord has been cut, and regardless of whether the expulsion or extraction occurs as a result of natural or induced labor, cesarean section, or induced abortion.

"**§ 90-21.141. Findings.**

The General Assembly makes the following findings:

(1) If an abortion results in the live birth of an infant, the infant is a legal person for all purposes under the laws of North Carolina and entitled to all the protections of such laws.

(2) Any infant born alive after an abortion or within a hospital, clinic, or other facility has the same claim to the protection of the law that would arise for any newborn, or for any person who comes to a hospital, clinic, or other facility for screening and treatment or otherwise becomes a patient within its care.

"**§ 90-21.142. Requirements for health care practitioners.**

In the case of an abortion or an attempt to perform an abortion that results in a child born alive, any health care practitioner present at the time the child is born alive shall do all of the following:

(1) Exercise the same degree of professional skill, care, and diligence to preserve the life and health of the child as a reasonably diligent and conscientious health care practitioner would render to any other child born alive at the same gestational age.

(2) Following the exercise of skill, care, and diligence required under subdivision (1) of this section, ensure that the child born alive is immediately transported and admitted to a hospital.

"**§ 90-21.143. Mandatory reporting of noncompliance.**

A health care practitioner or any employee of a hospital, a physician's office, or an abortion clinic who has knowledge of a failure to comply with the requirements of G.S. 90-21.142 shall immediately report the failure to comply to an appropriate State or federal law enforcement agency, or both.

"**§ 90-21.144. Bar to prosecution of mothers of infants born alive.**

The mother of a child born alive may not be prosecuted for a violation of, or attempt to or conspiracy to commit a violation of, G.S. 90-21.142 or G.S. 90-21.143 involving the child who was born alive.

"**§ 90-21.145. Penalties.**

(a) In General. – Except as provided in subsection (b) of this section, unless the conduct is covered under some other provision of law providing greater punishment, a person who violates G.S. 90-21.142 or G.S. 90-21.143 is guilty of a Class D felony, which shall include a fine of not more than two hundred fifty thousand dollars ($250,000).

(b) Unlawful Killing of Child Born Alive. – Any person who intentionally performs or attempts to perform an overt act that kills a child born alive shall be punished as under G.S. 14-17(c) for murder.

"**§ 90-21.146. Civil remedies; attorneys' fees.**

(a) Civil Remedies. – If a child is born alive and there is a violation of this Article, a claim for damages against any person who has violated a provision of this Article may be sought by the woman upon whom an abortion was performed or attempted in violation of this Article. A claim for damages may include any one or more of the following:

(1) Objectively verifiable money damage for all injuries, psychological and physical, occasioned by the violation of this Article.

(2) Statutory damages equal to three times the cost of the abortion or attempted abortion.

(3) Punitive damages pursuant to Chapter 1D of the General Statutes.

(b) Attorneys' Fees. – If judgment is rendered in favor of the plaintiff in any action authorized under this section, the court shall also tax as part of the costs reasonable attorneys' fees in favor of the plaintiff against the defendant. If judgment is rendered in favor of the defendant and the court finds that the plaintiff's suit was frivolous or brought in bad faith, then the court shall tax as part of the costs reasonable attorneys' fees in favor of the defendant against the plaintiff."

SECTION 3.(b) G.S. 14-17(c) reads as rewritten:

"(c) For the purposes of this section, it shall constitute murder where a child is born alive but (i) dies as a result of injuries inflicted prior to the child being born ~~alive.~~ alive or (ii) dies as a result of an intentional, overt act performed after the child is born alive. The degree of murder shall be determined as described in subsections (a) and (b) of this section."

SECTION 3.(c) Prosecutions for offenses committed before the effective date of this section are not abated or affected by this section, and the statutes that would be applicable but for this section remain applicable to those prosecutions.

SECTION 3.(d) This section becomes effective July 1, 2023, and applies to offenses committed on or after that date.

PART IV. REFORMS TO REDUCE INFANT AND MATERNAL MORTALITY AND MORBIDITY AND INCREASE ACCESS TO CONTRACEPTIVES

SECTION 4.1. Effective July 1, 2023, there is appropriated from the General Fund to the Department of Health and Human Services, Division of Public Health, the sum of three million five hundred thousand dollars ($3,500,000) in recurring funds for each year of the 2023-2025 fiscal biennium to be used to award grants on a competitive basis to local health departments and nonprofit community health centers. Nonprofit community health centers selected to receive these grant funds shall use the funds to purchase and make available long-acting reversible contraceptives for underserved, uninsured, or medically indigent patients. As used in this section, the term "long-acting reversible contraceptives" means a contraceptive drug or device that meets all of the following criteria:

(1) Is a method of birth control that provides effective contraception for an extended period of time without depending upon user action.

(2) Is designed as a temporary method of birth control that the user can elect to discontinue.

(3) Has been approved by the United States Food and Drug Administration for use as a contraceptive.

(4) Is obtained under a prescription written by a health care provider authorized to prescribe medications under the laws of this State.

SECTION 4.2.(a) The Department of Health and Human Services, Division of Health Benefits (DHB), shall increase to at least seventy-one percent (71%) of the Medicare rate the Medicaid rate paid for obstetrics maternal bundle payments for pregnancy care. This rate increase shall be implemented as soon as practicable.

SECTION 4.2.(b) In order to incentivize the use of group prenatal care visits by Medicaid beneficiaries, DHB shall develop an add-on rate to the relevant capitated rates or payments that include prenatal care services. This add-on rate shall include amounts sufficient to make payments to providers that achieve a level of Medicaid beneficiary participation in group prenatal care visits. DHHS shall determine the level of patient participation required for a provider to receive these provider payments. These provider payments may be used by a provider to establish incentives for Medicaid beneficiary patients to attend group prenatal care visits. This rate increase shall be implemented as soon as practicable.

SECTION 4.2.(c) Effective July 1, 2023, there is appropriated from the General Fund to the Department of Health and Human Services, Division of Health Benefits, the sum of two million eight hundred thousand dollars ($2,800,000) in recuring funds for each year of the 2023-2025 fiscal biennium to implement the Medicaid-related changes outlined in this section. These funds shall provide a State match for five million five hundred thousand dollars ($5,500,000) in recurring federal funds for each year of the 2023-2025 fiscal biennium, and those federal funds are appropriated to the Division of Health Benefits to pay for costs associated with the Medicaid-related changes outlined in this section.

SECTION 4.3.(a) Article 1 of Chapter 90 of the General Statutes is amended by adding the following new section to read:

"**§ 90-18.8. Limitations on nurse-midwives.**

(a) Any Certified Nurse Midwife approved under the provisions of Article 10A of this Chapter to provide midwifery care may use the title "Certified Nurse Midwife." Any other person

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 26 of 48

who uses the title in any form or holds himself or herself out to be a Certified Nurse Midwife or to be so approved shall be deemed to be in violation of this Article.

(b) A Certified Nurse Midwife is authorized to write prescriptions for drugs if all of the following conditions are met:

(1) The Certified Nurse Midwife has current approval from the joint subcommittee established under G.S. 90-178.4.

(2) The joint subcommittee as established under G.S. 90-178.4 has assigned an identification number to the Certified Nurse Midwife that appears on the written prescription.

(3) The joint subcommittee as established under G.S. 90-178.4 has provided to the Certified Nurse Midwife written instructions about indications and contraindications for prescribing drugs and a written policy for periodic review of the drugs prescribed.

(c) The joint subcommittee of the North Carolina Medical Board and the Board of Nursing, established under G.S. 90-178.4, shall adopt rules governing the approval of individual Certified Nurse Midwives to write prescriptions with any limitations the joint subcommittee deems are in the best interest of patient health and safety, consistent with the rules established for nurse practitioners under G.S. 90-18.2(b)(1)."

SECTION 4.3.(b) G.S. 90-178.2 reads as rewritten:

"**§ 90-178.2. Definitions.**

~~As used in this Article:~~The following definitions apply in this Article:

(1) Certified Nurse Midwife. – A nurse licensed and registered under Article 9A of this Chapter who has completed a midwifery education program accredited by the Accreditation Commission for Midwifery Education, or its successor, passed a national certification examination administered by the American Midwifery Certification Board, or its successor, and has received the professional designation of "Certified Nurse Midwife" (CNM). Certified Nurse Midwives practice in accordance with the Core Competencies for Basic Midwifery Practice, the Standards for the Practice of Midwifery, the Philosophy of the American College of Nurse-Midwives (ACNM), and the Code of Ethics promulgated by the ACNM.

