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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF WASHINGTON

STATE OF WASHINGTON, et al.,

Plaintiffs,

v.

UNITED STATES FOOD AND DRUG ADMINISTRATION, et al.,

Defendants.

NO. 1:23-cv-03026-TOR

DECLARATION OF LAURYN K. FRAAS IN SUPPORT OF PLAINTIFF STATES' REPLY IN SUPPORT OF MOTION FOR SUMMARY JUDGMENT AND OPPOSITION TO DEFENDANTS' CROSS-MOTION FOR SUMMARY JUDGMENT

With Oral Argument:
TBD (see ECF No. 175)

I, Lauryn K. Fraas, declare as follows:

1. I am over the age of 18, competent to testify to the matters herein, and make this declaration based on my personal knowledge.

2. I am an Assistant Attorney General with the Washington State Office of the Attorney General and one of the attorneys representing Plaintiff State of Washington in the above-captioned matter.

3. Submitted herewith as Exhibit 1 is the Index of Plaintiff States' Supplemental Excerpts of Administrative Record (SEAR).

4. Submitted herewith as Exhibits 2 and 3 are volumes A through B of the Plaintiff States' Supplemental Excerpts of Administrative Record (SEAR). Volume A of the SEAR comprises true and correct copies of supplemental excerpts of the administrative record produced by Defendants in this matter; Volume B comprises true and correct copies of materials available from public websites maintained by Defendants FDA and HHS. The State of Washington has applied "SEAR__" Bates numbers to the excerpts.

5. Attached hereto as Exhibit 4 is a true and correct copy of Time Magazine's January 30, 2025 article *RFK Jr. Says He'll Follow Trumps Lead on Abortion* available at https://time.com/7210724/rfk-jr-abortion-position-senate-confirmation-hearing/.

6. Attached hereto as Exhibit 5 is a true and correct copy of The New York Times's March 17, 2025 article *Anti-Abortion Lawyer Pushed Out of F.D.A.*

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After Republican Senator's Pressure Campaign available at https://www.nytimes.com/2025/03/17/us/politics/lawyer-fda-abortion-josh-hawley.html.

I declare under penalty of perjury under the laws of the State of Washington and the United States of America that the foregoing is true and correct.

DATED and SIGNED this 31st day of March 2025, at Seattle, Washington.

s/ Lauryn K. Fraas
LAURYN K. FRAAS, WSBA #53238
Assistant Attorney General

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CERTIFICATE OF SERVICE

I hereby certify that on March 31, 2025, I electronically filed the foregoing with the Clerk of the Court using the CM/ECF System, which in turn automatically generated a Notice of Electronic Filing (NEF) to all parties in the case who are registered users of the CM/ECF system. The NEF for the foregoing specifically identifies recipients of electronic notice.

I declare under penalty of perjury under the laws of the State of Washington and the United States of America that the foregoing is true and correct.

DATED this 31st day of March 2025, at Seattle, Washington.

s/ Lauryn K. Fraas
LAURYN K. FRAAS, WSBA #53238
Assistant Attorney General

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Exhibit 1

Index of Plaintiff States' Supplemental Excerpts of Administrative Record (SEAR)

State of Washington, et al. v. United States
Food and Drug Administration, et al.
No. 1:23-cv-03026-TOR

VOLUME A			
Administrative Record			
Index Page Number	**Document Name**	**Document Date**	**Excerpted pages**
SEAR1- 9	Letter from Dr. Graham Chelius, SFP & Cal. Acad. of Family Physicians, to FDA **2021 REMS 1159-67***	9/29/2021	Entire range **Excerpted pages included at EAR141-142*
SEAR10-13	Sara Daniel et al., *Obstetrician-Gynecologist Willingness to Provide Medication Abortion with Removal of the In-Person Dispensing Requirement for Mifepristone,* 104 Contraception 73-76 (2021) **2021 REMS 001173-1176**	July 2021	Entire range
SEAR14-63	REMS Modification Rationale Review (Mifepristone) **2021 REMS 1561-1609***	12/16/2021	Entire range **Entire range at EAR150-198; re-filed as one page was inadvertently missing*
SEAR64-74	Laura Schummers et al., *Abortion Safety and Use with Normally Prescribed Mifepristone in Canada*, 386 New End. J. Med. 57-67 **2022 CP 99-109***	1/6/2022	Entire range **Excerpted pages included at EAR238-239*

SEAR75-78	Memorandum to File re: Referenced Publications **2023 SUPP 1077-80**	12/30/2022	Entire range
SEAR79-81	Memorandum to File re: AIM Study **2023 SUPP 1259-61**	1/3/2023	Entire range
VOLUME B			
Materials Available on FDA and HHS Webpages			
Index Page No.	**Webpage or Document Name**	**Date**	
SEAR82-94	REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary Guidance for Industry	April 2019 (accessed Mar. 16, 2025)	

Exhibit 2

Sept. 29, 2021

BY ELECTRONIC MAIL

Janet Woodcock, M.D.
Acting Commissioner
United States Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Evidence Supporting Elimination of the Mifepristone REMS

Dear Dr. Woodcock:

We are the health care providers and researchers engaged in litigation challenging the Risk Evaluation and Mitigation Strategy ("REMS") for mifepristone 200 mg for termination of early pregnancy. We are pleased that the U.S. Food and Drug Administration ("FDA") has initiated a comprehensive evaluation of the mifepristone REMS and its three elements to assure safe use ("ETASU"), and appreciate the opportunity to submit data and evidence for FDA's review.[1]

As you know, it is our position that a REMS is not medically necessary to ensure that the benefits of mifepristone outweigh its risks.[2] We note that one of the signatories to this letter (the Society of Family Planning) is the organization that represents Complex Family Planning Fellowship-trained obstetrician-gynecologists, who are the leaders in clinical care, medical education, and research relating to abortion and contraception. Other leading medical authorities—including the American Medical Association, the American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians—likewise support eliminating these restrictions.[3] We hope that, following a comprehensive evaluation incorporating new data and evidence from the past five years, FDA will reach the same conclusion.

The Mifepristone REMS with ETASU Does Not Enhance Safety

As extensively detailed in the letter submitted by the Society of Family Planning on August 11, 2021, peer-reviewed scientific evidence, including research published since the most recent FDA-approved labeling change in 2016, confirms that mifepristone is extremely safe and highly effective whether dispensed at a health center, pharmacy, or by home delivery, and does not require a clinician to oversee dispensing or specially certify their ability to provide appropriate care. The evidence is clear that the mifepristone REMS and its three ETASU confer no benefit in terms of safety, efficacy, or acceptability of the medication, are not "commensurate with" the risks of mifepristone,[4] and create barriers to use that reduce patient access and negatively impact public health, causing particular harm to communities of color, people with fewer resources, and people living in rural areas.

Mifepristone's strong safety and efficacy findings hold true across a range of regulatory contexts, including international and domestic studies operating outside of the ETASU C dispensing framework. For instance, as you are aware,[5] a recent large (N=52,218) retrospective cohort study reported on the safety, efficacy, and acceptability of telemedicine abortion at Britain's

largest abortion providers, which rapidly adapted to provide medication abortion using telemedicine during the spring and summer of 2020 in response to the COVID-19 pandemic.[6] Following a telehealth consultation, individuals with a last menstrual period dating the pregnancy up to 69 days and without symptoms of ectopic pregnancy were able to receive both mifepristone and misoprostol by mail for home administration. Aiken and colleagues found that medication abortion was equally effective in this telemedicine model (98.8%) versus the traditional in-clinic mifepristone administration model (98.2%, p=1.0); that 99.98% of patients using the telemedicine model experienced no serious adverse events compared to 99.96% of abortions with an in-person assessment; and that patients obtaining their medications by mail following a telemedicine consultation were able to initiate treatment *earlier* in pregnancy than patients utilizing the traditional in-clinic model. Similarly, in a large (N=1,157 abortions) national U.S.-based clinical trial of mifepristone dispensing by mail (the TelAbortion study), Chong and colleagues found that mifepristone dispensing by direct mail to consumers is effective (95% abortion completion with medication alone), with only 0.9% experiencing any serious adverse event, compared to a serious adverse event rate of 0.65% in a large (N=233,805 medication abortions) retrospective cohort study of in-clinic mifepristone administration.[7]

There is likewise no evidence that the ETASU A requirement that mifepristone prescribers attest to their ability to prescribe mifepristone mitigates any safety risks of the medication. Indeed, the evidence refutes this. For instance, in Canada, mifepristone-specific requirements for provider certification were lifted in November 2017. According to a comprehensive analysis of linked medical and financial records in Ontario, medication abortion remained extremely safe after deregulation, with a major complication rate of 0.33% compared to a rate of 0.31% in an analysis of a similar administrative dataset from California under the REMS, and consistent with a clinical review finding major complication rates below 1% across multiple studies of mifepristone use for early abortion.[8]

Finally, we agree with the recommendation of FDA's scientific review team in 2016 to eliminate ETASU D, after finding that this ETASU "does not add to safe use conditions" because the Patient Agreement is "generally duplicative of information contained in the Medication Guide and of information and counseling provided to patients under standard informed consent practices for medical care and under professional practice guidelines."[9]

The Mifepristone REMS Is an Outlier and Unwarranted by Mifepristone's Strong Safety Record

Consistent with strict statutory criteria,[10] FDA imposes REMS programs rarely: fewer than 3% of FDA-regulated drugs are subject to a REMS,[11] and the overwhelming majority of drugs subject to a REMS are opioids—which, in FDA's words, are "claiming lives at [such] a staggering rate" that they are "reducing life expectancy in the United States."[12] FDA subjects only 17 drugs (0.09%), including Mifeprex® and its generic, to a REMS requiring the patient to obtain the medication in a clinic, office, or hospital.[13] And for all such drugs *except* mifepristone, FDA also requires that the medication be taken under clinical supervision, either because of the administration form (e.g., intravenous) or because it can be safely administered only in certain settings (e.g., with monitoring for immediate reactions such as "life-threatening respiratory depression"). In short, mifepristone is the only drug in the nation that FDA requires patients to

pick up in a clinical setting yet permits patients to self-administer elsewhere without direct clinical supervision, based on data confirming the safety of home administration.[14]

While we recognize that there are multiple factors informing the determination of whether a REMS is necessary for any individual drug,[15] we note that FDA has determined that many other drugs posing risks of serious adverse events can be successfully regulated through labeling without a REMS. For example:

- Jeuveau® is an FDA-approved acetylcholine release inhibitor and a neuromuscular blocking agent "indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients"—i.e., it is indicated for a purely cosmetic purpose among a healthy population. Jeuveau carries a black-box warning for "[s]wallowing and breathing difficulties" that "can be life threatening" if this botulinum toxin product spreads beyond the area of injection, and the labeling notes that "there have been reports of death."[16]
- Propecia®, a drug "indicated for the treatment of male pattern hair loss," had its labeling updated in 2011 to reflect that this cosmetic medication may cause an "increased risk of high-grade prostate cancer."[17]
- NuvaRing® is an estrogen/progestin combination hormonal contraceptive ("CHC") inserted as a vaginal ring, which carries a black-box warning for "serious cardiovascular events" with increased risk among cigarette smokers.[18] Its labeling warns patients that CHCs pose a risk of "death from heart attack, blood clots or stroke."[19] Other serious risks associated with NuvaRing include Toxic Shock Syndrome and liver tumors.[20]
- Coumadin®, a common anticoagulant, carries a black box warning for "major or fatal bleeding," with risk ranging from 0.6 to 4.6% for patients with certain comorbidities.[21]

For all of these drugs, FDA has determined that the benefits outweigh the risks even in the absence of a REMS. Now, with the benefit of additional safety and efficacy data on mifepristone reported over the past five years, we urge you to find that mifepristone's risks likewise can be appropriately managed through labeling without a REMS.

The Mifepristone ETASU Are Unduly Burdensome

The REMS statute prohibits ETASU that are "unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas)."[22] The statute further requires that any ETASU be crafted to "minimize the burden on the health care delivery system," "[t]o the extent practicable."[23]Accordingly, FDA has emphasized that a "REMS should be designed to meet the relevant goals, not unduly impede patient access to the drug, and minimize the burden on the health care delivery system to the extent practicable."[24] While a drug sponsor may request changes to a REMS program, it is FDA that is responsible for ensuring that any REMS comports with all statutory and regulatory requirements and limitations, regardless of what the sponsor has proposed or requested.[25]

The mifepristone ETASU do not comply with these requirements. Extensive evidence shows that these ETASU significantly impede patient access, and do so in part by burdening health care providers. And, whereas FDA has long acknowledged that mifepristone is "important to the health of women,"[26] has underscored the need to prevent treatment delays for mifepristone patients,[27] and has stressed that unwanted pregnancy can be a "serious medical condition,"[28] substantial evidence shows that the mifepristone ETASU *cause* treatment delays and prevent some pregnant patients from obtaining a desired abortion at all.

Attached as appendices are several declarations that were submitted as part of the *Chelius v. Becerra* litigation, which provide first-hand physician narratives, research, and statistical analysis detailing how the mifepristone ETASU unduly burden the health care delivery system and patients' access to this medication. We appreciate your consideration of all of this relevant evidence, which we briefly summarize below:

First, the mifepristone ETASU reduce the pool of qualified clinicians providing medication abortion, including in the geographic areas most lacking in abortion access. For instance, in a nationally representative survey of currently practicing board-certified obstetrician-gynecologists, fewer than one in five respondents who see patients seeking abortion care reported having provided a medication abortion during the previous year—but the proportion of medication abortion providers would likely *double* if clinicians were permitted to prescribe mifepristone through a pharmacy.[29] Notably, the number of respondents in the South and Midwest who said they would begin providing medication abortion if not for the REMS was higher than the number who were currently providing such care.[30] This finding is of particular significance given the increasing efforts by states in the South and Midwest to ban abortion at all but the earliest weeks of pregnancy.[31] Put plainly, if there are more medication abortion providers in those states, more patients will be able to obtain abortions before confronting those (unconstitutional) gestational age limits. Moreover, while the overwhelming majority of current abortion providers practice in urban areas, 40% of OB-GYNs who responded that they would provide medication abortion care if not for the REMS identified their practices as "suburban" or "midsize town, rural, or military."[32]

Specifically, ETASU C burdens the health care delivery system and severely reduces patient access because of the challenges of obtaining institutional approval to dispense mifepristone onsite, and the complicated logistics necessary to do so. It is extremely unusual for health care providers to have to serve as, in effect, both prescribers and pharmacists; as noted above, fewer than 0.1% of FDA-approved drugs must be dispensed in a hospital, medical office, or clinic. Thus, health care institutions typically must develop unique protocols around the dispensing of mifepristone onsite, which can significantly delay clinicians' ability to prescribe this medication or prevent them from doing so at all. As just one example, it took five years and hundreds of hours of individual clinician and stakeholder advocacy before mifepristone was available to patients at the University of Michigan's Women's Clinic. After years of clinician lobbying to add mifepristone to the institution's formulary, personnel across the organization then had to develop protocols for ordering, storing, and dispensing the medication (including "opt-out" protocols for staff opposed to any involvement in such activities), as well as establish insurance and billing practices. Many clinicians would face none of these burdens if their patients could simply fill their mifepristone prescription through a retail or mail-order pharmacy.

Additionally, ETASU C exacerbates these logistical burdens by enabling interference by individuals opposed to abortion. Instead of being able to simply issue a mifepristone prescription for an eligible patient to fill at a pharmacy, clinicians seeking to prescribe mifepristone must—as a direct result of ETASU C—involve numerous other health care staff in the process of procuring, stocking, dispensing, and billing for mifepristone onsite. As a practical matter, this means that even a single colleague who objects to abortion can substantially delay, or altogether derail, a clinician's ability to prescribe a safe and effective medication that their patients urgently need.

ETASU A also deters many qualified clinicians from becoming mifepristone prescribers. In light of the long history of anti-abortion violence and harassment in this country, some physicians are unwilling to register with the mifepristone sponsors—fearful of what they and their families might face if abortion opponents were ever able to access their certification agreements. While the drug manufacturers and distributors are required to maintain that information strictly confidentially, these clinician fears are not unfounded; indeed, in our litigation, FDA was unwilling to provide Plaintiffs with the names or offices of agency staff who had been involved in any Mifeprex reviews, *even subject to a protective order* requiring strict confidentiality of Plaintiffs and their counsel.[33] Prescriber certification presents a real barrier to patient access, and, as discussed above, there is no evidence showing that this ETASU advances any countervailing safety interest sufficient to outweigh these burdens.

Second, ETASU C forces patients to travel unnecessarily to a mifepristone provider for no medical reason, and in sharp contrast with the expansion of telemedicine nationwide. Across virtually all other areas of medicine, a telemedicine revolution is increasing health care access in medically under-resourced communities and reducing the need for patients to travel long distances for care. But, while medically eligible mifepristone patients already can and do obtain all evaluation and counseling via telemedicine, the REMS prohibits patients from filling their prescription by mail or at a local pharmacy. Instead, FDA requires that mifepristone patients travel to a health center for the sole purpose of picking up the pill and signing a form.

