

**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, )  
Defendants. )

Case No.: 1:23-cv-77

**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. 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 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 an ultrasound in all cases.

6. Rejecting the regulatory framework imposed by Congress and FDA, North Carolina has imposed 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 state that abortion medications may be provided only in person, only by a physician, and only in a specially certified facility after state-mandated counseling, a 72-hour waiting period, and (in certain circumstances) an ultrasound. *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. 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 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.

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”)<sup>1</sup> (“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.

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<sup>1</sup> Available at [https://www.ncmedboard.org/images/uploads/other\\_pdfs/Compendium\\_Final\\_03.25.2022.pdf](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 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 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* 10A N.C. Admin. Code 14E.0101, *et seq.* 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). 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”)<sup>2</sup> (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 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,

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<sup>2</sup> *Available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rem-s-assessment-planning-and-reporting>.

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,<sup>3</sup> FDA's website lists only 56 currently approved REMS with ETASU.<sup>4</sup>

**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 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.

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<sup>3</sup> 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.").

<sup>4</sup> See *Approved Risk Evaluation and Mitigation Strategies (REMS)*, FDA.gov (2023), <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

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.<sup>5</sup> 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 federal regulatory balance based on such consideration.

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

## 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").

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).

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.” 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. 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").

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 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; 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, 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.” *Id.* § 90-21.82(1)(a).

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 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).

80. 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 § 14-45.1(a) may be guilty of a felony, *see id.* §§ 14-44, 14-45, and a physician who performs an abortion in knowing or reckless violation of the requirements in § 90-

21.82 may be subject to a civil action for damages and attorneys' fees. 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.

81. 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, 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 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, *supra*.

### **CAUSE OF ACTION**

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

83. 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. The restrictions imposed by North Carolina on the provision of mifepristone—including the in-person requirement, the specially certified facility requirement, the counseling and 72-hour waiting period requirement, the physician-only requirement, and the ultrasound requirement—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. 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. 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. 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, 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<sup>1</sup> 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*.

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<sup>1</sup> In this REMS, the terms “sign” and “signature” include electronic signatures.

- 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*

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.

- 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,

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.

## 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](http://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.



\*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](http://www.earlyoptionpill.com)

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](mailto:Mifeprex@dancodistributor.com) or fax to 1-866-227-3343.

Approved 01/2023 [Doc control ID]



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P.O. Box 4816-New York, NY 10185  
1-877-4-EARLY-OPTION (1-877-432-7596) [www.earlyoptionpill.com](http://www.earlyoptionpill.com)

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](http://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.



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103  
1-855-MIFE-INFO (1-855-643-3463) - [www.MifeInfo.com](http://www.MifeInfo.com)

- 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](mailto:RxAgreements@GenBioPro.com) or fax to 1-877-239-8036

Approved 01/2023 [Doc control ID]



GenBioPro Inc. - PO Box 32011 - Las Vegas, NV 89103  
 1-855-MIFE-INFO (1-855-643-3463) - [www.MifeInfo.com](http://www.MifeInfo.com)

# 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](http://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: \_\_\_\_\_



\*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](http://www.earlyoptionpill.com)

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Email: \_\_\_\_\_ Phone: \_\_\_\_\_ Preferred \_\_\_ email \_\_\_ phone

Pharmacy Name: \_\_\_\_\_

Pharmacy Address: \_\_\_\_\_

Return completed form to [Mifeprex@dancodistributor.com](mailto:Mifeprex@dancodistributor.com) or fax to 1-866-227-3343.



\*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](http://www.earlyoptionpill.com)

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](http://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](mailto: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 11 $\beta$ -[*p*-(Dimethylamino)phenyl]-17 $\beta$ -hydroxy-17-(1-propynyl)estra-4,9-dien-3-one. Its empirical formula is C<sub>29</sub>H<sub>35</sub>NO<sub>2</sub>. 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 adrenocorticotrophic 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  $\alpha_1$ -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 11β; 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<sub>2</sub>. 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	%
<b>Complete medical abortion</b>	<b>762</b>	<b>92.1</b>	<b>1605</b>	<b>95.5</b>
<u>Timing of expulsion</u>				
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)
<b>Surgical intervention</b>	<b>65</b>	<b>7.9</b>	<b>76</b>	<b>4.5</b>
<u>Reason for surgery</u>				
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)
<b>Total</b>	<b>827</b>	<b>100</b>	<b>1681</b>	<b>100</b>

*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 pombe* P1 cells; induction of unscheduled DNA synthesis in cultured HeLa cells; induction of chromosome aberrations in CHO cells; *in 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**

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

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>U.S. Trials</u>	<u>French Trials</u>
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°C (77°F); excursions permitted to 15-30°C (59-86°F) [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](http://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:

SUBJECT:

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

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

Summary of Effectiveness and Safety

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

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

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

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

### Chemistry/Manufacturing

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

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

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

### Labeling

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

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

### Black Box

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

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

Prescribers should make sure the patients receive and have an opportunity to discuss the Medication Guide and Patient Agreement."

### Misoprostol Administration

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

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

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

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

#### Access to Health Care and Emergency Services

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

#### Patient Agreement Form

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

#### Biopharmaceutics

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

#### Pharmacology-Toxicology

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

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

#### Medication Guide

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

#### Distribution System

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

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

#### Physician Qualifications

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

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

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

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

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

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

## Subpart H

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

- Mifepristone must be provided by or under the supervision of a physician who meets the following qualifications:
  - Ability to assess the duration of pregnancy accurately
  - Ability to diagnose ectopic pregnancies
  - Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or have made plans to provide such care through other qualified physicians, and are able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary
  - Has read and understood the prescribing information of Mifeprex
  - Must provide each patient with a Medication Guide and must fully explain the procedure to each patient, provide her with a copy of the Medication Guide and Patient Agreement, given her an opportunity to read and discuss both the Medication Guide and the Patient Agreement, obtain her signature on the Patient Agreement and must sign it as well
  - Must notify the sponsor or its designate in writing as discussed in the Package Insert under the heading DOSEAGE AND ADMINISTRATION in the event of an on-going pregnancy, which is not terminated subsequent to the conclusion of the treatment procedure
  - Must report any hospitalization, transfusion or other serious events to the sponsor or its designate
  - Must record the Mifeprex package serial number in each patient's record
  
- With respect to the aspects of distribution other than physician qualifications described above, distribution of Mifeprex will be in accordance with the system described in the Population Council's submission of March 30, 2000, which includes the following:
  - Secure manufacturing, receiving, and holding areas for the drug
  - Secure shipping procedures, including tamper-proof seals
  - Controlled returns procedures
  - Tracking system ability to trace individual packages to the patient level, while maintaining patient confidentiality
  - Use of authorized distributors and agents with necessary expertise to handle distribution requirements for the drug
  - Provision of drug through a direct, confidential physician distribution system that ensures only qualified physicians will receive the drug for patient dispensing

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

#### Phase 4 Commitments

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

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

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

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

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

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

### Public Comments Considered

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

### Risk Management Program

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

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

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

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

APPEARS THIS WAY  
ON ORIGINAL