(1a) Collaborating provider. – A physician licensed to practice medicine under Article 1 of this Chapter for a minimum of four years and has a minimum of 8,000 hours of practice and who is or has engaged in the practice of obstetrics or a Certified Nurse Midwife who has been approved to practice midwifery under this Article for a minimum of four years and 8,000 hours.

(1b) Collaborative provider agreement. – A formal, written agreement between a collaborating provider and a Certified Nurse Midwife with less than 24 months and 4,000 hours of practice as a Certified Nurse Midwife to provide consultation and collaborative assistance or guidance.

~~(2)~~(1c) "Interconceptional care" ~~includes~~ includes, but is not limited ~~to:~~to, the following:

a. ~~Family planning;~~Gynecologic care, including family planning, perimenopause, and postmenopause care.

b. Screening for cancer of the breast and reproductive ~~tract;~~tract.

c. Screening for and management of minor infections of the reproductive ~~organs;~~organs.

~~(3)~~(2) ~~"Intrapartum care" includes but~~ Intrapartum care. – Care that focuses on the facilitation of the physiologic birth process and includes, but is not limited ~~to:~~to, the following:

a. ~~Attending women in uncomplicated labor;~~Confirmation and assessment of labor and its progress.

b. ~~Assisting with spontaneous delivery of infants in vertex presentation from 37 to 42 weeks gestation;~~Identification of normal and deviations from normal and appropriate interventions, including management of complications, abnormal intrapartum events, and emergencies.

b1. Management of spontaneous vaginal birth and appropriate third-stage management, including the use of uterotonics.

c. Performing ~~amniotomy;~~amniotomy.

d. Administering local ~~anesthesia;~~anesthesia.

e. Performing episiotomy and ~~repair; and~~repair.

f. Repairing lacerations associated with childbirth.

~~(4)~~(3) ~~"Midwifery" means the~~ Midwifery. – The act of providing prenatal, intrapartum, postpartum, newborn and interconceptional care. The term does not include the practice of medicine by a physician licensed to practice medicine when engaged in the practice of medicine as defined by law, the performance of medical acts by a physician assistant or nurse practitioner when performed in accordance with the rules of the North Carolina Medical Board, the practice of nursing by a registered nurse engaged in the practice of nursing as defined by ~~law, or the rendering of childbirth assistance in an emergency situation.~~law, or the performance of abortion, as defined in G.S. 90-21.81.

~~(5)~~(4) ~~"Newborn care" includes~~ Newborn care. – Care that focuses on the newborn and includes, but is not limited ~~to:~~to, the following:

a. Routine assistance to the newborn to establish respiration and maintain thermal ~~stability;~~stability.

b. Routine physical assessment including APGAR ~~scoring;~~scoring.

c. Vitamin K ~~administration; and~~administration.

d. Eye prophylaxis for opthalmia neonatorum.

e. Methods to facilitate newborn adaptation to extrauterine life, including stabilization, resuscitation, and emergency management as indicated.

~~(6)~~(5) ~~"Postpartum care"includes~~ Postpartum care. – Care that focuses on management strategies and therapeutics to facilitate a healthy puerperium and includes, but is not limited ~~to:~~to, the following:

a. Management of the normal third stage of ~~labor;~~labor.

b. Administration of ~~pitocin and methergine~~ uterotonics after delivery of the infant when ~~indicated; and~~indicated.

c. Six weeks postpartum evaluation exam and initiation of family planning.

d. Management of deviations from normal and appropriate interventions, including management of complications and emergencies.

~~(7)~~(6) ~~"Prenatal care" includes~~ Prenatal care. – Care that focuses on promotion of normal pregnancy using management strategies and therapeutics as indicated and includes, but is not limited ~~to:~~to, the following:

a. ~~Historical and physical assessment;~~Obtaining history with ongoing physical assessment of mother and fetus.

b. Obtaining and assessing the results of routine laboratory ~~tests; and~~tests.

b1. Confirmation and dating of pregnancy.

c. Supervising the use of prescription and nonprescription medications, such as prenatal vitamins, folic acid, ~~iron, and nonprescription medicines.~~and iron."

SECTION 4.3.(c) G.S. 90-178.3 reads as rewritten:

"**§ 90-178.3. Regulation of midwifery.**

(a) No person shall practice or offer to practice or hold oneself out to practice midwifery unless approved ~~pursuant to~~ under this Article.

(b) A ~~person~~ Certified Nurse Midwife approved ~~pursuant to~~ under this Article may practice midwifery in a hospital or non-hospital ~~setting and~~ setting. The Certified Nurse Midwife shall ~~practice under the supervision of a physician licensed to practice medicine who is actively engaged in the practice of obstetrics.~~ consult, collaborate with, or refer to other providers licensed under this Article, if indicated by the health status of the patient. A ~~registered nurse~~ Certified Nurse Midwife approved ~~pursuant to~~ under this Article is authorized to write prescriptions for drugs in accordance with ~~the same conditions applicable to a nurse practitioner under G.S. 90-18.2(b).~~G.S. 90-18.8(b).

(b1) A Certified Nurse Midwife with less than 24 months and 4,000 hours of practice as a Certified Nurse Midwife shall (i) have a collaborative provider agreement with a collaborating provider and (ii) maintain signed and dated copies of the collaborative provider agreement as required by practice guidelines and any rules adopted by the joint subcommittee of the North Carolina Medical Board and the Board of Nursing. If a collaborative provider agreement is terminated before the Certified Nurse Midwife acquires the level of experience required for practice without a collaborative provider agreement under this Article, the Certified Nurse Midwife shall have 90 days from the date the agreement is terminated to enter into a collaborative provider agreement with a new collaborating provider. During the 90-day period, the Certified Nurse Midwife may continue to practice midwifery as defined under this Article.

(c) Graduate nurse midwife applicant status may be granted by the joint subcommittee in accordance with G.S. 90-178.4."

SECTION 4.3.(d) G.S. 90-178.4 is amended by adding the following new subsections to read:

"(a1) Any Certified Nurse Midwife who attends a planned birth outside of a hospital setting shall discuss with the patient the associated risks and obtain a signed informed consent agreement from the Certified Nurse Midwife's patient that shall include:

(1) Information about the risks associated with a planned birth outside of the hospital.

(2) A clear assumption of those risks by the patient.

(3) An agreement by the patient to consent to transfer to a health care facility when and if deemed necessary by the Certified Nurse Midwife.

(4) If the Certified Nurse Midwife is not covered under a policy of liability insurance, a clear disclosure to that effect.

(5) The joint subcommittee shall develop the contents of an informed consent agreement form to be used by a Certified Nurse Midwife when obtaining informed consent.

(a2) Any Certified Nurse Midwife who attends a planned birth outside of a hospital setting shall provide to each patient a detailed, written plan for emergent and nonemergent transfer, which shall include:

(1) The name of and distance to the nearest health care facility licensed under Chapter 122C or Chapter 131E of the General Statutes that has at least one operating room.

(2) The procedures for transfer, including modes of transportation and methods for notifying the relevant health care facility of impending transfer.

(3) An affirmation that the relevant health care facility has been notified of the plan for emergent and nonemergent transfer by the Certified Nurse Midwife.

(a3) Planned home births attended by a Certified Nurse Midwife shall be limited to low-risk pregnancies. Pregnancies deemed inadvisable for home births by the American College of Obstetricians and Gynecologists Committee on Obstetric Practice shall be prohibited. The joint subcommittee of the North Carolina Medical Board and the Board of Nursing created under G.S. 90-18.2 shall adopt rules governing the safety of home births attended by a Certified Nurse Midwife."

SECTION 4.3.(e) G.S. 90-178.4(b) reads as rewritten:

"(b) The joint subcommittee shall adopt rules ~~pursuant to~~ under this Article to ~~establish:~~establish each of the following:

(1) A fee which shall cover application and initial approval up to a maximum of one hundred dollars ~~($100.00);~~($100.00).

(2) An annual renewal fee to be paid by January 1 of each year by persons approved ~~pursuant to~~ under this Article up to a maximum of fifty dollars ~~($50.00);~~($50.00).

(3) A reinstatement fee for a lapsed approval up to a maximum of five dollars ~~($5.00);~~($5.00).

(4) The form and contents of the applications which shall include information related to the applicant's education and certification by the ~~American College of Nurse-Midwives; and~~American Midwifery Certification Board.

(5) The procedure for establishing ~~physician supervision~~ collaborative provider agreements as required by this Article."

SECTION 4.3.(f) G.S. 90-178.5 reads as rewritten:

"**§ 90-178.5. Qualifications for ~~approval.~~approval; independent practice.**

(a) In order to be approved by the joint subcommittee ~~pursuant to~~ under this Article, a person ~~shall:~~shall comply with each of the following:

(1) Complete an application on a form furnished by the joint ~~subcommittee;~~subcommittee.