It is important to understand that abortion access is very limited in the United States—in part due to the burdens of ETASU C and A, which reduce the number of clinicians able to provide this essential health care. A nationally representative sample of 8,000 abortion patients found that patients traveled, on average, 68 miles round-trip to receive an abortion.[34] In a majority of states, at least 20% of reproductive-age women live more than 100 miles round-trip from the nearest abortion clinic.[35] And while rural areas are particularly lacking, patients in urban areas also struggle. A 2018 study found that 27 major cities have no publicly advertised abortion provider within 100 miles.[36] Requiring patients to pick up their mifepristone pill in person at a health center thus in many cases requires significant travel.

Given the mifepristone patient population, such travel can be incredibly difficult and in some cases impossible. According to a nationally representative survey, in 2014 (the most recent year for which such data are available), 75 percent of abortion patients had incomes at or below the U.S. Official Poverty Measure.[37] Sixty percent of abortion patients identify as people of color, including 53 percent of patients who identify as Black or Hispanic.[38] And 60 percent of abortion patients have at least one child.[39] Forcing patients to travel in person to pick up the mifepristone tablet at one of the (few) abortion providers in the country imposes costs and burdens relating to

transportation, childcare, and lost wages for missed work that many in this patient population simply cannot afford. Indeed, a robust body of research, spanning multiple states and decades, confirms that forcing patients to travel even slightly farther (e.g., 10 miles) delays or blocks patients from accessing desired abortions.[40] In short, these ETASU specifically burden "patients who have difficulty accessing health care," in violation of the REMS statute.[41]

***

We welcomed FDA's April 2021 announcement that it intends to exercise enforcement discretion during the COVID-19 Public Health Emergency with respect to the dispensing of mifepristone through the mail or through a mail-order pharmacy when such dispensing is done by or under the supervision of a certified prescriber. We note that this enforcement discretion has mitigated some (though not all) of the burdens on patients and the health care delivery system described in the physician narratives attached as Appendices. Most significantly, enabling patients to obtain their mifepristone prescription through telemedicine and mail-order pharmacies where medically appropriate has prevented many patients from having to needlessly travel for health care during the pandemic, reducing treatment delays and COVID-19 risks and enabling some patients to access mifepristone who otherwise would not have been able to do so at all.

In addition, having the option to submit a prescription to a pharmacy and then have the pharmacy directly bill and dispense the mifepristone to their patient has enabled some qualified physicians—who previously had been impeded by the complex logistics and controversy around procuring, stocking, dispensing, and billing for mifepristone onsite at their health centers—to begin prescribing this medication for the first time. This is consistent with the nationally representative OB-GYN survey discussed above, which showed that eliminating the REMS would increase the pool of qualified mifepristone prescribers.[42] If the other barriers imposed by the mifepristone ETASU are lifted, even more qualified clinicians will be able to begin prescribing this safe and effective medication.

We appreciate FDA's careful consideration of the extensive evidence showing that the mifepristone REMS does not advance patient safety; causes treatment delays that undermine patients' health; subjects some patients who are unable to obtain mifepristone because of the REMS to the serious medical risks of ongoing pregnancy and childbirth; and unduly burdens both patients and the health care delivery system, with disproportionate harm to people living in rural and medically underserved areas, people with fewer financial resources, and people of color. Consistent with this sound evidence, we urge you to eliminate the mifepristone REMS.

Sincerely,

Dr. Graham Chelius
The Society of Family Planning
The California Academy of Family Physicians

Plaintiffs in *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw.)

CC: Dr. Patrizia Cavazzoni, Center for Drug Evaluation and Research
Dr. Catherine Sewell, Center for Drug Evaluation and Research

[1] *Chelius v. Becerra*, No. 1:17-cv-00493-JAO-RT (D. Haw.) [hereinafter *Chelius v. Becerra*], Joint Motion to Stay Case Pending Agency Review 2, Dkt. 148.

[2] 21 U.S.C. § 355-1(g)(4)(B)(i).

[3] *See, e.g.*, House of Delegates, Am. Med. Ass'n, *Memorial Resolutions Adopted Unanimously* No. 504 (2018), https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf; Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications; Cong. of Delegates, Am. Acad. of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization on Mifepristone* (May 24, 2018), https://www reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf.

[4] 21 U.S.C. § 355-1(f)(2)(A).

[5] *See* Letter from Janet Woodcock, M.D., Acting Commissioner of Food & Drug Admin., to Maureen G. Phipps, M.D., M.P.H., FACOG, and William Grobman, M.D., M.B.A. (Apr. 12, 2021), https://www.aclu.org/letter/fda-response-acog-april-2021.

[6] Abigail Aiken et al., *Effectiveness, Safety and Acceptability of No-Test Medical Abortion (Termination of Pregnancy) Provided Via Telemedicine: A National Cohort Study*, 128(9) BJOG 1464 (Aug. 2021), https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.16668.

[7] Erica Chong et al., *Expansion of a Direct-to-Patient Telemedicine Abortion Service in the United States and Experience during the COVID-19 Pandemic*, 104(1) Contraception 43 (July 2021), https://www.contraceptionjournal.org/article/S0010-7824(21)00091-3/fulltext; Kelly Cleland et al., *Significant Adverse Events and Outcomes after Medical Abortion*, 121(1) Obstetrics & Gynecology 166 (Jan. 2013), https://pubmed ncbi nlm nih.gov/23262942/.

[8] Laura Schummers et al, *Do Medication Abortion Complications Increase When Restrictive Risk Evaluation and Mitigation Strategy Regulations are Removed? A Population-Based Study Using Single-Payer Linked Health Administrative Data*, 102(4) Contraception 273 (Oct. 2020), https://www.contraceptionjournal.org/article/S0010-7824(20)30214-6/fulltext; Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications after Abortion*, 125(1) Obstetrics & Gynecology 175 (Jan. 2015), https://pubmed ncbi.nlm.nih.gov/25560122/; Nathalie Kapp & Patricia A. Lohr, *Modern Methods to Induce Abortion: Safety, Efficacy and Choice*, 63 Best Prac. & Res. Clinical Obstetrics & Gynecology 37 (Feb. 2020), https://www.sciencedirect.com/science/article/pii/S1521693419301762?via%3Dihub.

[9] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 020687Orig1s020: Summary Review(s)* 25 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020SumR.pdf; U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 020687Orig1s020: Risk Assessment and Risk Mitigation Review(s)* Ref ID: 3909589 at 2 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf.

[10] 21 U.S.C. § 355-1(a)(1).

[11] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶¶ 59–60.

[12] *Id.* at ¶¶ 59–60; U.S. Food & Drug Admin., *Opioid Medications* (Mar. 29, 2021), https://www.fda.gov/drugs/information-drug-class/opioid-medications.

[13] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶¶ 59, 61.

[14] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 020687Orig1s020: Medical Review(s)* 39 (Mar. 29, 2016) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

[15] 21 U.S.C. § 355-1(a)(1).

[16] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Application Number 761085Orig1s000: Labeling* (Jeuveau) (Feb. 2019), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761085Orig1s000Lbl.pdf.

[17] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Labeling* (Propecia) (Apr. 2012), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020788s020s021s023lbl.pdf.

[18] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Labeling* (NuvaRing) (Oct. 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021187s022lbl.pdf.

[19] *Id.*

[20] *Id.*

[21] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Labeling* (Coumadin) (Oct. 2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/009218s107lbl.pdf.

[22] 21 U.S.C. § 355-1(f)(2)(C).

[23] 21 U.S.C. § 355-1(f)(2)(D).

[24] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., Ctr. for Bio. Eval. & Res., *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* 5 (April 2019), https://www.fda.gov/media/100307/download.

[25] 21 U.S.C. § 355-1(a), (d), (f).

[26] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Mifeprex (mifepristone) NDA Approval Letter* 4 (Sept. 2000), *Chelius v. Becerra*, Dkt. 142-2, Ex. B.

[27] U.S. Food & Drug Admin., Ctr. for Drug Eval. & Res., *Final Risk Evaluation and Mitigation Strategy (REMS) Review: Mifeprex* (Oct. 2013), *Chelius v. Becerra*, Dkt. 85-8.

[28] Letter from Janet Woodcock, M.D., Director, Ctr. for Drug Eval. & Res., to Donna Harrison, M.D. et al., Denying Citizen Petition Asking the FDA to Revoke Approval of Mifeprex 4-5 (Mar. 29, 2016) (emphasis added), https://www.regulations.gov/document?D=FDA-2002-P-0364-0002.

[29] Sara Daniel et al., *Obstetrician-Gynecologist Willingness to Provide Medication Abortion with Removal of the In-Person Dispensing Requirement for Mifepristone*, 104(1) Contraception 73 (July 2021), https://www.contraceptionjournal.org/article/S0010-7824(21)00098-6/fulltext.

[30] *Id.*

[31] *See, e.g.*, *Whole Woman's Health v. Jackson*, No. 21A24, 2021 WL3910722 (U.S. Sept. 2, 2021) (denying request to block Texas's six-week abortion ban from taking effect); *Planned Parenthood S. Atl. v. Wilson*, No. 3:21-24 00508-MGL, 2021 WL 672406, at *2 (D.S.C. Feb. 29, 2021) (preliminary injunction of South Carolina six-week ban), *appeal filed*, No. 21-1369 (4th Cir. Apr. 5, 2021); *SisterSong Women of Color Reprod. Justice Collective v. Kemp*, 472 F. Supp. 3d 1297, 1312 (N.D. Ga. 2020) (preliminary injunction of Georgia six-week ban), *appeal filed*, No. 20-13024 (11th Cir. Aug. 11, 2020); *Memphis Ctr. for Reprod. Health v. Slatery*, No. 3:20-CV-00501, 2020 WL 4274198, at *2 (M.D. Tenn. July 24, 2020) (preliminary injunction of Tennessee six-week ban), *appeal filed*, No. 20-5969 (6th Cir. Aug. 24, 2020); *Preterm-Cleveland v. Yost*, 394 F. Supp. 3d 796, 804 (S.D. Ohio 2019) (preliminary injunction of Ohio six-week ban); *EMW Women's Surgical Ctr., P.S.C. v. Beshear*, No. 3:19-CV-178-DJH, 2019 WL 1233575, at *2 (W.D. Ky. Mar. 15, 2019) (temporary restraining order of Kentucky six-week ban).

[32] Daniel et al., *supra* n.29.

[33] *Chelius v. Becerra*, Joint Stips. of Facts, Dkt. 140, ¶ 47 ("In light of the violence and harassment surrounding the provision of abortion, FDA withheld FDA employee names and other identifying information from documents related to Mifeprex in the administrative record . . . . Because releasing this information would constitute an unwarranted invasion of personal privacy and could expose those employees to threats, intimidation, harassment and/or violence, FDA believes it is necessary not to disclose information that could be used to identify these employees to any person outside of FDA, including Plaintiffs' counsel subject to a protective order.").

[34] Liza Fuentes & Jenna Jerman, *Distance Traveled to Obtain Clinical Abortion Care in the United States and Reasons for Clinic Choice*, 28 J. Women's Health 1623, 1625 (2019), https://pubmed ncbi.nlm.nih.gov/31282804/.

[35] Jonathan M. Bearak et al., *Disparities and Change Over Time in Distance Women Would Need to Travel to Have an Abortion in the USA: A Spatial Analysis*, Lancet Pub. Health e493, e495–96 (2017), https://www.thelancet.come/action/showPDF?pii=S2468-2667%2817%2930158-5 (in six states, a majority of women of reproductive age live more than 50 miles away from the nearest abortion provider, including two states where a majority live more than 150 miles from the nearest provider).

[36] Alice Cartwright et al., *Identifying National Availability of Abortion Care and Distance from Major US Cities: Systematic Online Search*, 20 J. Med. Internet Res. 7 (2018), https://www.jmir.org/2018/5/e186/.

[37] Jenna Jerman et al., Guttmacher Inst., *Characteristics of U.S. Abortion Patients in 2014 and Changes Since 2008* 1, 7 (May 2016), https://www.guttmacher.org/report/characteristics-us-abortion-patients-2014.

[38] *Id.* at 1, 5; *Abortion Surveillance — United States, 2018*, Ctrs. for Disease Control & Prevention [hereinafter *CDC Abortion Surveillance*], at Table 5, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1 htm#T5_down (last updated Nov. 7, 2020).

[39] Jerman et al., *supra* n.37, at 1, 7; *CDC Abortion Surveillance* at Table 7, https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7_down.

[40] Jill Barr-Walker et al., *Experience of Women Who Travel for Abortion: A Mixed Methods Systematic Review*, PLOS ONE 14(4), at 2 (2019), https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0209991; Daniel Grossman et al., *Change in Distance to Nearest Facility and Abortion in Texas, 2012 to 2014*, 317 JAMA Network 437, 437–38 (2017), http://sites.utexas.edu/txpep/files/2017/10/Grossman-et-al-HB2-Change-in-Distance-Abortion-JAMA-2017.pdf (in Texas, when the distance to the nearest abortion clinic increased by 25–49 miles, abortions decreased 25.3%; when the change was 50–99 miles, abortions decreased by 35.7%; and when the change was 100 miles or more, abortions decreased by 50.3%); Sharon A. Dobie et al., *Abortion Services in Rural Washington State, 1983–1984 to 1993–1994: Availability and Outcomes*, 31 Fam. Plan. Persp. 241, 241–44 (1999), https://www.guttmacher.org/sites/default/files/article_files/3124199.pdf (in Washington, when a decline in the number of abortion providers led to a 12 mile increase in travel distance for rural women, the abortion rate among that population decreased by 27%); Robert W. Brown et al., *Provider Availability, Race, and Abortion Demand*, 67 Southern Eco. J. 656, 658 (2001) (in Texas, an increase of 10% in the travel distance from a woman's county to the nearest city with an abortion provider was associated with a 2.3% decline in the abortion rate for white women, 2.7% for African-American women, and 5.0% for Hispanic women); James D. Shelton et al., *Abortion Utilization: Does Travel Distance Matter?*, 8 Fam. Plan. Persp. 260, 260–62 (1976), https://jstor.org/stable/pdf/2134397.pdf?seq=1#page_scan_tab_contents (in Georgia, for every 10 miles of distance from the major abortion providers in Atlanta, the number of abortions declined by 6.7 per 1,000 live births); Alison H. Norris et al., *Abortion Access in Ohio's Changing Legislative Context, 2010–2018*, 110 Am. J. Pub Health 1228, 1232 (2020), https://pubmed.ncbi nlm nih.gov/32437269/ (abortion rate in rural counties disproportionately affected by clinic closures decreased more than 30% over study period); Ushma D. Upadhyay et al., *Denial of Abortion Because of Provider Gestational Age Limits in the United States*, Am. J. Pub. Health 1687, 1689 (2014), https://doi.org/10.2105/AJPH.2013.301378 (finding that 58.3% of patients turned away because they were beyond the abortion clinic's limit and 67% arriving just before the limit attributed their delay to "travel and procedure costs" and 29.8% cited "not knowing how to get to a provider"; for first trimester patients, travel and procedure cost was the second-most cited reason for delay).

[41] 21 U.S.C. 355-1(f)(2)(C)(ii).

[42] Daniels et al., *supra* n.29.

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Original Research Article

Obstetrician-gynecologist willingness to provide medication abortion with removal of the in-person dispensing requirement for mifepristone

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ABSTRACT

Objective: To estimate obstetrician-gynecologists' (ob-gyns) willingness to provide medication abortion if the in-person dispensing requirement for mifepristone were removed.
Study design: We analyzed a subsample (n = 868) from a 2016 to 2017 national survey of ob-gyns, focusing on questions related to provision of medication abortion.
Results: In the survey, 164 (19%) ob-gyns reported providing medication abortion in the prior year. When we asked those not providing medication abortion if they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed, 171 (24%) ob-gyns reported they would, suggesting a potential doubling of providers (+104%, 95% confidence interval (CI): 97%–112%). The largest theoretical increases were in the Midwest (+189%, 95% CI: 172%–207%) and South (+118%, 95% CI: 103%–134%). In multivariable regression analysis, female ob-gyns and those in university faculty practices had higher odds of reporting they would start providing medication abortion if the dispensing requirement were removed, while those in practice >10 years had lower odds.
Conclusions: Removal of the in-person dispensing requirement could increase provision of medication abortion, including in regions with limited abortion access.
Implications: In order to improve access to medication abortion, the mifepristone Risk Evaluation and Mitigation Strategy should be modified or removed to allow clinicians to prescribe the medication with dispensing by pharmacies, including mail-order pharmacies.

1. Introduction

Medication abortions have been steadily increasing in recent years, accounting for nearly 40% of abortions in the United States [1]. However, access to timely abortion care is hampered by various state and federal policies, including the Food and Drug Administration's Risk Evaluation and Mitigation Strategy (FDA REMS) for mifepristone, the primary drug used for medication abortion [2]. The mifepristone REMS requires the drug be dispensed directly to the patient, by a certified provider in a clinic, medical office, or hospital [2]. As such, clinicians who want to provide medication abortions must stock the drug in their practice, adding up-front costs and administrative burdens to clinics [3,4]. This requirement may be particularly burdensome to patients in the Midwest, South, and in rural areas because those regions have a limited number of abortion providers [5].

Obstetrician-gynecologists (ob-gyns) are well situated to provide timely abortion care as they may be the first clinicians to confirm an unintended pregnancy. A national survey of ob-gyns from 2016 to 2017 found that 72% had a patient in the prior year who needed or wanted an abortion; however, only 24% provided abortion care in their practice [4]. The survey also found that the mifepristone in-person dispensing requirement was a barrier to provision [4]. The purpose of this analysis was to explore physician and practice setting characteristics associated with willingness

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to provide abortion with removal of the in-person dispensing requirement.

2. Materials and methods

We used data from a cross-sectional survey conducted between August 2016 and March 2017 of a national sample of practicing ob-gyns, which we have previously described [4,6]. We invited 2500 Fellows and Junior Fellows of the American College of Obstetricians and Gynecologists (ACOG) to respond to an online survey on "selected ob-gyn practices." The sample included 1,000 members of a demographically representative research network of practicing ACOG members (the Collaborative Ambulatory Research Network) and 1500 non-network members selected using a proportionate stratified sample by geographic distribution using ACOG districts. Of note, the prior published national analysis of ob-gyn medication abortion provision focused only on the research network sample [4].

For this analysis, our primary outcome measure examined willingness to provide medication abortions if the mifepristone in-person dispensing requirement were not in place. Specifically, respondents who reported having patients seeking abortion care in the prior year but had not performed medication abortions were asked: "Currently, if you want to provide medical abortion, you must stock the medications in your office. Would you offer medical abortion to your patients if you could write a prescription for mifepristone and misoprostol, and your patient could obtain both medications at a pharmacy?" Response options were "yes," "no," and "not sure."

We limited our analyses to ob-gyns who reported they "had any patients in the last 12 months who wanted or needed an abortion or termination of pregnancy." We calculated abortion provision in the previous year by physician characteristics (age, gender, race and ethnicity, years in practice, and research network membership) and practice characteristics (region, practice setting, and practice location). We estimated willingness to provide medication abortion among those that did not provide medication abortion in the previous year, as well as the theoretical percent increase in medication abortion provision if the in-person dispensing requirement were removed. We performed bivariable and multivariable logistic regression of willingness to provide medication by physician and practice characteristics among all respondents that did not provide medication abortion in the previous year, including those that did not respond to the willingness question. We present adjusted odds ratios (aOR) and 95% confidence intervals (CI) by practice characteristics adjusting for gender and years in practice. We removed age group from our model as it was collinear with practice years and included all variables from the bivariate analyses that had a p-value <0.20. Reference category was selected based on sample sizes or meaningful comparison groups. To assess generalizability of our findings, we conducted a sensitivity analysis by limiting our sample to the demographically representative research network. We performed statistical analysis using Stata 16 (StataCorp LP, College Station, TX). The Allendale Investigational Review Board approved this study. We provided additional information on sample design and study procedures, as well as variables for physician and practice setting characteristics, in previous publications [4,6,7].

3. Results

Our final sample of 1,280 respondents (52% response rate; 62% for research network members vs. 42% for non-network members) was restricted further to respondents who reported having abortion-seeking patients in the last 12 months ($n = 868$, 68% of sample). Among those, 31% ($n = 267$) provided abortion in the past year, including 19% ($n = 164$) who provided medication abortion (Table 1). Among the 704 ob-gyns that did not provide medication abortion in the previous year, 24% ($n = 171$) reported that they would provide medication abortions if they could write a prescription for mifepristone and misoprostol, and their patient could obtain both medications at a pharmacy. The additional 171 ob-gyns expressing willingness to provide medication abortion if the in-person dispensing requirement were removed represents a potential doubling (+104%, 95% CI: 97%–112%) of the number of medication abortion providers from the existing 164. The largest theoretical increases in ob-gyns providing medication abortion were in the Midwest (+189%, 95% CI: 172%–207%) and South (+118%, 95% CI: 103%–134%) (Table 1). In the multivariable logistic regression, female ob-gyns, those working in a university faculty or "other" practice (compared to in a partnership or group), and those who were members of the research network who did not provide medication abortion in the past year had higher odds of reporting they would provide the method if the mifepristone in-person dispensing requirement were removed; those who had been in practice >10 years (compared to those in practice ≤ 10 years) had lower odds of reporting they would start providing (see Table 2). A sensitivity analysis including only the research network sample yielded results that were consistent with our primary analysis (data not shown).

4. Discussion

This analysis indicates that provision of medication abortion by ob-gyns would increase if the in-person dispensing requirement for mifepristone were removed, and this increase would be seen across all regions of the country and in all practice settings. Ob-gyns in the Midwest, South, and West were just as likely as those in the Northeast to report willingness to start providing medication abortion if the dispensing requirement were removed. This finding is notable given that ob-gyns in the Midwest and South were significantly less likely to currently provide abortion compared to those in the Northeast [4]. In fact, the largest theoretical increases in ob-gyn medication abortion providers were seen in the Midwest and South.

It is important to note that an additional 22% ($n = 155$) of those who had abortion-seeking patients but did not provide medication abortion indicated that they were "not sure" if they would offer medication abortion if the dispensing requirement were removed. As such, it is possible that we have underestimated the theoretical increase in medication abortion provision.

This analysis has several limitations. Our primary outcome is based on a hypothetical question and may not reflect actual practice if the policy were changed. Our unweighted findings and nonresponse bias may limit generalizability. In addition, the survey was conducted in 2016 to 2017, and physician perspectives may have changed over time. In particular, the COVID-19 pandemic has seen a marked increase in telemedicine [8], and ob-gyns might be more interested in providing medication abortion without an in-person visit. Alternatively, ob-gyns focused on providing their usual care during the pandemic may be less willing to introduce a new service in the near future, even if the dispensing requirement were removed.

The in-person dispensing requirement for mifepristone codified in the drug's REMS is a barrier to clinician provision of the method. Removing this requirement could increase the number of medication abortion providers across the country, including in settings with limited access.

Declaration of Competing Interest

The authors declare no conflict of interest.

Table 1
Characteristics of obstetrician-gynecologists by abortion provision in the prior year and willingness to provide medication abortion with removal of the in-person dispensing requirement for mifepristone

Characteristics	Total[a] n (%)	Provided abortion in past year n (%)	Provided medication abortion in past year n (%)	Would provide medication abortion with removal of in-person dispensing requirement for mifepristone, among those who did not provide medication abortion in past year. (n=704)[b], n (%)			Theoretical percent increase in medication abortion provision if in-person dispensing requirement were removed[c] (95% CI)
				Yes	No	Not sure	
Total	868 (100)	267 (31)	164 (18.9)	171 (24)	325 (46)	155 (22)	104 (97–112)
Physician characteristics							
Age							
30–45	266 (31)	86 (33)	53 (33)	69 (35)	69 (35)	60 (30)	
46–60	402 (47)	112 (43)	67 (42)	74 (24)	173 (57)	57 (19)	
61 or older	191 (22)	65 (28)	41 (25)	26 (16)	80 (56)	37 (26)	
Gender							
Male	304 (35)	87 (33)	51 (32)	41 (18)	143 (62)	48 (21)	
Female	555 (65)	175 (67)	109 (68)	128 (31)	181 (44)	105 (25)	
Race and ethnicity							
Asian-Pacific Islander, non-Hispanic	70 (8)	10 (11)	18 (11)	18 (36)	22 (44)	10 (20)	
Black, non-Hispanic	37 (4)	10 (4)	7 (4)	5 (17)	12 (41)	12 (41)	
Hispanic	44 (5)	11 (4)	8 (5)	8 (24)	20 (62)	5 (15)	
White, non-Hispanic	665 (77)	198 (75)	119 (74)	128 (25)	258 (51)	119 (24)	
Other, non-Hispanic	44 (5)	15 (6)	9 (6)	10 (32)	13 (42)	8 (26)	
Years in practice							
1-10	185 (23)	65 (26)	39 (25)	53 (40)	38 (29)	42 (32)	
11-20	266 (33)	79 (31)	50 (32)	48 (24)	109 (55)	41 (21)	
21 or more	358 (44)	108 (43)	66 (43)	60 (22)	150 (55)	61 (23)	
Collaborative Ambulatory Research Network member							
Yes	469 (54)	141 (53)	86 (52)	104 (28)	181 (50)	75 (26)	
No	399 (46)	126 (47)	78 (48)	67 (23)	144 (50)	80 (22)	
Practice characteristics							
Region							
Northeast	179 (21)	81 (31)	47 (29)	34 (28)	58 (48)	30 (25)	72 (57–88)
Midwest	198 (23)	35 (13)	19 (12)	36 (21)	88 (52)	46 (27)	189 (172–207)
South	256 (30)	58 (22)	38 (24)	45 (23)	113 (56)	41 (21)	118 (103–134)
West	219 (26)	87 (33)	56 (35)	53 (36)	60 (41)	35 (24)	95 (81–108)
Practice setting							
Solo private practice	107 (12)	30 (11)	21 (13)	14 (18)	46 (57)	20 (25)	67 (44–90)
Partnership or group	482 (56)	128 (48)	74 (48)	83 (22)	197 (52)	97 (26)	112 (101–123)
HMO/staff model	69 (8)	21 (8)	15 (9)	9 (19)	27 (57)	11 (23)	60 (33–87)
University faculty practice	184 (21)	79 (30)	49 (30)	56 (44)	46 (36)	25 (20)	114 (101–128)
Other	22 (3)	6 (2)	3 (2)	9 (50)	8 (44)	1 (6)	300 (265–335)
Practice location							
Urban inner city	179 (28)	76 (29)	49 (30)	48 (41)	53 (46)	15 (13)	98 (84–112)
Urban non inner city	254 (29)	85 (32)	53 (33)	56 (30)	89 (48)	41 (22)	106 (92–119)
Suburban	271 (31)	70 (26)	38 (23)	41 (19)	110 (51)	65 (30)	108 (92–123)
Midsize town, rural, or military	161 (19)	34 (13)	23 (14)	26 (20)	72 (55)	33 (25)	113 (93–133)

Note: Percentages may not add to 100% because of rounding or missing values. First 3 columns show column percentages, and the next 3 columns show row percentages.

[a] Sample is restricted to those who had any patients in the prior year who wanted or needed an abortion or termination of pregnancy.

[b] Sample further restricted to those who did not provide medication abortions in the past year (n = 704). Willingness to provide abortion with removal of in-person dispensing requirement for mifepristone is based on the following question "Would you offer medical abortion to your patients if you could write a prescription for mifepristone and misoprostol, and your patient could obtain both medications at a pharmacy?" Cross-tabulations exclude 53 (8%) survey respondents that did not respond to this question.

[c] Percentage increase in medication abortion provision if in-person dispensing requirement were removed is the number of ob-gyns willing to provide with removal of the in-person dispensing requirement divided by the number who provided medication abortion in the past year.

Table 2
Bivariable and multivariable logistic regression analysis of willingness to provide medication abortion with removal of the in-person dispensing requirement for mifepristone among those that did not provide medication abortion in the past year, by practice characteristics (n = 704)[a]

Characteristics	Crude OR (95% CI)	Adjusted OR[b](95% CI)
Physician characteristics		
Age		
30–45	1.00	
46–60	**0.59 (0.40–0.87)**[d]	Not included
61 or older	**0.44 (0.26–0.73)**[d]	
Gender		
Male	1.00	1.00
Female	**2.08 (1.41–3.08)**[e]	**1.60 (1.01–2.53)**[c]
Race and ethnicity		
Asian-Pacific Islander, non-Hispanic	1.73 (0.94–3.16)	
Black, non-Hispanic	0.65 (0.25–1.74)	
Hispanic	0.93 (0.41–2.10)	Not included
White, non-Hispanic	1.00	
Other, non-Hispanic	1.31 (0.61–2.79)	
Years in practice		
1–10	1.00	1.00
11–20	**0.50 (0.31–0.80)**[d]	**0.45 (0.27–0.76)**[d]
21 or more	**0.45 (0.29–0.71)**[e]	**0.46 (0.27–0.78)**[d]
Collaborative Ambulatory Research Network member		
Yes	1.41 (0.99–2.01)	**1.63 (1.08–2.47)**[c]
No	1.00	1.00
Practice characteristics		
Region		
Northeast	1.00	1.00
Midwest	0.72 (0.43–1.24)	0.78 (0.42–1.43)
South	0.75 (0.45–1.25)	0.75 (0.42–1.35)
West	1.39 (0.83–2.31)	1.65 (0.91–2.99)
Practice setting		
Solo private practice	0.76 (0.41–1.42)	0.91 (0.45–1.85)
Partnership or group	1.00	1.00
HMO/staff model	0.78 (0.37–1.67)	0.70 (0.31–1.58)
University faculty practice	**2.78 (1.83–4.22)**[e]	**2.43 (1.45–4.08)**[d]
Other	**2.52 (1.39–8.95)**[d]	**2.71 (1.00–7.36)**[c]
Practice location		
Urban inner city	**2.52 (1.45–4.40)**[d]	1.67 (0.86–3.26)
Urban non inner city	1.66 (0.98–2.82)	1.34 (0.74–2.43)
Suburban	0.92 (0.53–1.58)	0.96 (0.53–1.72)
Midsize town, rural, or military	1.00	1.00

[a] Sample is restricted to those who had any patients in the prior year who wanted or needed an abortion or termination of pregnancy. Includes all respondents that did not provide medication abortion in the past year, including those that responded, "Not Sure" (n = 155, 22%) and those that did not respond to this question (n = 53, 8%).
[b] Final model includes gender, practice years, and practice setting characteristics.
[c] $p < 0.05$
[d] $p < 0.01$.
[e] $p < 0.001$.

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Center for Drug Evaluation and Research (CDER)

(b) (6)

Application Type	NDA and ANDA
Application Number	020687 and 91178
Reviewer Names	(b) (6)
(b) (6)	(b) (6)
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Review Completion Date	December 16, 2021

Subject	REMS Modification Rationale Review
Established Name	Mifepristone REMS
Name of Applicants	Danco Laboratories, LLC and GenBioPro, Inc.
Therapeutic Class	Progestin antagonist
Formulation	Oral tablets

Table of Contents

EXECUTIVE SUMMARY

This review provides the [redacted] rationale and conclusions regarding modifications to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178.

ANDA 91178 was approved with the approval of the Mifepristone REMS Program on April 11, 2019 to mitigate the risk of serious complications associated with mifepristone 200 mg. The most recent REMS modification was approved on May 14, 2021. The REMS consists of elements to assure safe use (ETASU) under ETASU A, C and D, an implementation system, and a timetable for submission of assessments. To determine whether a modification to the REMS was warranted, FDA undertook a comprehensive review of the published literature; safety information collected during the COVID-19 public health emergency (PHE); the one-year REMS assessment report of the Mifepristone REMS Program; adverse event data; and information provided by advocacy groups, individuals and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation discussed below.

The modifications to the REMS will consist of:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to here as the "in-person dispensing requirement" for brevity)
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified

A REMS Modification Notification letter will be sent to both Applicants in the Single Shared System.

1. Introduction

In connection with the *Chelius v. Becerra* litigation, FDA agreed to undertake a full review of the Mifepristone REMS Program, in accordance with the REMS assessment provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act).[a] This review provides the analysis of the (b) (6) ((b) (6) and the (b) (6) ((b) (6) regarding whether any changes are warranted to the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone (hereafter referred to as the Mifepristone REMS Program) for new drug application (NDA) 20687 and abbreviated new drug application (ANDA) 91178. The Mifeprex REMS was initially approved in 2011; the single, shared system REMS for mifepristone 200 mg, known as the Mifepristone REMS Program, was approved in 2019.

The last time the existing REMS elements to assure safe use (under ETASU A, C and D) were reviewed was in the context of our review of supplement S-020 to NDA 20687; these ETASU were updated following review and approval of supplement S-020 on March 29, 2016. The key changes approved in 2016 are summarized below.

Changes to labeling included:

- Changing the dosing of Mifeprex to 200 mg orally x 1
- Extension of maximum gestational age through 70 days
- Inclusion of misoprostol in the indication statement
- Replacing the term “physician” with “licensed healthcare provider”
- Removal of the phrase “Under Federal Law”

The Mifeprex REMS and REMS materials were updated to reflect the changes above, and additional changes were made including:

- Removing the Medication Guide as part of the REMS but retaining it as part of labeling.

2. Background

2.1. PRODUCT AND REMS INFORMATION

[a] Section 505-1(g)(2) of the FD&C Act (21 U.S.C. § 355-1(g)(2)).

Mifepristone is a progestin antagonist indicated, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy (IUP) through 70 days gestation. Mifepristone is available as 200 mg tablets for oral use.

Mifeprex (mifepristone) was approved on September 28, 2000 with a restricted distribution program under 21 CFR 314.520 (subpart H)[b] to ensure that the benefits of the drug outweighed the risk of serious complications associated with mifepristone when used for medical abortion. Mifeprex was deemed to have a REMS under section 505-1 of the Federal Food, Drug, and Cosmetic Act with the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the Mifeprex REMS was approved on June 8, 2011. On March 29, 2016, as noted above, a supplemental application and REMS modification was approved for Mifeprex. On April 11, 2019, ANDA 091178 was approved, and the Mifepristone REMS Program was approved. The Mifepristone REMS Program is a single, shared system REMS that includes NDA 020687 and ANDA 91178.