(2) Submit evidence of certification by the ~~American College of Nurse-Midwives;~~American Midwifery Certification Board or its successor.

(3) Submit evidence of ~~arrangements for physician supervision; and~~a collaborative provider agreement as required by G.S. 90-178.3(b1).

(4) Pay the fee for application and approval.

(b) Upon submitting to the joint subcommittee evidence of completing 24 months and 4,000 hours of practice as a Certified Nurse Midwife pursuant to a collaborative provider agreement, a Certified Nurse Midwife is authorized to practice midwifery independently in accordance with this Article."

SECTION 4.3.(g) G.S. 90-178.7 reads as rewritten:

"**§ 90-178.7. Enforcement.**

(a) The joint subcommittee may apply to the Superior Court of Wake County to restrain any violation of this Article.

(b) ~~Any person who violates G.S. 90-178.3(a) shall be guilty of a Class 3 misdemeanor.~~No person shall perform any act constituting the practice of midwifery, as defined in this Article, or any of the branches thereof, unless the person shall have been first approved under this Article. Any person who practices midwifery without being duly approved and registered, as provided in this Article, shall not be allowed to maintain any action to collect any fee for such services. Any person so practicing without being duly approved shall be guilty of a Class 3 misdemeanor. Any person so practicing without being duly approved under this Article and who is falsely representing himself or herself in a manner as being approved under this Article or any Article of this Chapter shall be guilty of a Class I felony."

SECTION 4.3.(h) Article 10A of Chapter 90 of the General Statutes is amended by adding the following new section to read:

"**§ 90-178.8. Limit vicarious liability.**

(a) No physician or physician assistant, including the physician assistant's employing or supervising physician, licensed under Article 1 of this Chapter or nurse licensed under Article 9A of this Chapter shall be held liable for any civil damages as a result of the medical care or treatment provided by the physician, physician assistant, or nurse when both of the following occur:

(1) The physician, physician assistant, or nurse is providing medical care or treatment to a woman or infant in an emergency situation.

(2) The emergency situation arises during the delivery or birth of the infant as a consequence of the care provided by a Certified Nurse Midwife approved under this Article who attends a planned birth outside of a hospital setting.

(b) No health care facility licensed under Chapter 122C or Chapter 131E of the General Statutes shall be held liable for civil damages as a result of the medical care or treatment provided by the facility when both of the following occur:

(1) The facility is providing medical care or treatment to a woman or infant in an emergency situation.

(2) The emergency situation arises during the delivery or birth of the infant as a consequence of the care provided by a Certified Nurse Midwife approved under this Article who attends a planned birth outside of a hospital setting.

(b1) Notwithstanding the provisions of subsections (a) and (b) of this section, health care providers and health care facilities shall remain liable for their own independent acts of negligence.

(c) Nothing in this section shall be construed to limit liability when the civil damages to this section are the result of gross negligence or willful or wanton misconduct."

SECTION 4.3.(i) This section becomes effective October 1, 2023.

SECTION 4.4.(a) There is appropriated from the General Fund to the Department of Health and Human Services, Division of Public Health, the sum of two hundred fifty thousand dollars ($250,000) in nonrecurring funds for the 2023-2024 fiscal year and the sum of two hundred fifty thousand dollars ($250,000) in nonrecurring funds for the 2024-2025 fiscal year to fund expansion of the Safe Sleep North Carolina Campaign administered by the University of North Carolina Collaborative for Maternal and Infant Health, with the goal of strengthening the adoption of infant safe sleep practices across the State that reduce the risk of Sudden Infant Death Syndrome (SIDS) and other infant sleep-related deaths.

SECTION 4.4.(b) This section becomes effective July 1, 2023.

PART V. PAID PARENTAL LEAVE FOR STATE EMPLOYEES

SECTION 5.1.(a) Article 2 of Chapter 126 of the General Statutes is amended by adding a new section to read:

"**§ 126-8.6. Paid parental leave.**

(a) Definitions. – The following definitions apply in this section:

(1) Child. – A newborn biological child or a newly placed adopted, foster, or otherwise legally placed child under the age of 18 whose parent is a State employee eligible for leave under subsection (b) of this section.

(2) Parent. – Includes a parent by adoption, foster care, or another legal placement.

(3) Qualifying event. – When a State employee becomes a parent to a child.

(b) Paid Parental Leave. – The State Human Resources Commission shall adopt rules and policies to provide that a permanent, full-time State employee may take the following paid parental leave:

(1) Up to eight weeks of paid leave after giving birth to a child; or

(2) Up to four weeks of paid leave after any other qualifying event.

(c) Part-Time Employees. – The State Human Resources Commission shall adopt rules and policies to provide that a permanent, part-time State employee may take a prorated amount of paid leave after giving birth, not to exceed four weeks, or paid leave after any other qualifying event, not to exceed two weeks, in addition to any other leave available to the employee.

(d) Requirements. – The paid parental leave authorized by this section:

(1) Is available without exhaustion of the employee's sick and vacation leave and is awarded in addition to shared leave under G.S. 126-8.3, or other leave authorized by State or federal law.

(2) Has no cash value upon termination from employment.

(3) May not be used for calculating an employee's retirement benefits.

(e) The provisions of this section shall apply to employees of State agencies, departments, and institutions, including The University of North Carolina; to public school employees; and to community college employees. The appropriate governing board, officer, or entity shall adopt rules and policies to award paid parental leave to employees that are substantially equivalent to those adopted by the State Human Resources Commission."

SECTION 5.1.(b) G.S. 126-5 is amended by adding a new subsection to read:

"(c19) The provisions of G.S. 126-8.6 shall apply to all exempt and nonexempt State employees in the executive branch; to public school employees; and to community college employees. The legislative and judicial branches shall adopt parental leave policies."

SECTION 5.1.(c) G.S. 115C-302.1(j) reads as rewritten:

"(j) Parental Leave. – ~~A~~ In addition to paid parental leave authorized by G.S. 126-8.6, a teacher may use annual leave, personal leave, or leave without pay to care for a newborn child or for a child placed with the teacher for adoption or foster care. A teacher may also use up to 30 days of sick leave to care for a child placed with the teacher for adoption. The leave may be for consecutive workdays during the first 12 months after the date of birth or placement of the child, unless the teacher and local board of education agree otherwise."

SECTION 5.1.(d) G.S. 115C-336.1 reads as rewritten:

"**§ 115C-336.1. Parental leave.**

~~A~~ In addition to paid parental leave authorized by G.S. 126-8.6, a school employee may use annual leave or leave without pay to care for a newborn child or for a child placed with the employee for adoption or foster care. A school employee may also use up to 30 days of sick leave to care for a child placed with the employee for adoption. The leave may be for consecutive workdays during the first 12 months after the date of birth or placement of the child, unless the school employee and the local board of education agree otherwise."

SECTION 5.1.(e) There is appropriated from the General Fund to the Department of Public Instruction the sum of ten million dollars ($10,000,000) in recurring funds for the 2023-2024 fiscal year and the sum of ten million dollars ($10,000,000) in recurring funds for the 2024-2025 fiscal year to fund paid parental leave authorized by this section.

SECTION 5.1.(f) This Part becomes effective July 1, 2023, and applies to requests for paid parental leave related to births occurring on or after that date.

PART VI. CHILD PERMANENCY, SAFE SURRENDER OF INFANTS, FOSTER CARE, ADOPTION, AND SUPPORT FOR NEW MOTHERS

SECTION 6.1. There is appropriated from the General Fund the sum of seven hundred thousand dollars ($700,000) in recurring funds for each year of the 2023-2025 fiscal biennium to the Department of Health and Human Services to be allocated to the State Maternity Home Fund.

SECTION 6.2.(a) Chapter 7B of the General Statutes is amended by adding a new Article to read:

"Article 5A.
"Safe Surrender of Infants.

"**§ 7B-520. Purpose; limitations.**

(a) Purpose. – The purpose of this Article is to protect newborn infants by providing a safe alternative for a parent who, in a crisis or in desperation, may physically abandon or harm his or her newborn and to provide information for the parent regarding the parent's rights and alternatives.

(b) Limitations. – The provisions of this Article apply exclusively to safely surrendered infants as defined in G.S. 7B-101(19a). No person or agency shall act under the provisions of this Article if it is determined that any of the following are true:

(1) A surrendered infant is reasonably believed to be more than 30 days old.
(2) The infant shows signs of abuse or neglect.
(3) There is reason to believe the individual surrendering the infant was not the infant's parent.
(4) At the time the infant was surrendered, there was reason to believe the parent intended to return for the infant.