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

a. Requiring healthcare providers who prescribe mifepristone to be certified in the Mifepristone REMS Program (under ETASU A).
b. Ensuring that mifepristone is only dispensed in certain healthcare settings, by or under the supervision of a certified prescriber (under ETASU C).
c. Informing patients about the risk of serious complications associated with mifepristone (under ETASU D).

Under ETASU A, to become specially certified to prescribe mifepristone, a healthcare provider must review the prescribing information, complete and sign the *Prescriber Agreement Form,* and follow the guidelines for use of mifepristone. Under ETASU C, mifepristone must be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. Under ETASU D, mifepristone must be dispensed to patients with evidence or other documentation of safe use conditions (i.e., the patient must sign a *Patient Agreement Form*). The Mifepristone REMS Program also includes an implementation system, and a timetable for assessments (one year from the date of the initial approval of the REMS on April 11, 2019, and every three years thereafter).

[b] NDA approval letter Mifeprex (NDA 020687) dated September 28, 2000.

2.2. REGULATORY HISTORY AND EVENTS RELEVANT TO THIS REMS MODIFICATION RATIONALE REVIEW

The following is a summary of significant regulatory history since approval of the REMS modification on March 29, 2016:

- 03/29/2016: FDA approved an efficacy supplement (S-020) that, among other things, provided a new dosing regimen (200 mg mifepristone, followed in 24 to 48 hours by 800 mcg buccal misoprostol), increased the gestational age (GA) to which mifepristone may be used (through 70 days gestation), and modified the REMS.

- 03/29/2019: A Citizen Petition was received requesting that FDA revise the product labeling to reflect pre-2016 provisions (including limiting GA to 49 days and requiring patients to make 3 office visits) and that FDA maintain the REMS.

- 04/11/2019: ANDA 91178 was approved along with the Single Shared System REMS for Mifepristone 200 mg (Mifepristone REMS Program) for NDA 20687 and ANDA 91178.

- 01/31/2020: the COVID-19 public health emergency (PHE) was declared by the Secretary of Health and Human Services (HHS) as having existed since January 27, 2020.[c]

- 7/13/2020: The United States (US) District Court of Maryland granted a preliminary injunction in the *ACOG v. FDA* litigation to temporarily bar enforcement of the Mifepristone REMS Program in-person dispensing requirement during the COVID-19 PHE.

- 1/12/2021: US Supreme Court granted a stay of that injunction.

- 04/12/2021: FDA issued a General Advice Letter to both the NDA and ANDA Applicants, stating that provided that all other requirements of the Mifepristone REMS Program are met, and given that in-person dispensing of mifepristone for medical termination of early pregnancy may present additional COVID-related risks to patients and healthcare

[c] *See* Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued January 31, 2020, and subsequently renewed), available at https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx

personnel because it may involve a clinical visit solely for this purpose, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the in-person dispensing requirement in the Mifepristone REMS Program, including any in-person requirements that may be related to the *Patient Agreement Form.* FDA further stated that to the extent all of the other requirements of the Mifepristone REMS Program are met, FDA intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of mifepristone through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

- 05/07/2021: FDA stated that it would be reviewing the elements of the Mifepristone REMS Program in accordance with the REMS assessment provisions of section 505-1 of the FD&C Act.

- 05/14/2021: A modification was approved for the Mifepristone REMS Program. This modification was to revise the *Patient Agreement Form* to include gender-neutral language.

- 06/30/2021: An Information Request (IR) was sent to the Applicants for additional information on shipments and any program deviations, adverse events, or noncompliance with the REMS that occurred during the period from April 1, 2021 through September 30, 2021.

- 7/15/2021: An IR was sent to the Applicants to provide the total number of shipments during the period from April 1, 2021 to September 30, 2021 and details on whether any of those shipments were involved in any program deviation or non-compliance.

- 8/5/2021: An IR was sent to the Applicants for additional clinical and other information (e.g., adverse events and units of mifepristone shipped) for the period of March 29, 2016 through June 30, 2021, to be provided by August 31, 2021. This IR also requested information covering the period of July 1, 2021 through September 30, 2021 and an

aggregate summary (for the period of March 29, 2016 through September 30, 2021), to be provided by October 12, 2021.[d]

- 8/26/2021: The ANDA Applicant submitted a response to the IR issued on 8/5/2021.
- 08/27/2021: The NDA Applicant submitted a response to the IR issued on 8/5/2021.
- 10/08/2021: The NDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR. The NDA Applicant also included a follow-up to their initial response provided on August 27, 2021 to the August 5, 2021 IR.
- 10/12/2021: The ANDA Applicant submitted a response to the June 30 and July 15, 2021 IRs as well as an aggregate summary for the period March 29, 2016 through September 30, 2021 in response to the August 5, 2021 IR.
- 10/16/2021: The ANDA Applicant revised their Oct 12, 2012 response to provide a correction to the number of mifepristone tablets.
- (b) (4) .
- 11/02/2021: A (b) (6) ((b) (6) meeting was convened to obtain CDER concurrence on the removal of the in-person dispensing requirement and the addition of a certification requirement for pharmacies. The (b) (6) (b) (6) and senior CDER leadership concurred with removing the in-person dispensing and adding pharmacy certification.

3. Rationale for Proposed REMS Modification

[d] Multiple Information Requests were issued to obtain additional information on drug shipments, any program deviations or noncompliance, and use of alternative methods for drug distribution during the COVID-19 PHE. These IRs are referenced as appropriate in this document and the one-year REMS Assessment Review of the Mifepristone REMS Program, December 16, 2021.

3.1. CURRENT REQUIREMENTS FOR THE APPROVED REMS

The Mifepristone REMS Program includes elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. Elements to assure safe use in the current REMS include a prescriber certification requirement (ETASU A), a requirement that mifepristone be dispensed only in certain healthcare settings by or under the supervision of a certified prescriber (ETASU C), and a requirement that mifepristone be dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions under ETASU D consists of a *Patient Agreement Form* between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with mifepristone 200 mg for medical termination of early pregnancy.

3.2. EVALUATION OF THE EVIDENCE

We reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Applicants. Our review also included an examination of literature references provided by plaintiffs in the *Chelius v. Becerra* litigation. Below is an overview of how information relevant to the current Mifepristone REMS Program was retrieved, analyzed, and applied to each of the individual ETASUs to determine if further changes should be considered.

Methods for the literature search

(b) (6) conducted a literature search in PubMed and Embase to retrieve publications relevant to this review. The time period used for this literature search was between March 29, 2016 (when the Mifeprex labeling and REMS were last substantially revised) through July 26, 2021. The search terms used were “medical abortion” and “mifepristone” and “pregnancy termination and mifepristone.”

The search retrieved 306 publications from PubMed and 613 from Embase, respectively; the search yielded 646 unique publications after eliminating duplications between the two databases. The result of our literature search was also supplemented by an examination of literature references provided by advocacy groups, individuals, plaintiffs in the *Chelius* litigation, and the Applicants, as well as letters from healthcare providers and researchers.

References included in these letters were considered for inclusion in this review using identical selection criteria to the (b) (6) literature search (outlined below).

For this review of the REMS, (b) (6) focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS ETASUs. We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion. The following are examples of materials that were excluded from our literature search:

- Information from survey studies or qualitative studies that evaluated perspectives on and/or satisfaction with medical abortion procedures from patients, pharmacists, clinic staff, or providers, even if the study assessed REMS ETASUs. These surveys or qualitative studies did not include objective safety data related to outcomes of medical abortion.

- Opinions, commentaries, or policy/advocacy statements. These publications did not include objective safety data related to outcomes of medical abortion.

- Safety data related to mifepristone use for second trimester medical abortion. These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data related to mifepristone use for spontaneous first trimester abortion (i.e., miscarriages). These publications reported data not applicable to the approved indication for medical abortion up to 70 days gestation.

- Safety data that pertained only to surgical abortion or did not separate out medical abortion from surgical abortion.

- Other safety information unrelated to the REMS elements (e.g., articles limited to case reports or those discussing unrelated gynecologic or medical issues)

- Publications for which it was not possible to conduct a full review of the methods or results, i.e., the references were limited to an abstract of the study methods and results.

- Publications that provided only general statistics on abortion care in the United States.

- Information pertinent to molecular or other basic science aspects of mifepristone.

- Data on the logistics of accessing abortion care in general, such as time to appointment or the distance traveled to obtain care.

- Publications that provided data not related specifically to abortion care or the REMS (e.g., references focused on federal poverty guidelines, poverty data, or the financial impact of the COVID-19 pandemic).

One exception to the above literature search criteria was the inclusion in Section 3.2.2 of this review, which discusses the *Patient Agreement Form*, of publications that discussed changes in provider volume. The data discussed in relation to provider volume was obtained from surveys. This data was included because changes in provider volume could only be obtained from well-conducted survey studies.

Regarding medical/scientific references submitted with letters from the plaintiffs in the *Chelius* litigation, we applied the same criteria as for the literature search, as described above.

Letters from the plaintiffs in the *Chelius* litigation included several references that preceded our 2016 review of the REMS. Two of those pre-2016 studies were not captured in our 2016 literature search. These two studies were assessed as part of our current review; their results are consistent with the existing safety profile of the approved medical abortion regimen, and therefore, support our current conclusions regarding the REMS. See Appendix A.

3.2.1. Evaluation of the requirement for healthcare providers who prescribe the drug to be specially certified (ETASU A)

In order to become specially certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the *Prescriber Agreement Form*. In signing the *Prescriber Agreement Form*, prescribers agree they meet the qualifications listed below:

- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to

ensure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the *Patient Agreement Form* with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the *Patient Agreement Form*.
- Provide the patient with a copy of the *Patient Agreement Form* and the Medication Guide.
- Place the signed *Patient Agreement Form* in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

The literature review was the primary source of information that contributed to our reassessment of ETASU A.

We continue to be concerned that absent these provider qualifications, serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed. Our review of the literature did not identify any studies comparing providers who met these qualifications with providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention or arrange for such care through others if needed, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our review continues to support the conclusion that a healthcare provider who prescribes mifepristone should meet the above qualifications. We conclude it is reasonable to maintain the requirement for a one-time prescriber certification where prescribers attest to having the ability to diagnose an intrauterine

pregnancy, to diagnose an ectopic pregnancy,[e] and to either manage serious complications themselves or arrange for other providers to provide the needed care in a timely manner.

In addition, in signing the *Prescriber Agreement Form* and placing it in the patient's medical record, the prescribers acknowledge the requirement to report patient deaths associated with mifepristone to the manufacturer. Such a requirement ensures that the manufacturer receives all reports of patient deaths and, in turn, fulfills its regulatory obligations to report those deaths to the FDA.

As discussed in Section 3.2.2 below, there is a potential for doubling of the number of prescribers of mifepristone if the in-person dispensing requirement in ETASU C is removed from the Mifepristone REMS Program. Given the potential addition of new prescribers, in addition to the considerations described above, we conclude that we should maintain the requirement for prescriber certification, to ensure that providers meet the necessary qualifications and adhere to the guidelines for use. Our literature review supports that these requirements are still necessary, and the potential increase in new prescribers under the REMS is a further reason to maintain prescriber certification. Healthcare provider certification continues to be a necessary component of the REMS to ensure the benefits of mifepristone for medical abortion outweigh the risks. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one time for each applicant.

3.2.2. Evaluation of the requirement for the drug to be dispensed with evidence or other documentation of safe-use conditions (ETASU D)

In order to receive mifepristone for medical termination of pregnancy through 70 days gestation, the patient must sign a *Patient Agreement Form* indicating that the patient has received, read, and been provided a copy of the *Patient Agreement Form* and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The *Patient Agreement Form* ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication.

[e] American College of Obstetricians and Gynecologists (ACOG) Practice Bulleting Number 191, February 2018. Tubal Ectopic Pregnancy. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2018/03/tubal-ectopic-pregnancy. Mifepristone is not effective for terminating ectopic pregnancy. Some of the expected symptoms experienced with a medical abortion (abdominal pain, uterine bleeding) may be similar to those of a ruptured ectopic pregnancy. A missed ectopic pregnancy that ruptures is a medical emergency that requires immediate surgical intervention.

In a number of approved REMS, *Patient Agreement Forms* or *Patient Enrollment Forms* ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.[f]

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the *Patient Agreement Form* with the patient, fully explaining the risks of the treatment regimen, and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the *Patient Agreement Form*, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the *Patient Agreement Form* serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed *Patient Agreement Form* in the patient's medical record.

Prior to the March 29, 2016 approval of the S-020 efficacy supplement for Mifeprex, FDA undertook a review of all elements of the REMS. At that time, the (b) (6) ((b) (6)), along with the (b) (6) ((b) (6)), recommended removal of the *Patient Agreement Form* (ETASU D). This recommendation received concurrence from the (b) (6) on February 23, 2016. The rationale for this recommendation in the 2016 review[g] is summarized here as follows:

- The safety profile of Mifeprex is well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile has not changed over the period of surveillance.
- Established clinical practice includes patient counseling and documentation of informed consent and evidence shows that practitioners are providing appropriate patient

[f] REMS@FDA, https://www.accessdata fda.gov/scripts/cder/rems/index.cfm, Accessed November 15, 2021.
[g] (b) (6) Clinical Review, NDA 020687/S20, dated March 29, 2016. https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af803dc7bd&_afrRedirect=386175573203745

counseling and education; the *Patient Agreement Form* is duplicative of these established practices.

- Medical abortion with Mifeprex is provided by a small group of organizations and their associated providers. Their documents and guidelines are duplicated in the *Patient Agreement Form*.
- ETASUs A and C remain in place: The *Prescriber Agreement Form* and the requirement that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals under the supervision of a certified prescriber, remain in place.

In light of a memorandum from the Director of the Center for Drug Evaluation and Research, an addendum to the [redacted] (b) (6) March 29, 2016 review and a memorandum from the signatory authority in [redacted] (b) (6) indicated that the *Patient Agreement Form* would be retained in the REMS.[h,i]

The current review of literature from March 29, 2016 to July 26, 2021, is relevant to our assessment of the necessity of the *Patient Agreement Form* as part of the REMS. While our literature search yielded no publications which directly addressed this element of the REMS, we identified the following literature that focused on the informed consent process. These studies were reviewed for their potential relevance on this topic, though the articles do not directly assess the need for the *Patient Agreement Form* as a condition necessary to assure safe use of Mifepristone under ETASU D.

- Two studies[1,2] (both authored by Dr. Grossman in 2021) used the *Patient Agreement Form* and additional clinic-specific written informed consent forms as part of the study methodology. One study evaluated medical abortion with pharmacist dispensing of mifepristone and another evaluated mail-order pharmacy dispensing. Safety and efficacy outcomes were not assessed regarding the element of consent in isolation or the *Patient Agreement Form*.
- Several studies included use of electronic or verbal consent. Two studies were conducted using signed electronic consent (Chong[3], Kerestes[4]). Aiken[5] reported that patients had the option of providing consent verbally and the discussion had to be recorded in the notes. Rocca[6] described obtaining verbal informed consent from patients seeking medical abortion provided in pharmacies or government-certified

h [redacted] (b) (6) Review of proposed REMS modifications to Mifeprex. March 29, 2106.
i [redacted] (b) (6) Summary of Regulatory Action for Mifeprex. March 29, 2016.

public health facilities by auxiliary nurse midwives (ANMs) in Nepal. Outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

- A retrospective chart review (Wiebe[7]) was conducted in Canada. This study included telemedicine abortions between January 31, 2017 and January 31, 2019 and a similar group of controls seen in the clinic during the same time frame, matched by date of initial appointment. As part of the telemedicine process, patients read a consent form (not specified whether they could view an electronic version) and gave verbal consent "witnessed by the counselor". Again, outcomes were not assessed regarding the single element of consent and its role in the efficacy of medical abortion.

After review, we conclude that there are no outcome data from these studies that address the need for the *Patient Agreement Form* as a condition necessary to assure safe use of mifepristone. Nor do any of these studies provide evidence of whether the patient's informed consent has been adequately documented under the process set out in the study protocol. Therefore, these studies do not provide evidence that would support removing ETASU D.

Although (b) (6) agrees that informed consent in medicine is an established practice, the National Abortion Federation's 2020 Clinical Policy Guidelines for Abortion Care[8] continue to include a detailed section on patient education, counseling, and informed consent. The guidelines state that these steps are essential parts of the abortion process; that they should be conducted by appropriate personnel, with accurate information, including about alternatives and potential risks and benefits; and that the patients must have an opportunity to have any questions answered to their satisfaction prior to any intervention. Under these guidelines, documentation must show that the patient affirms that they understand all the information provided and that the decision to undergo an abortion is voluntary. The guidelines specifically list the risks that must be addressed at a minimum, including those pertinent to medical abortion: hemorrhage, infection, continuing pregnancy, and death. Additionally, Practice Bulletins from ACOG[9] and the Society of Family Planning also support detailed patient counseling.

In addition, trends in US clinical practice are developing which could negatively impact adequate patient counseling about the risks of medical abortion. One survey by Jones 2017[10] of abortion providers in the United States and Canada prior to the COVID-19 pandemic did reveal strong adherence to evidence-based guidelines. However, this same survey noted continued increasing uptake of medical abortion by US providers. Grossman[11] conducted a US survey in

2019 which suggested that the number of obstetrician/gynecologists providing medical abortion care may be increasing and that uptake might increase if mifepristone were dispensed by pharmacies instead of being dispensed in-person. A subsequent survey of US obstetricians/ gynecologists by Daniel in 2021[12] evaluated a subsample (n = 868) from a prior national survey of providers and found that 164 (19%) reported providing medical abortion in the previous year. Of those obstetrician/gynecologists not providing medical abortion, 171 (24%) said they would offer the method to their patients if the in-person dispensing requirement for mifepristone were removed. This indicates a potential doubling of providers (+ 104%, 95% confidence interval (CI): 97% −112%). There were geographical variations, with the largest potential increases being in the Midwest (+ 189%, 95% CI: 172% −207%) and the South (+ 118%, 95% CI: 103% −134%).

Based on the articles discussed above, removal of the in-person dispensing requirement from the Mifepristone REMS Program (as discussed below in section 3.2.3) could significantly increase the number of providers to a larger group of practitioners. The *Patient Agreement Form* is an important part of standardizing the medication information on the use of mifepristone that prescribers communicate to their patients, and also provides the information in a brief and understandable format for patients. The requirement to counsel the patient, to provide the patient with the *Patient Agreement Form*, and to have the healthcare provider and patient sign the *Patient Agreement Form*, ensures that each provider, including new providers, informs each patient of the appropriate use of mifepristone, risks associated with treatment, and what to do if the patient experiences symptoms that may require emergency care. The single-page *Patient Agreement Form* is in line with other elements of this REMS, in that it supports the requirement that certified prescribers be able to accurately assess a patient, counsel a patient appropriately and recognize and manage potential complications. The form is placed in the patient's medical record to document the patient's acknowledgment of receiving the information from the prescriber and a copy is provided to the patient. We determined, consistent with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients, and that the *Patient Agreement Form* remains necessary to assure the safe use of Mifepristone.

After considering potential burden on healthcare providers and patients and considering the available data discussed above, including the potential for increased prescribing of mifepristone if in-patient dispensing is removed from the REMS, we conclude that the *Patient Agreement Form* should remain a safe use condition in the REMS.

3.2.3. Evaluation of the requirement for drug to be dispensed only in certain healthcare settings (ETASU C)

Mifepristone applicants must ensure that mifepristone is available to be dispensed to patients only in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber. This creates what we refer to in this document as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office or hospital when the drug is dispensed. The mifepristone REMS document states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than these.

The following information contributed to our analysis of this requirement: Mifepristone REMS Program year-one assessment data, postmarketing safety information and literature review.

REMS Assessment Data

Reporting period for the Mifepristone REMS Program - April 11, 2019 through February 29, 2020

We evaluated information included in the one-year (1st)[j] REMS assessment reports for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, compliance data, audit results and patient exposure data.[13] The assessment reports were submitted on April 10, 2020 by the NDA Applicant and April 15, 2020 by the ANDA Applicant and cover a reporting period from April 11, 2019 through February 29, 2020. During this reporting period, the NDA Applicant reported (b) (4) newly certified healthcare providers, and the ANDA Applicant reported (b) (4) newly certified healthcare providers in the Mifepristone REMS Program. The NDA Applicant reported a total of (b) (4) certified healthcare providers (includes new and previously certified) ordered mifepristone during the assessment reporting period, and the ANDA Applicant reported a total of (b) (4) certified healthcare providers ordered mifepristone during the assessment reporting period. The NDA Applicant estimated that a total of (b) (4) patients were exposed to mifepristone during the assessment reporting period. The ANDA Applicant reported an estimated total of (b) (4) patients were exposed to mifepristone during the reporting period.

During the reporting period, a small number of non-compliance events were reported. The authorized distributor for the NDA applicant reported to the NDA Applicant that they experienced deviations with scanning of the product serial numbers which were confirmed during the February 2020 audit. The authorized distributor conducted a root cause analysis and developed a corrective and preventive action (CAPA) on February 12, 2020. The CAPA was

[j] This REMS assessment report was the first to be submitted following the approval of the single, shared system REMS for mifepristone.

validated and deployed with monitoring of the system through April 10, 2020. The corrective action will prevent similar events from occurring in the future.

January 27, 2020 through September 30, 2021

During the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not being enforced.

- On July 13, 2020, the United States District Court for the District of Maryland granted a preliminary injunction in the *ACOG* case to temporarily bar enforcement of the in-person dispensing requirement during the COVID-19 PHE.
- On January 12, 2021, the United States Supreme Court issued a stay of the injunction.
- On April 12, 2021, the FDA issued a General Advice Letter informing the applicants of the Agency's intent to exercise enforcement discretion during the COVID-19 public health emergency regarding the in-person dispensing requirement in the Mifepristone REMS Program.[k,l]

To better understand whether there was any impact on safety or noncompliance during the periods when the in-person dispensing requirement was not being enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or noncompliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. As part of an additional request for information for the REMS assessment report, the Applicants were also asked to submit the adverse events to FAERS and to notify FDA that the reports were submitted.

Between January 27, 2020 and September 30, 2021, the NDA Applicant distributed (b) (4) shipments representing (b) (4) tablets. The NDA Applicant reported that there were (b) (4) shipments representing a total of (b) (4) tablets sent to (b) (4) non-certified healthcare providers.[m,n] (b) (4) of these healthcare providers subsequently became certified while (b) (4) did not. Of the (b) (4) healthcare providers who were not subsequently certified, (b) (4) returned a total of (b) (4)

[k] FDA General Advice Letter for NDA 20687, April 12, 2021.
[l] FDA General Advice Letter for ANDA 091178, April 12, 2021.

[m] NDA 020687 September 9, 2021 response to the FDA's September 2, 2021 Information Request.
[n] NDA 020687 October 8, 2021 response to the FDA's June 30, 2021 Information Request.

Mifeprex tablets to the distributor. (b) (4) non-certified healthcare provider dispensed (b) (4) to a patient; no adverse events were reported. The NDA Applicant attributed the non-compliance observed to the authorized distributor's transition to a new platform. The NDA Applicant implemented a corrective and preventative action to address this issue, which we found to be acceptable.

The ANDA Applicant distributed (b) (4) shipments representing (b) (4) tablets of mifepristone from January 27, 2020 to September 30, 2021 and reported no instances of shipments to non-certified healthcare providers during this timeframe.

The NDA and the ANDA applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described in the section below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events. Further analysis of the adverse events is included below in the section on Pharmacovigilance Data.

Pharmacovigilance Data

The (b) (6) ((b) (6) conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy.[o,p]

The data for this time period were then further divided into date ranges when the in-person dispensing requirement was being enforced per the REMS (January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021) versus when the in-person dispensing requirement was not being enforced (July 13, 2020 - January 12, 2021 (in-person dispensing requirement was temporarily enjoined) & April 13, 2021 - September 30, 2021 (in-person dispensing requirement was not being enforced because of the COVID-19 PHE)).

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[o] (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized April 12, 2021.

[p] (b) (6). Pharmacovigilance Memorandum: Mifepristone and All Adverse Events. NDA 020687 and ANDA 091178. (b) (6) # 2007-525. Finalized December 16, 2021.

A total of eight cases that met the search criteria were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when the in-person dispensing requirement in the REMS was being enforced (i.e., January 27, 2020 - July 12, 2020 & January 13, 2021 - April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when the in-person dispensing requirement was not being enforced (i.e., July 13, 2020 - January 12, 2021 & April 13, 2021 - September 30, 2021). These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Although these adverse events occurred during the period when the in-person dispensing requirement was not being enforced, the narratives provided in the FAERS reports for cases 5, 6, and 7 explicitly stated that mifepristone was dispensed in-person. Of note, ongoing pregnancy, and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case from July 2021 reported the occurrence of oral pain/soreness (case 8) but did not provide sufficient information to determine the exact date of the adverse event. Based upon the U.S. postmarketing data reviewed, no new safety concerns were identified by (b) (6)

In addition to the FAERS data provided above, (b) (6) routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy. (b) (6) has not identified any new safety concerns with the use of mifepristone for medical termination of pregnancy.

To enable additional review of adverse events, the Applicants were requested[q] to provide a summary and analysis of adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department (ED)/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided a summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021, on August 27 and October 8, 2021. During the time period in question, (b) (4) tablets were shipped, and

[q] On August 5, 2021, an IR was sent to the Applicants requesting a summary and analysis of adverse events from March 29, 2016 through June 30, 2021 and from July 1, 2021 through September 30, 2021.

48 adverse events were received. The 48 adverse events included 4 deaths (one of which occurred in 2010 but was reported in 2017), 25 incomplete abortions requiring surgical intervention, 17 blood transfusions following heavy vaginal bleeding, 2 ectopic pregnancies, 7 infections (1 sepsis and 6 infection without sepsis), 13 hospitalizations, and 43 ED or urgent care visits related to medical abortion. For the period between January 27, 2020 and September 30, 2021, a time frame that includes the entire period when the COVID-19 public health emergency (PHE) has been in effect, there were three adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 1 (uterine/vaginal bleeding), case 2 (uterine/vaginal bleeding and sepsis), and case 4 (drug intoxication and death).

The ANDA Applicant provided a summary of postmarketing safety information from April 11, 2019 (date of ANDA approval) through September 30, 2021. On August 26, 2021, the Applicant provided distribution and adverse event information from April 11, 2019 through June 30, 2021. During this time period, a total of (b) (4) tablets were shipped. There were 7 adverse events including 3 deaths (1 from sepsis, 1 from bilateral pulmonary artery thromboemboli, 1 in a patient who complained of not being able to breathe), 1 ongoing pregnancy treated with uterine aspiration, 2 blood transfusions, 1 sepsis (with death), 1 hospitalization, and 3 ED or urgent care visits related to medical abortion. On October 12, 2021 the Applicant provided information from July 1, 2021 to September 30, 2021; there were no additional adverse events. For the period between January 27, 2020 and September 30, 2021, there were four adverse events reported corresponding to the above cases from FAERS identified by (b) (6) case 3 (ongoing pregnancy), case 5 (death unknown cause), case 6 (sepsis and death), and case 7 (pulmonary embolism).[r]

The postmarketing data from FAERS were analyzed by (b) (6) to determine if there was a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. Based on this review, we conclude that there does not appear to be a difference in adverse events between periods when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced. This suggests that mifepristone may be safely used without an in-person dispensing requirement.

[r] The eighth FAERS case, oral pain/soreness, was not within the scope of the August 5, 2021 IR and was not considered for this review of postmarketing safety information submitted by the Applicants in response to the IRs.

(b) (6) review of the Applicants' IR responses, which included the same cases identified by (b) (6) from FAERS, did not change our conclusion.[s]

Literature Review

Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or an equivalent healthcare provider in countries other than the US). Some studies have examined replacing in-person dispensing in certain health care settings with dispensing at retail pharmacies (Grossman[2], Wiebe[7], Rocca[6]) and dispensing mifepristone from pharmacies by mail (Grossman[1], Upadhyay[14], Hyland[15]). Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to women (Gynuity study [Raymond[16], Chong[3], Anger[17]], Kerestes[4], Aiken[5] (2021)) and (2) prescribers using couriered delivery of medications (Reynolds-Wright[18]). Other studies have evaluated dispensing mifepristone by mail by an entity described as "a partner organization" (Aiken[19] (2017), Norton[20], Endler[21]). For ease of review, in the sections below that describe these studies, we have separated relevant references by the methodology used to dispense mifepristone.

Retail pharmacy dispensing

Three studies report medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation. Grossman[2] conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic where the participant had an evaluation by ultrasound and counseling. Of the 266 participants enrolled, 260 had known abortion outcomes. Complete abortion without additional procedure occurred in 243 participants (93.5% of those with known outcomes). Seventeen participants (6.5% of those with known outcomes) were diagnosed with incomplete abortion and underwent uterine aspiration. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. However, the finding represents a lower-than-expected efficacy based on the cohort's GA (84% of participants were at ≤ 56 days GA, a cohort for which the labeled success rate is 96.8%). No participants experienced a serious adverse event, were hospitalized, or required transfusion. Three participants had ED visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study's

[s] The reporting period of (b) (6) assessment of the adverse events in FAERS is not identical to the time period for summaries of adverse events in the IRs to the Applicants. Therefore, the numbers of cases and adverse events summarized in (b) (6) assessment may differ from the numbers of cases and adverse events summarized by the Applicants in their responses to IRs (note that each case report may include more than one adverse event).

safety and efficacy outcomes are consistent with labeled frequencies. The majority of participants (65%) were very satisfied with the experience. There were some complaints from participants about not receiving all prescribed medications at the initial pharmacy visit, privacy not being adequately maintained, and perceived negative pharmacist attitude.

Overall, we conclude that this study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to US retail pharmacies; there is insufficient information to assess this. Rocca[6] conducted an observational study evaluating 605 participants at ≤63 days GA who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. Participants who presented to pharmacy study sites underwent clinical screening including a pelvic exam by trained nurse midwives at the pharmacy (which was equipped with an examination room) and if eligible for medical abortion, were dispensed mifepristone and misoprostol in the pharmacy at the time of their visit. Participants who presented to public health facilities underwent clinical screening including pelvic examination by abortion providers including trained nurse midwives and if eligible for medical abortion were dispensed mifepristone and misoprostol in the clinic at the time of their visit. The authors reported that, with respect to complete abortion (>97%) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,[7] in a retrospective, chart review study conducted in Canada, compared abortion outcomes of 182 women at ≤ 70 days GA who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of 199 women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (90%, calculated maintaining subjects with unknown outcomes in the denominator; ≥ 95% calculated with known outcomes only). The telemedicine group had one case of hemorrhage (0.5%) and one case of infection requiring antibiotics (0.5%) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3% compared to 1.5% in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

None of the three studies described above allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the studies to the current retail pharmacy environment in the US. The outcome findings from the one US study (Grossman[2]), in which the pharmacies were partnered with prescribers, may not be generalizable to much of the US as they do not reflect typical prescription medication availability with use of retail pharmacy dispensing. Although retail pharmacy dispensing of mifepristone and misoprostol in Canada has been described in the literature, there are important differences in healthcare systems between Canada and the US that render the findings from studies in Canada (Wiebe[7]) not generalizable to the US. In the Wiebe study, timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that allow timely access to medications for medical abortion would occur in retail pharmacies throughout the US. Canada's federal government has reaffirmed that abortion is an essential health service[t] which may have implications affecting access to medical abortion from retail pharmacies in Canada. The Rocca[6] study evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the US retail setting.

Mail order pharmacy

Grossman[1] published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. All participants were evaluated for eligibility during a clinic visit with GA up to 63 days confirmed with either an ultrasound or examination; instead of receiving medication at the clinic visit, participants received medications from a mail-order pharmacy. A total of 240 participants have been enrolled; three participants did not take either medication. A total of 227 (94.6%) provided some outcome information, of whom 224 provided abortion outcome information. Complete abortion without additional procedures occurred in 217 participants (96.9% of those with known outcomes). Two (0.9%) participants experienced serious adverse events (SAE); one received a blood transfusion, and one was hospitalized overnight. Nine (4%) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies. With respect to the time interval between a

[t] As noted in Mark[23] and Martin[24], most provincial and federal health insurance programs in Canada cover medical abortion, and covered services are free at the point of care.

participant's clinic visit and receipt of medications, of the 224 participants with known abortion outcomes, 184 (82.1%) received medication within 3 days. However, 17% received between 4-7 days and one participant waited over 7 days for receipt. Seven of 216 (3.2%) participants who completed the day-3 survey reported compromised confidentiality (e.g., someone found their medication, privacy concerns).

Upadhyay[14] reports findings from a retrospective cohort study of 141 women undergoing medical abortion in the US without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Three interactions via text, messaging or telephone occurred to confirm medication administration, assessment of expulsion and pregnancy symptoms, and results of a 4-week home pregnancy test. Abortion outcome was determined by either the day 3 assessment or the 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95% (105 participants out of 110 for whom outcomes were known) and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. Additionally, a substantial number of participants (31) provided no outcomes information. Among the 141 participants enrolled, 128 had any follow-up contact with the study staff, and 110 provided outcomes information. Excluding outcomes of 22% of the cohort is a limitation of this study. This study used a model with numerous deviations from standard provision of medical abortion in the US, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication, no confirmation of self-reported medical, surgical, and menstrual history. Further, follow-up information based on a 3-day period is insufficient to determine outcome rates or safety findings. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland[15] describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. All participants obtained screening tests including ultrasound confirmation of GA. A total of 1010 participants completed the screening process and were provided mifepristone and misoprostol. Abortion outcomes were determined for 754 (75%) of the 1010. Outcomes for the remaining 256 participants (25%) were not included because 31 provided no relevant information after shipment, 14 reported not taking misoprostol, and 211 did not have "full follow up" (i.e., known outcome of either complete medical abortion, uterine evacuation, or ongoing pregnancy with plan to continue).