"**§ 7B-521. Persons to whom infant may be surrendered.**

The following individuals shall, without a court order, take into temporary custody an infant reasonably believed to be not more than 30 days of age that is voluntarily delivered to the individual by the infant's parent who does not express an intent to return for the infant:

(1) A health care provider, as defined under G.S. 90-21.11, who is on duty or at a hospital or at a local or district health department or at a nonprofit community health center.
(2) A first responder, including a law enforcement officer, a certified emergency medical services worker, or a firefighter.
(3) A social services worker who is on duty or at a local department of social services.

"**§ 7B-522. Duties of person taking safely surrendered infant into temporary custody.**

An individual who takes an infant into temporary custody under G.S. 7B-521 shall perform any act necessary to protect the physical health and well-being of the infant and immediately notify the department of social services in the county where the infant is surrendered. The individual may inquire as to the parents' identities, the date of birth of the infant, any relevant medical history, and the parents' marital status and may advise the parent that if the parent provides that information, it may facilitate the adoption of the child. However, the individual shall notify the parent that the parent is not required to provide the information. The individual, if practical, shall provide the surrendering parent with written information created by the Department of Health and Human Services, Division of Social Services, as set forth in G.S. 7B-528.

"**§ 7B-523. Immunity for those receiving infant.**

An individual to whom an infant was surrendered under G.S. 7B-521 is immune from any civil or criminal liability that might otherwise be incurred or imposed as a result of any omission or action taken pursuant to the requirements of this Article as long as that individual was acting in good faith. The immunity established by this section does not extend to gross negligence, wanton conduct, or intentional wrongdoing that would otherwise be actionable.

"**§ 7B-524. Confidentiality of information and records.**

(a) Except as otherwise provided in subsection (b) of this section, unless a parent consents to its release, an individual who takes an infant into temporary custody under this Article and any facility involved in the care of the infant at the time the infant is taken into temporary custody shall keep information regarding the surrendering parent's identity confidential.

(b) An individual taking an infant into temporary custody under this Article shall provide to the director of the department of social services any information known about the infant, the infant's parents, including their identity, any medical history, and the circumstances of surrender.

(c) All information about the surrendering parent's identity that is received or obtained by the department of social services shall not be disclosed except for (i) notice to local law enforcement pursuant to G.S. 7B-525(b)(3), (ii) contact with the non-surrendering parent, or (iii) as otherwise ordered by a court of this State.

(d) All information received by the department of social services related to the circumstances of the infant's safe surrender and the infant's condition shall be held in strictest confidence and shall not be disclosed except as provided in this section.

(1) The director may consult with and share information that the director determines is necessary or relevant to the case with (i) a health care provider that provided medical treatment to the safely surrendered infant before, at the time of, or after the safe surrender, (ii) a placement provider, including a foster care placement or pre-adoptive placement, for the infant, (iii) a court exercising jurisdiction over an adoption proceeding for the infant, and (iv) any agency that a court in an adoption proceeding requires to conduct a preplacement assessment, report to the court, or equivalent.

(2) A guardian ad litem appointed in a termination of parental rights proceeding resulting from the infant's safe surrender may examine and obtain written copies of the record.

(3) A district or superior court judge of this State presiding over a civil, criminal, or delinquency matter in which the department of social services is not a party may order the department to release confidential information after providing the department with reasonable notice and an opportunity to be heard and then determining that the information is relevant and necessary to the trial of the matter before the court and unavailable from any other source. The department of social services shall surrender the requested records to the court, which shall conduct an in-camera review prior to releasing the confidential records.

(e) This section shall not apply if the department determines the juvenile is not a safely surrendered infant or is the victim of a crime.

"**§ 7B-525. Social services response.**

(a) A director of a department of social services who receives a safely surrendered infant pursuant to this Article has, by virtue of the surrender, the surrendering parent's rights to legal and physical custody of the infant without obtaining a court order. A county department of social services to whom an infant has been safely surrendered may, after the notice by publication set forth in G.S. 7B-526 has been completed, apply ex parte to the district court for an order finding that the infant has been safely surrendered and confirming that the county department of social services has legal custody of the minor for the purposes of obtaining a certified copy of the child's birth certificate, a social security number, or federal and State benefits for the minor.

(b) The director of social services receiving the infant shall do the following in an expeditious manner:

(1) Ascertain from a health care provider that the surrendered infant is, to a reasonable medical certainty, not more than 30 days old and without signs of abuse or neglect. If both conditions are not satisfied, the provisions of the Article do not apply and the director shall treat the infant as a juvenile who has been reported to be an abused, neglected, or dependent juvenile.

(2) Make an inquiry of the person who received the infant as a safe surrender whether the surrendering parent was provided with information in accordance with G.S. 7B-526 and document the response.

(3) Notify law enforcement of the safely surrendered infant and provide law enforcement with information necessary to investigate through the North Carolina Center for Missing Persons and other national and State resources whether the infant is a missing child.

(4) Contact the non-surrendering parent when their identity is known to inform the non-surrendering parent that the infant was surrendered.

(5) Respond to any inquiry by a non-surrendering parent about whether their child was safely surrendered.

(6) When a surrendering or non-surrendering parent seeks custody of the infant, arrange for genetic marker testing of that parent and the infant if there is uncertainty as to parentage.

(7) After 60 days from the date of surrender, if the surrendering parent has not sought to regain custody of the infant and the infant is not placed with the non-surrendering parent, initiate a termination of parental rights for the surrendering parent under G.S. 7B-1111(a)(7).

(c) Where the non-surrendering parent's identity is known and the non-surrendering parent has been contacted and located by the director of the department of social services, the director shall place custody of the safely surrendered infant with the non-surrendering parent, and any custodial rights of the department of social services shall terminate only if all of the following apply:

(1) There exists the rebuttable presumption the non-surrendering parent is the safely surrendered infant's parent through (i) the child's legitimation through marriage or (ii) genetic marker testing arranged by the director to establish parentage that indicates the probability of parentage is ninety-seven percent (97%) or higher.

(2) The non-surrendering parent asserts their parental rights to their child.

(3) The director does not have cause to suspect the infant is an abused, neglected, or dependent juvenile due to the circumstances created by the non-surrendering parent.

(d) Where the identity of the non-surrendering parent is known by the director and the director has cause to suspect the infant may be an abused, neglected, or dependent juvenile due to circumstances created by the non-surrendering parent, the director shall proceed as if there was a report of abuse, neglect, or dependency in accordance with G.S. 7B-302. The surrendering parent shall not be part of the department assessment conducted under G.S. 7B-302. If a petition alleging abuse, neglect, or dependency is filed with the district court pursuant to G.S. 7B-302, in accordance with G.S. 7B-401.1(b), the surrendering parent shall not be a party unless the court orders otherwise or a surrendering parent comes forward to regain custody of the child.

(e) If the surrendering parent seeks to regain custody of the infant, the provision of G.S. 7B-527(a) shall apply.

"**§ 7B-526. Notice by publication of the safely surrendered infant.**

(a) Within 14 days from the date of the safe surrender of an infant, the director shall provide notice by publication as specified in subsection (b) of this section that an infant has been surrendered and taken into custody by the department of social services.

(b) The notice shall be published in a newspaper qualified for legal advertising in accordance with G.S. 1-597 and G.S. 1-598 and published in the county in which the surrender was made and in any other county that the director has reason to believe either parent may be residing. The publication shall be once a week for three successive weeks. The notice shall state each of the following:

(1) The infant was surrendered by a person claiming to be the infant's mother or father who did not express an intent to return for the infant and that the infant was surrendered to an individual pursuant to G.S. 7B-521 by specifying (i) the

profession of the individual authorized to accept the surrendered infant, (ii) the name and location of the facility at which the infant was surrendered, and (iii) the date of surrender.

(2) The physical characteristics of the infant at the time of surrender.

(3) The infant is now in the physical and legal custody of the department of social services in the county where the infant was surrendered.

(4) The surrendering mother or father has the right to request the infant's return to their custody by contacting the department of social services in the county that the infant was surrendered before the department initiates an action to terminate their parental rights in district court. If the surrendering parent seeks to regain custody of the infant from the department of social services, the director shall treat the infant as a juvenile who has been reported as a neglected juvenile and requires that the director conduct an assessment, at which point, the surrendering parent's rights to have his or her identity be confidential no longer apply.

(5) The department is making efforts to identify, locate, and contact the non-surrendering parent. The non-surrendering parent has the right to contact the department of social services to inquire about and seek custody of the infant. The department may place the infant with the non-surrendering parent, terminating the department's custodial rights to the infant, when that parent's identity and location are known and there is no cause to suspect the infant is an abused, neglected, or dependent juvenile due to circumstances created by the non-surrendering parent.

(6) Each parent has the right to contact the department of social services in the county where the infant was surrendered.

(7) If neither parent seeks the infant's custody from the department of social services or executes a relinquishment for adoption within 60 days of the date of the surrender, which shall be stated clearly on the notice, the department will initiate a court action to terminate both parents' parental rights. Unless the court orders otherwise, the notice of the petition to terminate parental rights will be published in the same newspaper with the court name "In re Baby Doe."

(8) How to contact the department of social services about the safely surrendered infant and the parents' rights.

(c) If a termination of parental rights for the safely surrendered infant is commenced, an affidavit of the publisher of the notice by this section shall be filed with the court at the preliminary hearing required by G.S. 7B-1105.1.

"**§ 7B-527. Rights of surrendering parent.**

(a) Right to Regain Custody. – Prior to the filing of a termination of parental rights petition under Article 11 of this Subchapter, a surrendering parent has the right to contact the county department of social services where the infant was surrendered and request the infant's return to his or her custody. The director shall treat any such request as a report of neglect and comply with the provisions of G.S. 7B-302.

(b) Right of Relinquishment. – The safe surrender of an infant under this Article does not preclude the surrendering parent from executing a relinquishment of their parental rights for adoption with the local department of social services which received the safely surrendered infant.

(c) Immunity. – A parent surrendering an infant pursuant to this Article is immune from any civil liability or criminal prosecution in accordance with G.S. 14-322.3 as long as the surrendering parent was acting in good faith. The immunity established by this section does not

extend to gross negligence, wanton conduct, or intentional wrongdoing that would otherwise be actionable.

"**§ 7B-528. Information to surrendering parent.**

(a) The Department of Health and Human Services, Division of Social Services, shall create printable and downloadable information about infant safe surrender and the rights of the parents. The information shall be written in a user-friendly manner and translated to commonly spoken and read languages in this State. The Division shall post the information on its website and make the information available for distribution to agencies where persons identified in G.S. 7B-521 are on duty and to other agencies that request the information.

(b) The information shall explain each of the following:

(1) Who is a safely surrendered infant, surrendering parent, and non-surrendering parent.

(2) The requirements for how a safe surrender of an infant may occur under this Article.

(3) The right to have the surrendering parent's identity remain confidential with the exception of communicating with the non-surrendering parent, known medical providers who provided treatment to the infant prior to the safe surrender, law enforcement for purposes of a missing child assessment, or a court order.

(4) The information set forth in G.S. 7B-526(b)(3) through (b)(8).

(5) That the information contains a relevant medical history form for the infant that would assist the department of social services in obtaining any necessary medical services for the infant and in facilitating the infant's placement, including adoption. Completing the form is optional.

(6) An explanation that services may be available to the surrendering parent and infant accompanied by contact information for the local department of social services.

(c) The Division shall create a printable and downloadable medical history form as referred to in subsection (b) of this section, and the form must include instructions on how to complete it and where to return it."

SECTION 6.2.(b) G.S. 7B-101 reads as rewritten:

"**§ 7B-101. Definitions.**

As used in this Subchapter, unless the context clearly requires otherwise, the following words have the listed meanings:

…

(15) Neglected juvenile. – Any juvenile less than 18 years of age (i) who is found to be a minor victim of human trafficking under G.S. 14-43.15 or (ii) whose parent, guardian, custodian, or caretaker does any of the following:

a. Does not provide proper care, supervision, or discipline.

b. Has abandoned the ~~juvenile.~~juvenile, except where that juvenile is a safely surrendered infant as defined in this Subchapter.

c. Has not provided or arranged for the provision of necessary medical or remedial care.

d. Or whose parent, guardian, or custodian has refused to follow the recommendations of the Juvenile and Family Team made pursuant to Article 27A of this Chapter.

e. Creates or allows to be created a living environment that is injurious to the juvenile's welfare.

f. Has participated or attempted to participate in the unlawful transfer of custody of the juvenile under G.S.14-321.2.

g. Has placed the juvenile for care or adoption in violation of law.

…

(15b) Non-surrendering parent. – A parent of a safely surrendered infant other than the parent who physically surrenders the parent's infant pursuant to Article 5A of this Subchapter.

…

(19a) Safely surrendered infant. – An infant reasonably believed to be not more than 30 days of age and without signs of abuse or neglect who is voluntarily delivered to an individual in accordance with Article 5A of this Subchapter by the infant's parent who does not express an intent to return for the infant. In determining whether there are signs of neglect, the act of surrendering the infant, in and of itself, does not constitute neglect.

~~(19a)~~(19b) Serious neglect. – Conduct, behavior, or inaction of the juvenile's parent, guardian, custodian, or caretaker that evidences a disregard of consequences of such magnitude that the conduct, behavior, or inaction constitutes an unequivocal danger to the juvenile's health, welfare, or safety, but does not constitute abuse.

…

(21a) Surrendering parent. – A parent who physically surrenders the parent's infant pursuant to Article 5A of this Subchapter.

…."

SECTION 6.2.(c) G.S. 7B-401.1(b) reads as rewritten:

"(b) Parents. – The juvenile's parent shall be a party unless one of the following applies:

…

(2) The parent has relinquished the juvenile for adoption, or safely surrendered the infant and has not sought the return of the infant prior to the filing of a termination of parental rights, unless the court orders that the parent be made a party.

…."

SECTION 6.2.(d) G.S. 7B-500 reads as rewritten:

"**§ 7B-500. Taking a juvenile into temporary custody; civil and criminal immunity.**

(a) Temporary custody means the taking of physical custody and providing personal care and supervision until a court order for nonsecure custody can be obtained. A juvenile may be taken into temporary custody without a court order by a law enforcement officer or a department of social services worker if there are reasonable grounds to believe that the juvenile is abused, neglected, or dependent and that the juvenile would be injured or could not be taken into custody if it were first necessary to obtain a court order. If a department of social services worker takes a juvenile into temporary custody under this section, the worker may arrange for the placement, care, supervision, and transportation of the juvenile.

(b) ~~The following individuals shall, without a court order, take into temporary custody an infant under seven days of age that is voluntarily delivered to the individual by the infant's parent who does not express an intent to return for the infant:~~The process for taking into temporary custody a safely surrendered infant is as provided under Article 5A of this Subchapter.

~~(1) A health care provider, as defined under G.S. 90-21.11, who is on duty or at a hospital or at a local or district health department or at a nonprofit community health center.~~

~~(2) A law enforcement officer who is on duty or at a police station or sheriff's department.~~

~~(3) A social services worker who is on duty or at a local department of social services.~~

~~(4) A certified emergency medical service worker who is on duty or at a fire or emergency medical services station.~~

~~(c) An individual who takes an infant into temporary custody under subsection (b) of this section shall perform any act necessary to protect the physical health and well-being of the infant and shall immediately notify the department of social services or a local law enforcement agency. Any individual who takes an infant into temporary custody under subsection (b) of this section may inquire as to the parents' identities and as to any relevant medical history, but the parent is not required to provide the information. The individual shall notify the parent that the parent is not required to provide the information.~~

~~(d) Any adult may, without a court order, take into temporary custody an infant under seven days of age that is voluntarily delivered to the individual by the infant's parent who does not express an intent to return for the infant. Any individual who takes an infant into temporary custody under this section shall perform any act necessary to protect the physical health and well-being of the infant and shall immediately notify the department of social services or a local law enforcement agency. An individual who takes an infant into temporary custody under this subsection may inquire as to the parents' identities and as to any relevant medical history, but the parent is not required to provide the information. The individual shall notify the parent that the parent is not required to provide the information.~~

~~(e) An individual described in subsection (b) or (d) of this section is immune from any civil or criminal liability that might otherwise be incurred or imposed as a result of any omission or action taken pursuant to the requirements of subsection (c) or (d) of this section as long as that individual was acting in good faith. The immunity established by this subsection does not extend to gross negligence, wanton conduct, or intentional wrongdoing that would otherwise be actionable.~~"

SECTION 6.2.(e) G.S. 7B-501(a) reads as rewritten:

"(a) A person who takes a juvenile into custody without a court order under G.S. 7B-500 shall proceed as ~~follows:~~follows, except that the person shall proceed in accordance with G.S. 7B-522 for a safely surrendered infant:

…."