Complete abortions without additional procedures occurred in 727 participants (96% of those with definitively documented outcomes) and is consistent with labeled efficacy. Of the 754 participants included in the analysis 717 (95%) had no face-to-face clinical encounters after medications were mailed while 21 (3%) were admitted to the hospital and 16 (2%) had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have "full follow up". The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. The reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported number of hospitalizations (3%) is higher than the less than 1% in the FDA-approved mifepristone labeling, conclusions regarding the safety findings in this study cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters, and not reporting outcomes of 25% of the enrolled cohort.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that the efficacy of medical abortion is maintained with mail order pharmacy dispensing. In the Grossman[1] study, the interim analysis, although small, does not raise serious safety concerns. We note that 18% of participants did not receive medications within 3 days; the potential for delay in receiving medication by mail could limit the GA eligible for medical abortion through mail order pharmacy dispensing, because women at GA closer to 70 days might not receive medication in time. A small proportion (3%) of participants raised concerns regarding the issues of confidentiality and privacy. Safety findings from the Hyland[15] study are difficult to interpret. Although only one transfusion is reported, and the authors state the findings demonstrate safety, the higher hospitalization rates, and lack of information on the reasons for hospitalization do not allow any conclusions about safety findings. Lastly, the Upadhyay[14] study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the US.

Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail.[3,4,5,16,17] Gynuity Health Projects conducted a prospective cohort study (the "TelAbortion" study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population

exclusively: Raymond[16] from May 2016 to December 2018, Chong[3] from May 2016 to September 2020 and Anger[17] from March 2020 to September 2020. Due to the pandemic, the Gynuity study deviated from the protocol requirement of confirmation of GA by examination or ultrasound for many participants treated from March 2020 onward (although none of the three publications reported on the single element of dispensing mifepristone from the healthcare setting by mail). A fourth study, Kerestes,[4] reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020: seventy-five (of whom 71 were enrolled in the Gynuity study) of the 334 participants in Kerestes were dispensed mifepristone by mail after a telemedicine consult. The section below discusses these four studies from the US as well as a large UK study by Aiken[5] (2021).

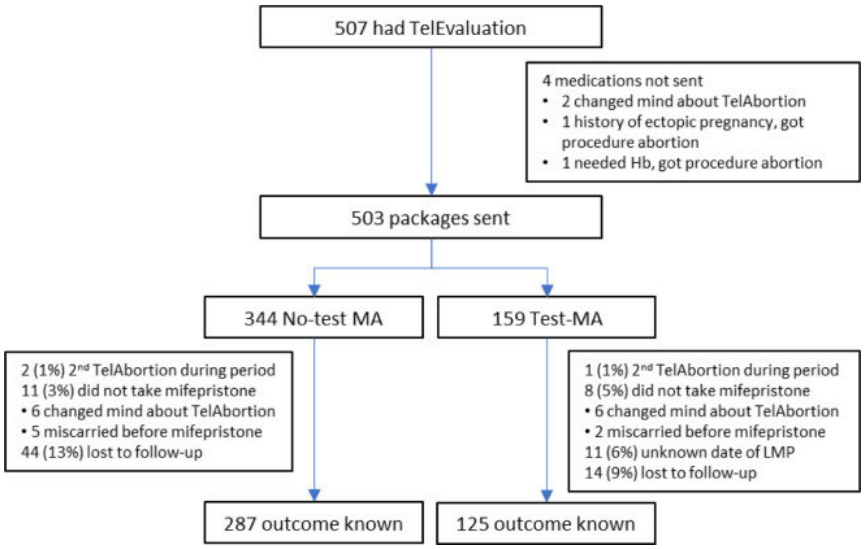
Raymond [16] (2019) reported outcomes from the Gynuity study prior to the pandemic. In the TelAbortion study, participants were not required to have an in-person clinic visit; rather, they obtained screening tests at laboratories and radiology offices and then communicated with the abortion provider by videoconference. If the participant was eligible for treatment, the provider dispensed the medications by mail. Of 433 women screened, 165 (38%) either declined to schedule the videoconference or did not keep the videoconference appointment. Among the 268 participants evaluated via videoconference, medication packages were sent to 248. Abortion outcomes were determined for 190 (77%) of the 248; outcomes for 58 (23%) participants were unknown. Complete abortion without additional procedures occurred in 177 participants (93% of those with known outcomes). The investigators obtained follow-up information from 217 participants after package shipment; there were two hospitalizations (one received a transfusion for severe anemia despite having had a complete abortion), and 16 other participants (7%) had clinical encounters in ED and urgent care centers. The reported outcomes in Raymond[16] (2019) are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7%) exceeded the ED visits in approved labeling (2.9-4.6%). The authors note that half of the ED/urgent care visits did not entail any medical treatment and opine that the increased number of visits may have been due to the study participants living farther from the abortion providers.[16] All participants received medications within 8 days.

Chong[3] updated the findings from the Gynuity study described in Raymond[16] and reported on 1157 medical abortion outcomes, of which approximately 50% occurred during the period of the COVID-19 PHE. Although a screening ultrasound was required per the protocol, sites determined in 52% (346/669) of abortions that occurred during the period of the COVID-19 PHE that, in order to avoid potential exposure to COVID-19 at a health care facility, those

participants were not required to obtain a screening ultrasound. Use of urine pregnancy test to confirm abortion completion also increased from 67% (144/214) in the 6 months prior to the pandemic to 90% (602/669) in the 6 months during the pandemic. Of the 1390 participants to whom medicine packages (containing both mifepristone and misoprostol) were mailed, 1157 (83.2%) had known abortion outcomes. Complete abortion without a procedure occurred in 1103 participants (95% of the those with a known outcome). Ten women experienced an SAE (5 transfusions (0.4%) and 7 hospitalizations (0.7%)) and 70 (6%) participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 47 participants (4.1% of 1390) to complete abortion. The reported outcomes in this study are similar to outcomes described in approved labeling, except that the combined ED/urgent care center encounters (6%) exceeded the ED visits in approved labeling (2.9-4.6%).

Anger[17] compared outcomes among participants enrolled in the Gynuity study who did versus did not have confirmation of GA/intrauterine location with an examination or ultrasound from 10 jurisdictions across the US. These participants were screened for enrollment from March 25 through September 15, 2020. All participants had a telemedicine consultation and received mifepristone and misoprostol by mail from the healthcare facility. Determination of which participants did not require confirmation of GA by examination or ultrasound to be eligible depended on the study clinician's assessment of eligibility for "no-test medication abortion"[u] based on a sample protocol published by Raymond[22] (2020). There were two key differences between the two groups. Participants for whom the study clinician determined a pre-abortion ultrasound was required were more likely than the participants who had no ultrasound or examination to live further than 150 miles from the clinic (51.2% vs. 31.7%) and were more likely to have a GA above 63 days (12.0% vs. 1.7%). The study sites shipped 503 medication packages during the analysis period; 344 packages went to the "no test" group while 159 went to the "test" medical abortion cohort (see figure below). However, because the two cohorts were not randomized in this study, they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

[u] "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination, or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al.[22]



Source: Figure 1 in this publication. MA= medical abortion.

The investigators' analyses excluded 91 (18% of 503; 57 in the no-test group and 34 in the test group) participants because they did not provide a date of the last menstrual period (LMP), did not take mifepristone, or did not have a recorded abortion outcome. Overall, 410 participants (81.5% of 503) provided outcomes data. There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the no-test group, complete medical abortion was confirmed in 271 participants who took medications (94% among those with known outcome). In the no-test cohort, two participants were "hospitalized and/or blood transfusion," and 36 (12.5%) had an unplanned clinical encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion).

In the test medical abortion group, complete abortion was confirmed in 123 participants (of 125 with known outcomes); the completion rate was 98% among those with known outcomes. In the test medical abortion group, one participant was "hospitalized and/or blood transfusion," and 10 (8.0%) had an unplanned clinical encounter. The authors concluded that, compared to participants who had an ultrasound prior to medical abortion, those without an examination prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.

Kerestes[4] was the only publication that linked outcomes of medical abortion with different delivery models. Participants included in the report had GA up to 77 days and received

medications in Hawaii between April 2020 and January 2020. A total of 334 medication packages (to 330 unique participants) were dispensed containing mifepristone and misoprostol; three different delivery models were used concurrently: 110 (32.9%) had traditional in-person visits, 149 (44.6%) had telemedicine consultation with in-person pick-up of medications, and 75 (22.5%) were sent medications by mail (71 of these were enrolled through Gynuity's TelAbortion study). Seven participants of the 330 participants who received 334 medication packages reported that they did not take them and were excluded from analysis of the outcomes. Among participants with follow-up data, the rates of successful medical abortion without surgery were 93.6%, 96.8%, and 97.1% in the in-clinic group, telemedicine + in-person pickup group, and telemedicine + mail group, respectively; these were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine + in-person pickup group). Eleven participants went to an ED. Although ED visits occurred the most frequently in the telemedicine + mail group (four participants or 5.8%) and the least in the in-person group (two participants or 2.1%), the study reported no increases in other serious adverse events.

Taken together, the three Gynuity study reports[3,16,17] and Kerestes[4] support dispensing mifepristone and misoprostol by mail after a telemedicine visit. Efficacy was maintained in all four studies. All of the studies reported SAEs frequencies comparable to labeled rates, except two of the Gynuity study reports (Raymond[16], Chong[3]) and Kerestes[4] report a higher frequency of ED/urgent care visits than the labeled frequency of ED visits. We do not know whether the reporting of combined ED and urgent care visits represents an increased rate of ED visits compared to the labeled rate of ED visits (2.9-4.6%). Other labeled SAEs (e.g., transfusion) occur infrequently (< 1%).

Aiken[5] (2021) reports outcomes of medical abortion up to 70 days GA in the UK before and during the pandemic in a retrospective cohort study. In the UK, prior to the COVID-19 pandemic, all patients attended an in-clinic visit where they received an ultrasound, were administered mifepristone in the clinic, and given misoprostol in-clinic for use at home (traditional model). During the pandemic, medical abortion consultations were performed remotely by telephone or video. Based on the consultation and questionnaire (including date of last menstrual period; menstrual, contraceptive and medical history; symptoms; risk for ectopic pregnancy), an assessment of eligibility for treatment via telemedicine was made. If eligible, medications were delivered to participants via mail or were made available for collection from the clinic for use at home. If the participant was assessed to be ineligible for treatment via

telemedicine, an in-person assessment with ultrasound was performed and medications were provided from the clinic for home use (hybrid model).

The study compared the two cohorts: 22,158 obtained medical abortion before the pandemic and had in-person visits and dispensing (traditional model) and 29,984 obtained medical abortion during the pandemic with either in-person visit and in-person dispensing, or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Outcomes were obtained from electronic records and incident databases. Outcomes of all hospitalizations related to abortion, ED visits, infection without sepsis, and hemorrhage without transfusion were not reported. The investigators' analysis for non-inferiority determined the efficacy and safety were comparable between both cohorts. Complete abortion occurred in > 98% in both cohorts. Hemorrhage requiring transfusion was reported in 0.04% and 0.02% of the traditional and hybrid cohorts, respectively; this is lower than the labeled 0.5% transfusion rate. There were no severe infections requiring hospitalization, major surgery or deaths reported.

A secondary analysis of the hybrid cohort was reported. Within the 29,984-person hybrid model cohort, 11,549 (39%) abortions were conducted in-person (in-person assessment with ultrasound was performed and medications provided from the clinic for home use) and 18,435 (61%) abortions were provided by telemedicine visit, without tests or confirmation of GA/intrauterine position by ultrasound, and medications either mailed or picked up from the clinic. Outcomes stratified by type of mifepristone dispensing were not reported. The rate of complete abortion was slightly higher in the telemedicine group (99.2%) than that in the in-person group (98.1%). There were no significant differences in the rates of reported SAEs. Adjustments for clinical and demographic characteristics were made because the two groups differed in baseline characteristics, including a higher proportion of pregnancies with GA over 6 weeks in the in-person group (68.2% compared with 55.1%). The authors conclude a hybrid model for medical abortion that includes no-test medical abortion[u] (no ultrasound, no pelvic exam, no pregnancy test) is effective and safe.

We conclude that although the Aiken[5] (2021) study has a large sample size and includes 85% of all medical abortions performed in England and Wales during the study period, the study has limitations. The authors acknowledge the main limitation of their study was that analysis was based on deidentified information in the NHS database and the investigators were unable to verify the outcomes extracted. Other limitations included that their search only captured

outcomes in electronic records and incident databases that met the authors' defined threshold for SAE reporting, and that the labeled abortion outcomes considered serious, such as hospitalizations related to abortion, infection without sepsis, hemorrhage without transfusion, or ED/urgent care visits, were not all included in the authors' definition of serious adverse event.

Data from the mail order dispensing studies with telemedicine visits from Gynuity (Raymond, Chong and Anger),[3,16,17] Kerestes[4], and Aiken[5] (2021) support that efficacy of medical abortion was maintained. The Aiken[5] study appears to be of sufficient sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings. Study reports of Raymond[16] Chong[3], and Kerestes[4] all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail without increases in other adverse events. Anger's[17] comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. Overall, despite the limitations noted, these studies support that dispensing by mail is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other SAEs related to mifepristone use. One reason for the increase in frequent ED/urgent care visits in the Raymond[16] publication, according to its authors, may have been that a substantial proportion of participants lived significant distances from their providers and increased distances have been associated with higher use of ED following treatment. Raymond[16] reported that half of the participants who had an ED/urgent care visit did not require medical treatment.

Clinic dispensing by courier

Reynolds-Wright[18] reported findings from a prospective cohort study of 663 women at less than 12 weeks' GA in Scotland undergoing medical abortion at home with use of telemedicine during the pandemic (from April 1 to July 9, 2020). The majority of medical abortions (78.7%) used telemedicine visits, eliminated pre-abortion ultrasound, and provided mifepristone for pick up at the service or by couriered delivery to woman's home. The number of couriered deliveries was not reported; thus, this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. With access to NHS regional hospital databases, the investigators were able to verify pregnancy outcomes and complications. Of the 663 participants, 642 (98.2%) were under 10 weeks GA, 21 (1.8%) were between 10 and 12 weeks

GA, and one participant was never pregnant. A total of 650 participants had complete abortion without requiring surgical intervention (98%), 5 (0.8%) an ongoing pregnancy and 4 (0.6%) an incomplete abortion. The outcomes from this study in Scotland are consistent with labeled mifepristone outcomes. The study shares the same limitations as the Aiken[5] (2021) study.

Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail.[v] Medical abortion eligibility is determined using an online questionnaire with asynchronous physician review. If eligible, medications are mailed to the women. WoW provides help and support by email or instant messaging.

Aiken[19] (2017) conducted a population-based study analyzing findings from 1,636 women in the Republic of Ireland and Northern Ireland who were sent medications between 2010 and 2012. Receipt of medications was confirmed for 1,181 women, among whom 1,023 confirmed use of mifepristone and misoprostol; outcome information was available for 1,000 (61% of women sent medications). Of the 1,000 women, the majority (781, 78%) were less than 7 weeks GA and 219 (22%) were at 7-9 weeks. Complete abortion without surgical intervention occurred in 947 (94.7% of 1,000 with known outcome); 7 (0.7%) women received a blood transfusion, 26 (2.6%) received antibiotics (route of administration undetermined) and 87 (8.7%) sought medical care at a hospital or clinic for symptoms related to medical abortion. Hospitalizations related to abortion were not reported. The reported proportion of complete abortion is within the range labeled for medical abortion up to 70 days (92.7-98.1%). However, the finding of 94.7% complete abortion represents a lower-than-expected efficacy based on the cohort's GA (almost 80% less than 7 weeks, labeled success for medical abortion ≤ 49 days is 98.1%). This study has limitations, including outcomes based on self-report without validation of completed abortion by examination or laboratory testing, and no known outcomes for 39% of study cohort. Additionally, the authors noted medical abortion was provided in a legally-restrictive setting, where the law provided a maximum penalty of life imprisonment for the woman undergoing the abortion, which may affect participants' self-reporting.

[v] In March 2019, FDA sent a WL to Aidaccess.org, a group affiliated with WoW. Aidaccess.org received this WL because it was introducing misbranded and unapproved new drugs into the U.S. In the context of this REMS review, studies involving WoW are included solely for purposes of evaluating of data regarding the methods of dispensing mifepristone.

Endler[21] and Norten[20] have reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail, because neither provide meaningful outcomes data for consideration. Endler[21] compared the outcomes of self-reported heavy bleeding and clinical visits occurring during the "first or second day of abortion" that occurred in women undergoing medical abortion at 9 weeks GA or less, with outcomes from women at more than 9 weeks GA. Outcome data from day 1 or 2 is of limited usefulness. Norten[20] describes findings from a survey of women who were sent medical abortion medication through WoW and provided self-reported outcomes. Results were based on surveys returned from only 37% of participants, a return rate that is too low for the study to be considered valid.

WoW uses a model with numerous deviations from the standard provision of medical abortion in the US. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Further, although Aiken[19] (2017) is a large cohort study, the outcomes are self-reported with no verification of complete abortion by laboratory or clinical evaluation and 39% of outcomes are unaccounted for. These limitations in the Aiken study result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

4. Discussion

After review of the published literature, safety information collected during the COVID-19 PHE, postmarketing data, information from the first Mifepristone REMS Program assessment report, responses to information requests to the Applicants, and information provided by advocacy groups, individuals and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that the REMS can be modified to reduce burden without compromising patient safety.

Prescriber Certification

None of the publications we reviewed would support a conclusion that a healthcare provider who prescribes mifepristone does not need to meet the qualifications included in the Mifepristone REMS Program as described above in section 3.2.1. Absent these provider qualifications, serious complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, would not be detected or appropriately managed.