SECTION 6.2.(f) Article 11 of Chapter 7B of the General Statutes is amended by adding a new section to read:

"**§ 7B-1105.1. Preliminary hearing; safely surrendered infant.**

(a) Within 10 days from the date of filing of a petition to terminate the parental rights of a surrendering or non-surrendering parent of a safely surrendered infant, or during the next term of court in the county where the petition is filed if there is no court in the county in that 10-day period, the court shall conduct a preliminary hearing to address the infant's safe surrender. The preliminary hearing shall be recorded and shall be closed unless the surrendering parent appears and requests that it be open. The purpose of the hearing shall be to ascertain the circumstances of the safe surrender in order to determine any efforts that should be made to ascertain the identity and location of either parent and to establish appropriate notice regarding termination of parental rights proceedings.

(b) The court shall inquire of the director of the department of social services as to all of the following:

(1) The circumstances of the safe surrender.

(2) Whether, at the time of surrender, the surrendering parent was provided the information pursuant to G.S. 7B-528.

(3) Whether notice of a safe surrender was made by publication as required by G.S. 7B-526. An affidavit of the publisher of that notice shall be filed with the court at this preliminary hearing.

(4) Whether either parent has made any efforts to contact the department of social services and the nature of those contacts.

(5) Whether the identities or locations of either parent are known to the director of the department of social services.

(c) The court shall determine whether any diligent efforts are required to identify or locate the surrendering parent considering the need to protect the confidentiality of that parent's identity and the parent's due process rights. The court may specify the type of diligent efforts the department of social services is required to take. The court shall determine whether the surrendering parent shall be served pursuant to Rule 4 of the Rules of Civil Procedure and, if so, may specify the type of service that must be provided in lieu of Rule 4 whether the parent shall be served by publication in accordance with subsection (e) of this section.

(d) When the identity of the non-surrendering parent is known, the court shall order service pursuant to Rule 4 of the Rules of Civil Procedure. When the non-surrendering parent's identity is not known, service shall be by publication in accordance with subsection (e) of this section.

(e) The court shall specifically order the place or places of publication and the contents of the notice that the court concludes is most likely to identify the juvenile to either of the juvenile's parents without including the name of the surrendering parent. The notice shall be published in a newspaper qualified for legal advertising in accordance with G.S. 1-597 and G.S. 1-598 and published in the counties directed by the court, including in the county where the local department of social services that received the safely surrendered infant is located and where the parent is residing, if known, once a week for three successive weeks. The notice shall do each of the following:

(1) Designate the court in which the petition is pending.

(2) Be directed to "the mother (father) (mother and father) of a male (female) juvenile born on or about _____ (date) and if known in _____ (hospital or health care facility where the infant was born.) _____ (County), _____ (City), _____ (State), respondent."

(3) Designate the docket number and title of the case which shall be "In re Baby Doe."

(4) State that the infant was surrendered by a person claiming to be the infant's mother or father who did not express an intent to return for the infant and that the infant was surrendered to an individual pursuant to G.S. 7B-521 by specifying (i) the profession of the person authorized to accept the surrendered infant, (ii) the facility at which the infant was surrendered, and (iii) the date of surrender.

(5) State the physical characteristics of the infant at the time of the surrender.

(6) State that a petition seeking to terminate the parental rights of the respondent has been filed and the purpose of the termination hearing.

(7) Notice that if the parent is indigent, the parent is entitled to appointed counsel and may contact the clerk immediately to request counsel.

(8) State the date and time of the pretrial hearing pursuant to G.S. 7B-1108.1 and notice that the parent may attend the hearing.

(9) Direct the respondent to file with the clerk a written answer to the petition within 30 days after a date stated in the notice, exclusive of such date, which date so stated shall be the date of first publication of notice and be substantially in the form as set forth in G.S. 1A-1, Rule 4(j1).

(10) State that if the parent fails to answer the petition within the time prescribed and the court determines the ground for termination has been proved and that termination of that parent's rights is in the best interests of the juvenile, the respondent's parental rights to the juvenile will be terminated.

Upon completion of the service by publication, an affidavit of the publisher shall be filed with the court.

(f) The court shall issue the order required by this section within 30 days from the date of the preliminary hearing unless the court shall determine that additional time for investigation is required.

(g) No summons is required for a parent who is served by publication."

SECTION 6.2.(g) G.S. 7B-1111(a) reads as rewritten:

"(a) The court may terminate the parental rights upon a finding of one or more of the following:

…

(7) The parent has willfully abandoned the juvenile for at least six consecutive months immediately preceding the filing of the petition or motion, or the parent has voluntarily abandoned an infant as a safely surrendered infant pursuant to ~~G.S. 7B-500~~ Article 5A of this Subchapter for at least 60 consecutive days immediately preceding the filing of the petition or motion.

…

(9) The parental rights of the parent with respect to another child of the parent have been terminated involuntarily by a court of competent jurisdiction and the parent lacks the ability or willingness to establish a safe home. This ground shall not apply to a parent whose parental rights were terminated as a result of the other child being a safely surrendered infant.

…."

SECTION 6.2.(h) G.S. 115C-47(52) reads as rewritten:

"**§ 115C-47. Powers and duties generally.**

In addition to the powers and duties designated in G.S. 115C-36, local boards of education shall have the power or duty:

…

(52) To Ensure That Certain Students Receive Information Annually on Lawfully Abandoning a Newborn Baby. – Not later than August 1, 2008, local boards of education shall adopt policies to ensure that students in grades nine through 12 receive information annually on the manner in which a parent may lawfully abandon a newborn baby with a responsible person, in accordance with ~~G.S. 7B-500.~~Article 5A of Chapter 7B of the General Statutes."

SECTION 6.2.(i) G.S. 115C-218.75(a) reads as rewritten:

"(a) Health and Safety Standards. – A charter school shall meet the same health and safety requirements required of a local school administrative unit. The Department of Public Instruction shall ensure that charter schools provide parents and guardians with information about meningococcal meningitis and influenza and their vaccines at the beginning of every school year. This information shall include the causes, symptoms, and how meningococcal meningitis and influenza are spread and the places where parents and guardians may obtain additional information and vaccinations for their children.

…

The Department of Public Instruction shall also ensure that charter schools provide students in grades nine through 12 with information annually on the manner in which a parent may lawfully abandon a newborn baby with a responsible person, in accordance with ~~G.S. 7B-500.~~Article 5A of Chapter 7B of the General Statutes.

…."

SECTION 6.2.(j) G.S. 115C-548 reads as rewritten:

"**§ 115C-548. Attendance; health and safety regulations.**

…

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 41 of 48

The Division of Nonpublic Education, Department of Administration, shall also ensure that information is available to these schools so that they can provide information on the manner in which a parent may lawfully abandon a newborn baby with a responsible person, in accordance with ~~G.S. 7B-500.~~Article 5A of Chapter 7B of the General Statutes."

SECTION 6.2.(k) G.S. 115C-556 reads as rewritten:

"**§ 115C-556. Attendance; health and safety regulations.**

…

The Division of Nonpublic Education, Department of Administration, shall also ensure that information is available to each qualified nonpublic school so that the school can provide information on the manner in which a parent may lawfully abandon a newborn baby with a responsible person, in accordance with ~~G.S. 7B-500.~~Article 5A of Chapter 7B of the General Statutes."

SECTION 6.2.(*l*) G.S. 115C-565 reads as rewritten:

"**§ 115C-565. Requirements exclusive.**

…

The Division of Nonpublic Education, Department of Administration, shall also provide to home schools information on the manner in which a parent may lawfully abandon a newborn baby with a responsible person, in accordance with ~~G.S. 7B-500.~~ Article 5A of Chapter 7B of the General Statutes. This information may be provided electronically or on the Division's Web page."

SECTION 6.2.(m) This section becomes effective October 1, 2023, and applies to infants safely surrendered on or after that date.

SECTION 6.3.(a) The Legislative Research Commission shall study streamlining the laws surrounding adoption and foster care and report its findings and any legislative proposals to the 2024 Regular Session of the 2023 General Assembly upon its convening.

SECTION 6.3.(b) This section is effective when it becomes law.

SECTION 6.4.(a) G.S. 14-322.3 reads as rewritten:

"**§ 14-322.3. Abandonment of an infant ~~under seven~~ not more than 30 days of age.**

When a parent abandons an infant ~~less~~ not more than ~~seven~~ 30 days of age by voluntarily delivering the infant as provided in ~~G.S. 7B-500(b) or G.S. 7B-500(d)~~ Article 5A of Chapter 7B of the General Statutes and does not express an intent to return for the infant, that parent shall not be prosecuted under G.S. 14-322, 14-322.1, or 14-43.14."