We conclude that prescriber certification (ETASU A) should be maintained. The current process requires the prescriber to agree to the requirements of the Mifepristone REMS Program and to attest that they meet the qualifications described in section 3.2.1 above. The REMS has been structured to minimize burden to prescribers by requiring only a one-time certification by the prescriber for each Applicant. We have determined that healthcare provider certification continues to be necessary to ensure the benefits outweigh the risks, especially considering that, if the in-person dispensing requirement is removed from the Mifepristone REMS Program, the number of new providers may increase (see discussion in section 3.2.2 above).

Drug to be dispensed with evidence or other documentation of safe use conditions

The requirement to counsel the patient and provide them with the *Patient Agreement Form* ensures that each patient is informed of the appropriate use of mifepristone, the risks associated with treatment, and what to do if they experience symptoms that may require emergency care.

In 2016, we initially recommended eliminating the *Patient Agreement Form* (see section 3.2.2), though the form was ultimately maintained as part of the REMS. As discussed above, our current literature review has indicated that there is no basis to remove the *Patient Agreement Form* from the REMS. In addition, surveys we reviewed suggest that if the in-person dispensing requirement for mifepristone is removed, there could be a potential doubling of medical abortion providers. This potential doubling of medical abortion providers supports the continued need to ensure that patients are consistently provided patient education under the Mifepristone REMS Program regarding the use and risks of mifepristone. The *Patient Agreement Form* is an important part of standardizing the medication information that prescribers communicate to their patients, including new prescribers, and also provides the information in a brief and understandable format to patients. We determined, in accordance with section 505-1(f)(2) of the FD&C Act, that this does not impose an unreasonable burden on providers or patients.[w]

Given the likelihood of a potential increase in new prescribers if the in-person dispensing requirement is removed from the Mifepristone REMS Program, we conclude that maintaining the *Patient Agreement Form* remains necessary to assure safe use at this time.

[w] *The Patient Agreement Form* can be signed in person or through other means.

Drug to be dispensed only in certain healthcare settings

As discussed above in section 3.2.3, our evaluation of information submitted by the applicants in the one-year (1st) REMS assessment report for the Mifepristone REMS Program and in response to follow-up requests from the Agency indicates that the number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use is small, and the data provide no indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these adverse events. We further conclude, based our review of the postmarketing safety data from FAERS during the COVID-19 PHE and information submitted by the applicants for the timeframe of January 27, 2020 through September 30, 2021, that there does not appear to be a difference in adverse events between periods during the COVID-19 PHE when the in-person dispensing requirement was being enforced and periods when the in-person dispensing requirement was not being enforced; nor have we identified any new safety concerns with the use of mifepristone for medical termination of early pregnancy.

Alternatives to in-person dispensing of mifepristone have been investigated in several studies and countries. The literature review identified 15 publications[x] that assessed safety outcomes from various medication delivery models (US, UK, Canada, Ireland, Australia, Nepal), including dispensing by retail and mail order pharmacies, prescribers mailing medications or using couriered service to deliver medications, and dispensing by "partner organizations". The ability to generalize the results of these studies to the US population is hampered by differences in pre-abortion care (e.g., telemedicine versus in-person, testing), and the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy.

In addition, there are factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation; for example, most studies on mail dispensing of mifepristone also include telemedicine consultation, and (2) because most SAEs with medical abortion are infrequent, though they can be life threatening, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the US.

[x] The 15 publications correspond to endnote numbers: 1-7, 14-21.

Based on the literature identified by our review, dispensing mifepristone by mail from the clinic or from a mail order pharmacy does not appear to jeopardize the efficacy of medical abortion. The studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, although the safety and efficacy outcomes reported in these studies remain within the ranges described in mifepristone labeling except for increased numbers of ED/urgent care visits and hospitalizations.

Four publications (Raymond[16], Chong[3], Anger[17] and Kerestes[4]), describe a relevant US cohort where dispensing mifepristone from the clinic by mail was paired with telemedicine visits. These studies showed that efficacy was maintained and there was no increased frequency of SAEs except for higher ED/urgent care visits. The increased ED/urgent care visits were not associated with increases of other SAEs, and in the view of one study's authors (Raymond[16]), may be associated with participants being located significant distances from their providers. The Aiken[5] (2021) study of a large UK cohort where the clinics mailed mifepristone report small (lower than labeled) occurrences of transfusion and no significant infections requiring hospitalization. In Grossman[1] and Hyland[15], where the pharmacies mailed mifepristone after prescribers confirmed GA, efficacy is maintained. Grossman's[1] interim analysis found no increases in SAEs. Hyland[15] reported higher numbers of hospitalizations but did not report increases of other SAEs. Overall, while the studies assessing mifepristone dispensing by mail suggest more frequent encounters with healthcare providers, they generally support a conclusion that dispensing by mail is safe. Despite the limitations of the studies we reviewed, we conclude that overall, the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe, and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, our review of the literature, and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, we conclude that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met, and pharmacy certification is added as described below.

Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to

ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the REMS, the Mifepristone REMS Program should be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

New requirement to be added for pharmacy certification

The current distribution model requires the certified prescriber to dispense mifepristone directly to the patient in a clinic, medical office, or hospital. During the periods when the in-person dispensing requirement was not being enforced, both applicants used mail order pharmacies to receive and hold mifepristone on behalf of the certified healthcare providers who had purchased the product.[j,y,z] Pursuant to a prescription for mifepristone, the mail order pharmacy would ship the product to a named patient.

The Mifepristone REMS Program continues to require that mifepristone be prescribed only by certified prescribers. With the removal of the in-person dispensing requirement, however, the drug is no longer required to be dispensed only in a clinic, medical office or hospital. Under the REMS as modified, mifepristone can be dispensed through a pharmacy, provided the product is prescribed by a certified prescriber and all other requirements of the REMS are met. Given this modification to the dispensing requirements in the REMS, it is necessary to add a requirement for certification of pharmacies under ETASU B. Adding the pharmacy certification requirement incorporates pharmacies into the REMS, ensures that pharmacies are aware of and agree to follow applicable REMS requirements, and ensures that mifepristone is only dispensed pursuant to prescriptions that are written by certified prescribers. Without pharmacy certification, a pharmacy might dispense product that was not prescribed by a certified prescriber. Adding pharmacy certification ensures that ETASU A is met prior to dispensing the product to a patient; certified prescribers, in turn, have agreed to meet all the conditions of the REMS, including ensuring that the *Patient Agreement Form* (ETASU D) is completed. In addition, wholesalers and distributors can only ship to certified pharmacies. Based on our review of the safety data and our consideration of the distribution model implemented by the Applicants during the periods

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y ANDA 091178: September 23, 2021 response to the September 15, 2021 information request; October 11 and 16, 2021 responses to the June 30, 2021 and July 15, 2021 information requests; October 26, 2021 response to the October 22, 2021 information request; October 29, 2021 response to the October 27 information request.
z NDA 020687: September 20, 2021 response to the September 15, 2021 information request; October 26, 2021 response to the October 22 information request.

when the in-person dispensing requirement was not being enforced, as well as REMS assessment data and published literature, we conclude that provided all other requirements of the REMS are met, the REMS program, with the removal of the in-person dispensing requirement and the addition of a requirement for pharmacy certification, will continue to ensure the benefits of mifepristone for medical abortion outweigh the risks while minimizing the burden imposed by the REMS on healthcare providers and patients. As modified, the REMS would allow, for example, dispensing by mail order or specialty pharmacies, similar to the distribution model used by applicants during the periods when the in-person dispensing requirement was not being enforced.[aa]

The above recommendations were discussed with the (b) (6) ((b) (6) and senior leadership from CDER on November 2, 2021. The (b) (6) (b) (4) along with senior CDER leadership, concurred with removing the in-person dispensing requirement provided that all of the remaining REMS requirements are met, including but not limited to prescriber certification where prescribers need to attest to having certain qualifications, and maintaining the *Patient Agreement Form*. The (b) (6) (b) (4) and senior leadership from CDER were also in favor of adding pharmacy certification to assure the safe use of mifepristone.

5. Conclusions and Recommendations

Based on the results of REMS assessments; our review of safety data collected during the PHE as well as data from FAERS; our literature search; and information provided by advocacy groups, individuals, the Applicants, and the plaintiffs in the *Chelius v. Becerra* litigation, (b) (6) and (b) (6) have concluded that a REMS modification is necessary and should include the following changes:

- Removing the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.
- Adding a requirement under ETASU B that pharmacies that dispense the drug be specially certified.

[aa] Our current conclusion that the REMS would allow dispensing by mail order or specialty pharmacies is based on data received from Applicants relating to the periods when the in-person dispensing requirement was not enforced and mail-order pharmacies were used to dispense the product, as well as our analysis of postmarketing safety data and available literature. At this time we do not have data (from the Applicants or from other sources) to assess the certification of retail pharmacies under the REMS. We have not yet determined the details of pharmacy certification requirements, including whether any limitations on the types of pharmacies that may dispense the product are necessary.

(b) (6) and (b) (6) recommend the Applicants be issued a REMS Modification Notification Letter that requests submission within 120 days from the date of the letter.

6. References

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7. Appendix A

References Cited in Letters from Plaintiffs

References cited in letter from *Chelius v. Becerra* Plaintiffs (September 29, 2021)	
References included in the REMS review	
Aiken A et al. BJOG 2021: 128 (9): 1464-1474	
Chong, et al. Contraception 2021; 104(1) 43-48	
Daniel S. et al. Contraception 2021; 104(1): 73-76	
References excluded from the REMS review	**Rationale for Exclusion**
Am. Coll. of Obstetricians & Gynecologists, *Position Statement: Improving Access to Mifepristone for Reproductive Health Indications* (June 2018), https://www.acog.org/clinical-information/policy-and-position-statements/position-statements/2018/improving-access-to-mifepristone-for-reproductive-health-indications	Policy/advocacy statement
House of Delegates, Am. Med. Ass'n., *Memorial Resolutions Adopted Unanimously No. 504 (2018)* https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/hod/a18-resolutions.pdf	Policy/advocacy statement
Cong. Of Delegates, Am. Acad. Of Fam. Physicians, *Resolution No. 506 (CoSponsored C) Removing Risk Evaluation and Mitigation Strategy (REMS) Categorization of Mifepristone* (May 24, 2018) https://www.reproductiveaccess.org/wp-content/uploads/2019/02/Resolution-No.-506-REMS.pdf	Policy/advocacy statement
Schummers L et al, Contraception 2020; 102(4): 273	Abstract
Upadhyay UD et al.) Obstet & Gynecol 2015; 125: 175	Published prior to March 29, 2016-July 26, 2021 timeframe for current literature review. We note that the extensive literature review conducted as part of the 2016 review, which was consistent with the division's standard approach for reviewing an efficacy supplement

	and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
Kapp N et al. Best Pract Clin Obstet Gynaecol. 2020;63:37-44	Abstract. Also outside the scope of first trimester medical abortion.
Fuentes L et al. J Women's Health 2019; 28 (12): 1623, 1625 Bearak JM, Lancet Pub Health 2017 Nov;2(11): e493, e495-96 Cartwright A et al 20 J Med Internet Res 2018 20(5):e10235 Barr-Walker J, et al PLoS One 2019;14(4): e0209991 Grossman et al JAMA Network 2017;317(4):437, 437-438 Dobie S et al 31 Fam Plan Persp 1999; 31(5): 241-244 Shelton JD 8 Fam Plan Persp 1976; 8(6):260, 260-262 Norris AH et al Am J Pub Health 2020; 110 (8): 1228,1232 Upadhyay UD et al Am J Pub Health 2014; 104(9):1687, 1689	Focused on the logistics of accessing abortion care.
CDC MMWR Abortion Surveillance – United States, 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T5_down	Contains primarily general statistics on abortion care by state.

References cited in appendix from *Chelius v. Becerra* Plaintiffs (September 29, 2021)
References included in the REMS review
None

References excluded from the REMS review	Rationale for Exclusion
Jones RK et al Guttmacher Institute Abortion Incidence and Service Availability in the United States, 2017 (2019) Guttmacher Inst, Induced Abortion in the United States (2019)	Contains primarily general statistics on abortion care and logistics of accessing abortion care.
University of Minnesota Healthy Youth Dev. Prevention Rsch Ctr, 2019 Minnesota Adolescent Sexual Health Report 3 (2019)	Not related specifically to abortion care.
Jerman J et al Guttmacher Inst, Characteristics of U.S. Abortion Patients in 2014 and Changes since 2008 (2016)	Contains figures on patient characteristics from 2008-2014.
Roberts CM et al Women's Health Issues 2014; 24:e211, e215	Focused on cost of abortion.
CDC MMWR Abortion Surveillance 2018 https://www.cdc.gov/mmwr/volumes/69/ss/ss6907a1.htm#T7 down (last updated Nov. 7, 2020)	Contains primarily statistics on number of abortions in the US.
Jones RK Persp on Sexual & Reprod Health 2017; 49:17, 20	Focused on abortion incidence and service availability.
Fuentes L et al (as above) Bearak JM et al (as above) Cartwright A et al (as above) Johns NE et al. BMC Health Serv Res 2017; 17: 287, 294	Focused on logistics of accessing abortion care.

References cited in letter from Society of Family Planning (August 11, 2021)
References included in the REMS review
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Grossman D et al. Obstet Gynecol 2021; 137 (4): 613-622.	
Winikoff B et al. Obstet Gynecol 2012; 120: 1070-1076 reviewed in 2016 clinical memo	
Chen MJ et al. Obstet Gynecol 2015;126(1):12-21 reviewed in 2016 memo	
Chong et al. Contraception 2021;104(1): 43-48	
Aiken A et al. BJOG 2021; 128 (9): 1464 -1474	
Hyland 2018 et al. Aust New Zeal J Obstet Gynaecol 2018; 58 (3): 335-340	
References excluded from the REMS review	**Rationale for Exclusion**
Schummers L et al. BMJ Sex Reprod Heal 2021;47(e1)	Abstract
Kapp et al. 2020 (as above)	Abstract
Upadhyay et al. 2015 (as above)	(See rationale above)
Srinivasulu et al. Contraception 2021; 104(1):92-97	Survey on clinician perspectives on access to mifepristone.
Calloway D et al. Contraception 2021; 104(1): 24-28	Primarily addresses provider stigma around abortion care.
Rasmussen et al. Contraception; 104(1): 98-103	Opinion/commentary
Cleland et al. Obstet Gynecol 2013;121(1):166-171	Published prior to March 29, 2016 - July 26, 2021 timeframe for current literature review. We note that the extensive literature search conducted as part of the 2016 clinical review, which was consistent with the division's standard approach for reviewing an efficacy supplement and encompassed 90 references, did not capture this publication. However, the authors' conclusion in this publication is consistent with our review of the safety data in 2016.
National Academy of Sciences, Engineering, and Medicine. Safety and Quality of Abortion Care in the US 2018	General information about abortion care in the US. Did not provide safety data relevant to the elements of the REMS
Raymond EG. Obstet Gynecol 2012: 119(2): 215-219	Does not separate out medical and surgical abortion.

Bartlett LA et al. Obstet Gynecol 2004; 103(4): 729-737	Focused on surgical abortion.
Jones RK, Jerman J. Time to appointment and delays in accessing care among U.S. abortion patients, Guttmacher 2016	Focused on logistics of accessing abortion care.
Foster DG et al. Perspect Sex Reprod Health 2013; 45(4):210-218	Focused on second trimester abortion.
Ely G et al. Heal Soc Work 2019;44(1):13-21	Focused on logistics of accessing abortion care.
Munro S et al. Ann Fam Med 2020; 18(5):413-421.	Survey on physician perspectives on implementing medical abortion with mifepristone.

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SPECIAL ARTICLE

Abortion Safety and Use with Normally Prescribed Mifepristone in Canada

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ABSTRACT

BACKGROUND

In the United States, mifepristone is available for medical abortion (for use with misoprostol) only with Risk Evaluation and Mitigation Strategy (REMS) restrictions, despite an absence of evidence to support such restrictions. Mifepristone has been available in Canada with a normal prescription since November 2017.

METHODS

Using population-based administrative data from Ontario, Canada, we examined abortion use, safety, and effectiveness using an interrupted time-series analysis comparing trends in incidence before mifepristone was available (January 2012 through December 2016) with trends after its availability without restrictions (November 7, 2017, through March 15, 2020).

RESULTS

A total of 195,183 abortions were performed before mifepristone was available and 84,032 after its availability without restrictions. After the availability of mifepristone with a normal prescription, the abortion rate continued to decline, although more slowly than was expected on the basis of trends before mifepristone had been available (adjusted risk difference in time-series analysis, 1.2 per 1000 female residents between 15 and 49 years of age; 95% confidence interval [CI], 1.1 to 1.4), whereas the percentage of abortions provided as medical procedures increased from 2.2% to 31.4% (adjusted risk difference, 28.8 percentage points; 95% CI, 28.0 to 29.7). There were no material changes between the period before mifepristone was available and the nonrestricted period in the incidence of severe adverse events (0.03% vs. 0.04%; adjusted risk difference, 0.01 percentage points; 95% CI, −0.06 to 0.03), complications (0.74% vs. 0.69%; adjusted risk difference, 0.06 percentage points; 95% CI, −0.07 to 0.18), or ectopic pregnancy detected after abortion (0.15% vs. 0.22%; adjusted risk difference, −0.03 percentage points; 95% CI, −0.19 to 0.09). There was a small increase in ongoing intrauterine pregnancy continuing to delivery (adjusted risk difference, 0.08 percentage points; 95% CI, 0.04 to 0.10).