SECTION 6.4.(b) This section becomes effective December 1, 2023, and applies to offenses committed on or after that date.

SECTION 6.5.(a) G.S. 48-3-203 reads as rewritten:

"**§ 48-3-203. Agency placement adoption.**

…

(a1) No agency shall deny or delay (i) the opportunity to become an adoptive parent or (ii) the placement of a child for adoption on the basis of race, color, or national origin of the person or the child involved.

…."

SECTION 6.5.(b) G.S. 131D-10.1 is amended by adding a new subsection to read:

"(a1) No agency or other State entity shall deny or delay (i) the opportunity to become a foster parent or (ii) the placement of a child in foster care on the basis of race, color, or national origin of the person or the child involved."

SECTION 6.5.(c) This section is effective when it becomes law.

SECTION 6.6.(a) Effective six months after this bill becomes law, and notwithstanding any other provision of law or rule to the contrary, the Department of Health and Human Services, Division of Social Services (Division), shall develop and implement a policy that allows an individual who is related by blood, marriage, or adoption to a child and providing foster care, as defined under G.S. 131D-10.2(9), to a child in a family foster home to be

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 42 of 48

reimbursed for the provision of care without having to meet the requirements for licensure under G.S. 131D-10.3 pursuant to rates set forth in subsection (b) of this section. For purposes of this section, "family foster home" means the private residence of one or more individuals who permanently reside as members of the household and who provide continuing full-time foster care for a child or children who are related to the adult members of the household by blood, marriage, or adoption.

SECTION 6.6.(b) The maximum rates for State participation in reimbursement for unlicensed kinship foster care are established on a graduated scale as follows:

(1) $351.00 per child per month for children from birth through 5 years of age.
(2) $371.00 per child per month for children 6 through 12 years of age.
(3) $405.00 per child per month for children at least 13 but less than 18 years of age.

SECTION 6.6.(c) The State and a county participating in unlicensed kinship care shall each contribute fifty percent (50%) of the nonfederal share of the cost of care for a child placed by a county department of social services or child-placing agency in a family foster home.

SECTION 6.6.(d) There is appropriated from the General Fund to the Department of Health and Human Services, Division of Social Services, the sum of five million seven hundred sixty-six thousand three hundred ninety dollars ($5,766,390) in recurring funds for each year of the 2023-2025 fiscal biennium to provide funds for the State portion of unlicensed kinship care reimbursement rates set forth in subsection (b) of this section.

SECTION 6.7.(a) G.S. 108A-49.1 reads as rewritten:

"**§ 108A-49.1. Foster care and adoption assistance payment rates.**

(a) The maximum rates for State participation in the foster care assistance program are established on a graduated scale as follows:

(1) ~~$514.00~~ $702.00 per child per month for children from birth through five years of age.
(2) ~~$654.00~~ $742.00 per child per month for children six through 12 years of age.
(3) ~~$698.00~~ $810.00 per child per month for children at least 13 but less than 21 years of age.

(b) The maximum rates for the State adoption assistance program are established consistent with the foster care rates as follows:

(1) ~~$514.00~~ $702.00 per child per month for children from birth through five years of age.
(2) ~~$654.00~~ $742.00 per child per month for children six through 12 years of age.
(3) ~~$698.00~~ $810.00 per child per month for children at least 13 but less than 21 years of age.

…."

SECTION 6.7.(b) There is appropriated from the General Fund to the Department of Health and Human Services, Division of Social Services, the sum of ten million ninety-four thousand three hundred sixty-four dollars ($10,094,364) in recurring funds for each year of the 2023-2025 fiscal biennium to implement the foster care and adoption assistance rate increases set forth in subsection (a) of this section.

SECTION 6.8. There is appropriated from the General Fund to the Department of Health and Human Services, Division of Social Services, the sum of one million seven hundred twenty-five thousand five hundred thirty-one dollars ($1,725,531) in recurring funds for each year of the 2023-2025 fiscal biennium to provide the State portion of the total cost of care to implement, with the associated county and federal shares, an increase to the administrative rate for foster care and adoption assistance.

SECTION 6.9. There is appropriated from the General Fund to the Department of Health and Human Services, Division of Social Services, the sum of eleven million eight hundred thousand dollars ($11,800,000) in nonrecurring funds for the 2023-2024 fiscal year to provide

additional funding to cover a loss in federal receipts from the Family First Prevention Services Act regarding congregate care for foster care.

SECTION 6.10. There is appropriated from the General Fund the sum of one million five hundred thousand dollars ($1,500,000) in recurring funds for each year of the 2023-2025 fiscal biennium to the North Carolina Community College System for allocation to the NC Finish Line Grants Program.

SECTION 6.11. Except as otherwise provided, this Part becomes effective July 1, 2023.

PART VII. EXPANDING ACCESS TO CHILD CARE

SECTION 7.1.(a) From July 1, 2023, through September 30, 2023, the Department of Health and Human Services, Division of Child Development and Early Education, shall maintain the child care subsidy market rates at the seventy-fifth percentile as recommended by the 2018 Child Care Market Rate Study for children in three-, four-, and five-star-rated child care centers and homes.

SECTION 7.1.(b) Beginning October 1, 2023, the Department of Health and Human Services, Division of Child Development and Early Education, shall increase the child care subsidy market rates to the seventy-fifth percentile as recommended by the 2021 Child Care Market Rate Study for children in three-, four-, and five-star-rated child care centers and homes.

SECTION 7.1.(c) There is appropriated from the General Fund to the Department of Health and Human Services, Division of Child Development and Early Education, the sum of thirty-two million dollars ($32,000,000) in recurring funds for the 2023-2024 fiscal year and the sum of forty-three million dollars ($43,000,000) in recurring funds for the 2024-2025 fiscal year to implement the market rate increases set forth in subsections (a) and (b) of this section.

SECTION 7.1.(d) It is the intent of the General Assembly to use a portion of the anticipated increase in funds to the Child Care and Development Fund Block Grant to supplement funding for the child care market rate increases described in subsection (b) of this section.

SECTION 7.2.(a) The Division of Child Development and Early Education shall decouple private tuition payment rates from the subsidized child care market rates for licensed child care centers and homes.

SECTION 7.2.(b) Section 9C.4(c) of S.L. 2021-180 reads as rewritten:

"**SECTION 9C.4.(c)** Payments for the purchase of child care services for low-income children shall be in accordance with the following requirements:

(1) Religious sponsored child care facilities operating pursuant to G.S. 110-106 and licensed child care centers and homes that meet the minimum licensing standards that are participating in the subsidized child care program shall be paid the one-star county market rate or the rate they charge privately paying ~~parents, whichever is lower,~~ parents unless prohibited by subsection (f) of this section.

(2) Licensed child care centers and homes with two or more stars shall receive the market rate for that rated license level for that age group ~~or the rate they charge privately paying parents, whichever is lower,~~ unless prohibited by subsection (g) of this section.

…."

SECTION 7.3. This Part becomes effective July 1, 2023.

PART VIII. EXPAND SATELLITE-BASED MONITORING FOR VIOLENT AND REPEAT SEXUAL OFFENDERS, INCREASE PUNISHMENT FOR ASSAULT ON A PREGNANT WOMAN, AND ESTABLISH THE CRIME OF MISDEMEANOR DOMESTIC VIOLENCE

SECTION 8.1.(a) G.S. 14-208.40A reads as rewritten:

"**§ 14-208.40A. Determination of satellite-based monitoring requirement by court.**

(a) When an offender is convicted of a reportable conviction as defined by G.S. 14-208.6(4), during the sentencing phase, the district attorney shall present to the court any evidence ~~that~~ of the following:

~~(i)~~(1) That the offender has been classified as a sexually violent predator pursuant to ~~G.S. 14-208.20,~~ G.S. 14-208.20.

~~(ii)~~(2) That the offender is a ~~reoffender,~~ reoffender.

~~(iii)~~(3) That the conviction offense was an aggravated ~~offense,~~ offense.

~~(iv)~~(4) That the conviction offense was a violation of G.S. 14-27.23 or ~~G.S. 14-27.28, or~~ G.S. 14-27.28.

~~(v)~~(5) That the offense involved the physical, mental, or sexual abuse of a minor.

The district attorney shall have no discretion to withhold any evidence required to be submitted to the court pursuant to this subsection. The offender shall be allowed to present to the court any evidence that the district attorney's evidence is not correct.

(b) After receipt of the evidence from the parties, the court shall determine whether the offender's conviction places the offender in one of the categories described in G.S. 14-208.40(a), and if so, shall make a finding of fact of that determination, specifying ~~whether~~ each of the following:

~~(i)~~(1) Whether the offender has been classified as a sexually violent predator pursuant to ~~G.S. 14-208.20,~~ G.S. 14-208.20.

~~(ii)~~(2) Whether the offender is a ~~reoffender,~~ reoffender.

~~(iii)~~(3) Whether the conviction offense was an aggravated ~~offense,~~ offense.

~~(iv)~~(4) Whether the conviction offense was a violation of G.S. 14-27.23 or ~~G.S. 14-27.28, or~~ G.S. 14-27.28.

~~(v)~~(5) Whether the offense involved the physical, mental, or sexual abuse of a minor.

(c) ~~If~~ The court shall order that the Department of Adult Correction do a risk assessment of the offender if the court finds any of the following:

(1) ~~that the~~ The offender has been classified as a sexually violent ~~predator, is a reoffender,~~ predator.

(2) The offender has committed an aggravated ~~offense, or~~ offense.

(3) The offender was convicted of G.S. 14-27.23 or ~~G.S. 14-27.28, the court shall order that the Division of Adult Correction and Juvenile Justice do a risk assessment of the offender.~~G.S. 14-27.28.

(4) The offender is a reoffender of a crime under G.S. 14-27.21, 14-27.22, 14-27.23, 14-27.24, 14-27.25(a), 14-27.26, 14-27.27, 14-27.28, 14-27.29, 14-27.30(a), 14-43.11, 14-43.13, 14-178(b)(1) and (b)(2), 14-190.16, 14-205.2(d), 14-205.3(b), 14-318.4(a1), or 14-318.4(a2).

The ~~Division of Adult Correction and Juvenile Justice~~ Department shall have up to 60 days to complete the risk assessment of the offender and report the results to the court. The ~~Division of Adult Correction and Juvenile Justice~~ Department may use a risk assessment of the offender done within six months of the date of the hearing.

(c1) Upon receipt of a risk assessment from the ~~Division~~ Department of Adult Correction ~~and Juvenile Justice~~ pursuant to subsection (c) of this section, the court shall determine whether, based on the ~~Division of Adult Correction and Juvenile Justice's~~ Department's risk assessment and all relevant evidence, the offender requires the highest possible level of supervision and monitoring. If the court determines that the offender does require the highest possible level of supervision and monitoring, the court shall order the offender to enroll in a satellite-based monitoring program for ~~a period of 10 years.~~the life of the offender.

(d) ~~If~~ The court shall order that the Department of Adult Correction do a risk assessment of the offender if the court finds ~~that the~~ each of the following:

(1) The offender committed an offense that involved the physical, mental, or sexual abuse of a ~~minor, that the~~ minor.

(2) The offense under subdivision (1) of this subsection is not an aggravated offense or a violation of G.S. 14-27.23 or ~~G.S. 14-27.28 and the~~ G.S. 14-27.28.

(3) The offender is not a reoffender, ~~the court shall order that the Department of Adult Correction do a risk assessment of the offender.~~ or is a reoffender of a crime under G.S. 14-27.31, 14-27.32, 14-27.33, 14-178(b)(3), 14-190.6, 14-190.9(a1), 14-190.17, 14-190.17A, 14-202.1, 14-202.3, 14-202.4(a), or 14-205.2(c).

The Department shall have up to 60 days to complete the risk assessment of the offender and report the results to the court. The ~~Division of Adult Correction and Juvenile Justice~~ Department may use a risk assessment of the offender done within six months of the date of the hearing.

(e) Upon receipt of a risk assessment from the Department of Adult Correction pursuant to subsection (d) of this section, the court shall determine whether, based on the Department's risk assessment and all relevant evidence, the offender requires the highest possible level of supervision and monitoring. If the court determines that the offender does require the highest possible level of supervision and monitoring, the court shall order the offender to enroll in a satellite-based monitoring program for a period of time to be specified by the court, not to exceed ~~10~~ 50 years."

SECTION 8.1.(b) This section becomes law October 1, 2023, and applies to court orders for enrollment in satellite-based monitoring programs issued on or after that date.

SECTION 8.2.(a) G.S. 14-33(c) reads as rewritten:

"(c) Unless the conduct is covered under some other provision of law providing greater punishment, any person who commits any assault, assault and battery, or affray is guilty of a Class A1 misdemeanor if, in the course of the assault, assault and battery, or affray, he or she:

…

(2a) Assaults a pregnant woman;

…."

SECTION 8.2.(b) This section becomes effective December 1, 2023, and applies to offenses committed on or after that date.

SECTION 8.3.(a) Article 8 of Chapter 14 of the General Statutes is amended by adding a new section to read:

"**§ 14-32.5. Misdemeanor crime of domestic violence.**

(a) Offense and Punishment. – A person is guilty of a Class A1 misdemeanor if that person uses or attempts to use physical force, or threatens the use of a deadly weapon, against another person and the person who commits the offense is:

(1) A current or former spouse, parent, or guardian of the victim.

(2) A person with whom the victim shares a child in common.

(3) A person who is cohabitating with or has cohabitated with the victim as a spouse, parent, or guardian.

(4) A person similarly situated to a spouse, parent, or guardian of the victim.

(5) A person who has a current or recent former dating relationship with the victim.

(b) Definition. – For purposes of this section, the term "dating relationship" is as defined in 18 U.S.C. § 921."

SECTION 8.3.(b) G.S. 14-415.12(b)(8a) reads as rewritten:

"(8a) Is or has been adjudicated guilty of or received a prayer for judgment continued or suspended sentence for one or more crimes of violence constituting a misdemeanor under ~~G.S. 14-33(c)(1),~~ G.S. 14-32.5,

Case 1:23-cv-00077-CCE-LPA Document 73-3 Filed 06/02/23 Page 46 of 48

14-33(c)(1), 14-33(c)(2), 14-33(c)(3), 14-33(d), 14-277.3A, 14-318.2, 14-134.3, 50B-4.1, or former G.S. 14-277.3."

SECTION 8.3.(c) This section becomes effective December 1, 2023, and applies to offenses committed on or after that date.

PART IX. EXEMPTION FROM STATUTORY PROVISION CONCERNING ORDER OF APPROPRIATION BILLS

SECTION 9. The provisions of G.S. 143C-5-2 do not apply to this act.

PART X. APPLICABILITY

SECTION 10. Nothing in this act shall be construed as creating or recognizing a right to abortion, nor shall the act make lawful an abortion that is otherwise unlawful.

PART XI. REVISOR OF STATUTES

SECTION 11. The Revisor of Statutes is authorized to alphabetize, number, and renumber the definitions listed in G.S. 90-21.120 and G.S. 90-21.81, as amended by this act, to ensure that all of the definitions are listed in alphabetical order and numbered accordingly.

PART XII. SEVERABILITY CLAUSE

SECTION 12. If any provision of this act or its application is held invalid, the invalidity does not affect other provisions or applications of this act that can be given effect without the invalid provisions or application and, to this end, the provisions of this act are severable.

PART XIII. EFFECTIVE DATE

SECTION 13. Except as otherwise provided, this act is effective when it becomes law.

In the General Assembly read three times and ratified this the 4th day of May, 2023.

s/ Bill Rabon
Presiding Officer of the Senate

s/ Tim Moore
Speaker of the House of Representatives

VETO Roy Cooper
Governor

Became law notwithstanding the objections of the Governor at 8:39 p.m. this 16th day of May, 2023.

s/ Mr. James White
House Principal Clerk

UNITED STATES DISTRICT COURT
MIDDLE DISTRICT OF NORTH CAROLINA
DURHAM DIVISION

AMY BRYANT, MD, Plaintiff, v. JOSHUA H. STEIN, in his official capacity as Attorney General for the State of North Carolina, *et al.*, Defendants, and TIMOTHY K. MOORE and PHILIP E. BERGER, Intervenors.	Case No.: 1:23-cv-00077-WO-LPA

[PROPOSED] ORDER

Plaintiff Amy Bryant, M.D., moved the Court for an order for leave to file and serve an amended complaint. For good cause shown, this motion is GRANTED and Plaintiff shall have up to and including _____ to file the proposed Amended Complaint. The Court deems Intervenors' pending motion to dismiss as applying to the Amended Complaint. Intervenors may file a Supplemental Motion to Dismiss, limited to

addressing any new matter raised by the Amended Complaint, within seven days of this order, and Plaintiff may file a response to any such Supplemental Motion to Dismiss within seven days after it is filed.

SO ORDERED, this _____ day of June 2023.

_____
United States District Judge /
United States Magistrate Judge /
Clerk of Court