CONCLUSIONS

After mifepristone became available as a normal prescription, the abortion rate remained relatively stable, the proportion of abortions provided by medication increased rapidly, and adverse events and complications remained stable, as compared with the period when mifepristone was unavailable. (Funded by the Canadian Institutes of Health Research and the Women's Health Research Institute.)

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Access to safe abortion is a human right and a key component of reproductive health, yet inadequate access remains a global concern.[1] A medical abortion regimen of mifepristone and misoprostol has been shown to be safe.[2-4] Mifepristone is approved for use in the United States with Risk Evaluation and Mitigation Strategy (REMS) restrictions[5] (including mandatory prescriber certification, observed dosing, dispensing by the prescriber or medical facility with the exclusion of pharmacies, and submission of a prespecified patient consent form) and elsewhere with similar restricted approvals.[6,7] Professional organizations have called for the removal of REMS restrictions because they impede access to abortion services without improving safety.[8] However, high-quality data with respect to abortion safety and effectiveness when mifepristone is available without REMS-like restrictions are lacking.[9]

Mifepristone was first marketed in Canada in January 2017 as a 200-mg tablet combined with 800 μg of misoprostol.[10] Approval came more than 15 years after approval in the United States and more than 25 years after similar rulings in France, Sweden, and the United Kingdom.[11] Initially, regulatory restrictions in Canada were similar to REMS restrictions.[12] By November 7, 2017, Canadian regulators had removed these restrictions so that mifepristone could be prescribed and dispensed as a normal prescription medication and had expanded approved use from 49 to 63 days after the patient's last menstrual period.[13] This action resulted in a globally unprecedented practice of permitting any physician or nurse practitioner to prescribe, any pharmacist to dispense, and patients to independently administer mifepristone when, where, and if they chose.[14] Before 2017, medically induced abortions made up only 4% of all abortions in Canada and used off-label regimens of misoprostol with or without methotrexate. These regimens have reduced effectiveness (84 to 97%) and a high risk of teratogenicity if the abortion fails.[4,15]

We compared abortion use, safety, and effectiveness during the period after mifepristone had become available without REMS-like restrictions with the period before mifepristone had been available in Ontario, Canada (representing nearly 40% of the Canadian population).

Methods

Data Set

In Canada, universal single-payer health care — including coverage for abortion services and management of its complications — is provided by each province or territory. We used linked administrative health data[16] to create a population-based cohort of all female Ontario residents between the ages of 12 and 49 years who had received abortion services from January 1, 2012, to March 15, 2020. We linked records from practitioner visits, all hospital visits, and outpatient prescriptions using a secure data platform at ICES (formerly known as the Institute for Clinical Evaluative Sciences) at McMaster University.[16,17] We excluded events that had occurred within 6 weeks before or after a missed abortion (pregnancy loss without expulsion) or spontaneous abortion (pregnancy loss with expulsion) and those occurring within 6 weeks after delivery at 25 weeks or more of gestation to avoid including procedures that could have been misclassified as abortions. Details regarding the data set are provided in Figure S1 and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Ethics approval for the study was granted by the University of British Columbia.

Exposure and Outcomes

The exposure we examined was the regulatory change that made mifepristone available as a normal prescription. Outcomes included measures of abortion use, safety, and effectiveness.

We evaluated outcomes regarding abortion use that included the abortion rate, which was calculated according to the international standard as the annual number of abortions among female residents between 15 and 49 years of age per 1000 female residents in that age group,[18] the percentage of all abortions that were medically induced, and the percentage of all abortions that were provided at 14 weeks or more of gestation (second-trimester abortion). (In the calculation of the abortion rate, the lower age for female residents was 15 years, as compared with a lower age of 12 years that was used for all other calculations in our study cohort.) Abortion safety outcomes within 6 weeks after abortion were severe adverse

events, including any blood transfusion, abdominal surgery (laparotomy, laparoscopy, or hysterectomy), admission to an intensive care unit, or sepsis that occurred during a hospitalization associated with an abortion-complication code. Complications of abortion included genital tract or pelvic infection, hemorrhage (delayed or excessive bleeding that complicated complete or incomplete abortion), embolism, shock, renal failure, damage to pelvic organs or tissues (including uterine perforation), venous complications, and other or unspecified complications. Outcomes regarding abortion effectiveness were the incidence of subsequent uterine evacuation (aspiration after medical abortion, reaspiration after surgical abortion, or subsequent abortion procedure), ongoing intrauterine pregnancy continuing until delivery, and ectopic pregnancy diagnosed within 6 weeks after the abortion date. Detailed outcome definitions are provided in Table S1.

STATISTICAL ANALYSIS

We tabulated the incidence of each outcome according to the mifepristone regulatory period. We then conducted interrupted time-series analysis using segmented generalized mixed-effects regression to compare the expected incidence and trend for each outcome based on the period before mifepristone had become available with the observed level and trend after the availability of mifepristone with a normal prescription. We used log binomial regression to model incidence outcomes and Poisson regression with population offset to calculate the abortion rate; models were adjusted for outcome trends before the approval of mifepristone and accounted for autocorrelation and correlated residuals (File 1 in the Supplementary Appendix).[19,20] We used 6-month moving averages to smooth the resulting estimates. We examined outcomes from January 1, 2017, through November 6, 2017, descriptively but excluded this period from our models because it included rapid, incremental regulatory changes.[13]

We graphed the observed and expected monthly outcome incidence (quarterly for outcomes with <6 events in any month) following best practices.[21] We estimated risk differences and risk ratios for each outcome by comparing the observed with expected values for September 2019, a time point selected a priori to balance model stability (greatest in the middle of the study period) and integration of mifepristone into practice (greatest at the end of the study period). We used bootstrapping with 200 samples drawn with replacement to estimate 95% confidence intervals[22] without adjustment for multiple comparisons. All analyses were conducted with the use of SAS software, version 7.51, and R software (code in File 2 in the Supplementary Appendix).

To examine the robustness of our findings to modeling specification, we conducted sensitivity analyses using segmented generalized least-squares regression, with autocorrelation terms selected on the basis of the Durbin–Watson test[23-25] and visual examination of autocorrelation function and partial autocorrelation function residuals.[25] We conducted subgroup analyses that were restricted to first-trimester abortions and then further restricted to first-trimester medical abortions.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

Of the 314,859 induced abortions in Ontario, Canada, from January 1, 2012, through March 15, 2020, the majority (89.3%) were surgical (with 94.6% performed by means of suction aspiration), approximately 10% were medical abortions, and less than 0.1% were unclassified. Table 1 shows cohort characteristics according to the regulatory period for mifepristone.

DESCRIPTIVE ANALYSES OF ABORTION OUTCOMES

The abortion rate per 1000 female residents of reproductive age and the incidence of all other outcomes are presented descriptively according to the regulatory period in Table 2. (Components of the composite outcomes are shown in Table S2.) The abortion rate decreased from 11.9 abortions per 1000 female residents between the ages of 15 and 49 years of age before mifepristone had become available to 11.3 per 1000 female residents after mifepristone had become available with a normal prescription. The percentage of all abortions that were provided medically increased from 2.2% before mifepristone had become available to 8.3% while mifepristone was restricted and then to 31.4% after mifepristone had become avail-

Table 1. Characteristics of Patients Undergoing Medical or Surgical Abortion, According to Period of Availability of Mifepristone.

Characteristic	Mifepristone Not Available (N=195,183)	Mifepristone Available with Restrictions (N=35,644)	Mifepristone Available without Restrictions (N=84,032)
	January 2012–December 2016	January 1, 2017–November 6, 2017	November 7, 2017–March 15, 2020
		number of patients (percent)	
Age — yr*			
<20	20,034 (10.3)	2,969 (8.3)	6,643 (7.9)
20–24	54,346 (27.8)	9,208 (25.8)	20,247 (24.1)
25–29	47,598 (24.4)	8,909 (25.0)	21,717 (25.8)
30–34	36,640 (18.8)	7,369 (20.7)	17,838 (21.2)
≥35	36,565 (18.7)	7,189 (20.2)	17,587 (20.9)
Nulliparous	104,824 (53.7)	19,030 (53.4)	45,902 (54.6)
Neighborhood income†			
Lowest quintile	55,076 (28.2)	9,737 (27.3)	22,360 (26.6)
Highest quintile	24,852 (12.7)	4,603 (12.9)	11,075 (13.2)
Neighborhood ethnic concentration‡			
Highest quintile	82,143 (42.1)	14,627 (41.0)	33,600 (40.0)
Lowest quintile	19,424 (10.0)	3,552 (10.0)	8,451 (10.1)
Rural residence§	11,709 (6.0)	2,174 (6.1)	5,195 (6.2)

* Trends regarding the patient's age at which abortion was performed in Ontario continued a historic gradual and steady increase over the study period, which was consistent with an increase in age in the population-based trends during this period.

† The neighborhood income quintile was drawn from the Registered Persons Database file from the Institute for Clinical Evaluative Sciences and was defined on the basis of the Nearest Census-Based Neighborhood Income Quintile from Census Canada.

‡ The neighborhood ethnic concentration, which is part of the Ontario Marginalization Index,[26] refers to high area-level percentages of recent immigrants and persons belonging to a "visible minority" group, which was defined by Statistics Canada as "persons, other than aboriginal peoples, who are non-Caucasian in race or non-white in color." The highest concentration of such residents is the top quintile, and the lowest concentration is the lowest quintile.

§ Rural residence is defined as all territory lying outside population centers.

able with a normal prescription. The rate of second-trimester abortions declined from 5.5% of all abortions to 5.1% after the availability of mifepristone with a normal prescription.

Abortion safety outcomes remained stable during the period before mifepristone had become available and during the period after its availability with a normal prescription (severe adverse events, 0.03% and 0.04%, respectively; and abortion complications, 0.67% and 0.74%, respectively). Subsequent uterine evacuation increased from 1.0% to 2.2%, and ongoing intrauterine pregnancy continuing until delivery increased from 0.03% to 0.08%. Ectopic pregnancy that was detected after abortion increased from 0.15% to 0.22%.

TIME-SERIES ANALYSES OF ABORTION OUTCOMES

Interrupted time-series graphs of abortion-use outcomes are presented in Figure 1, abortion safety outcomes in Figure 2, and abortion-effectiveness outcomes in Figure 3. Adjusted risk differences and risk ratios from these models comparing the period before mifepristone had become available with the nonrestricted period are presented in Table 2.

During the study period, the abortion rate continued an absolute decline, although as compared with the trend before the approval of mifepristone, we noted an increase of 1.2 abortions per 1000 female residents (95% confidence interval [CI], 1.1 to 1.4) over the predicted rate.

Table 2. Safety and Effectiveness of 314,859 Abortions Provided during the Study Period.*

Outcome	Mifepristone Not Available (N = 195,183)	Mifepristone Available with Restrictions (N = 35,644)	Mifepristone Available without Restrictions (N = 84,032)	Adjusted Risk Difference (95% CI)††	Adjusted Risk Ratio (95% CI)
	January 2012–December 2016	January 1, 2017–November 6, 2017	November 7, 2017–March 15, 2020		
Abortions provided					
No. of female residents in age cohort	3,268,428	3,272,448	3,312,061		
Annual rate of abortion per 1000 female residents in age cohort‡‡	11.9	10.9	11.3	1.2 (1.1 to 1.4)	1.1 (1.1 to 1.2)
Type of abortion — no. (%)					
Medical abortion	4,307 (2.2)	2,962 (8.3)	26,434 (31.4)	28.8 (28.0 to 29.7)	5.3 (4.7 to 5.9)
Second-trimester abortion at ≥14 wk of gestation	10,830 (5.5)	2,072 (5.8)	4,300 (5.1)	–0.22 (–0.63 to 0.19)	0.96 (0.88 to 1.04)
Abortion safety — no. (%)					
Severe adverse events§§	53 (0.03)	9 (0.03)	29 (0.04)	0.01 (–0.06 to 0.03)	1.2 (0.4 to 3.4)
Complications¶¶	1,434 (0.74)	239 (0.67)	578 (0.69)	0.06 (–0.07 to 0.18)	1.1 (0.9 to 1.3)
Ongoing pregnancy — no. (%)					
Subsequent uterine evacuation‖‖	2,029 (1.0)	518 (1.5)	1,882 (2.2)	1.1 (0.9 to 1.3)	2.0 (1.7 to 2.3)
Ongoing pregnancy continuing until delivery	51 (0.03)	15 (0.04)	70 (0.08)	0.08 (0.04 to 0.10)	7.8 (2.2 to 33.6)
Ectopic pregnancy detected after abortion	289 (0.15)	57 (0.16)	182 (0.22)	–0.03 (–0.19 to 0.09)	0.88 (0.54 to 1.40)

* Adjusted risk differences and risk ratios are for the period after mifepristone was available without restrictions as compared with the period before mifepristone was available. The calculations were performed by means of interrupted time-series segmented regression analyses among all surgical and medical abortions after adjustment for outcome trends during the period before mifepristone had been available. CI denotes confidence interval.

† The adjusted risk difference is shown in percentage points for all categories except for the abortion rate per 1000 female residents.

‡ The annual abortion rate was calculated as the number of abortions provided among female residents between the ages of 15 and 49 years per 1000 female residents in the same age cohort in the population per year.

§ Severe adverse events included blood transfusion, abdominal surgery (laparotomy, laparoscopy, and hysterectomy), admission to an intensive care unit, or sepsis, all concurrent with an abortion complication. A detailed definition is provided in Table S1 in the Supplementary Appendix.

¶ Abortion complications included incomplete or complete abortion complicated by infection, hemorrhage, embolism, damage to pelvic organs, venous complications, or other complications after an induced abortion.

‖ Subsequent uterine evacuation included aspiration, reaspiration, or subsequent abortion procedure in the same pregnancy.

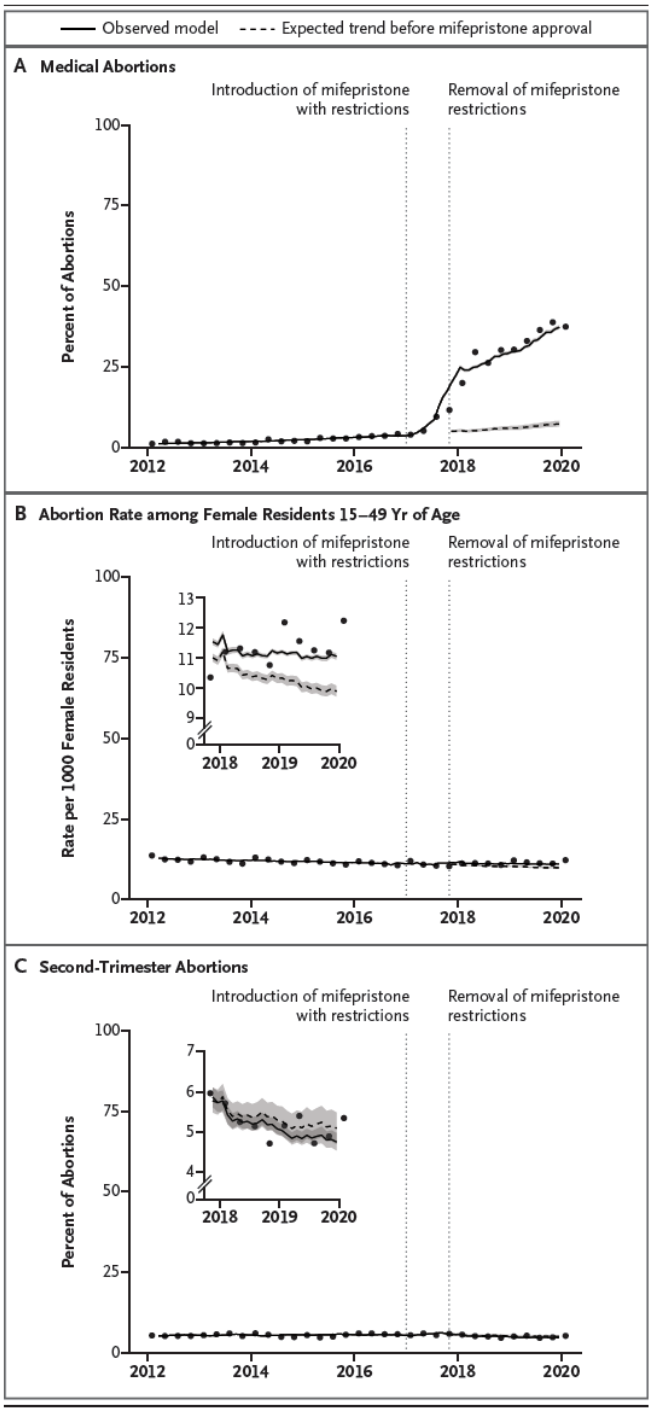

Figure 1. Changes in the Percentages of Medical and Second-Trimester Abortions among All Abortions and in Abortion Rates.

Shown are the results of interrupted time-series analyses of the level and trend of abortion outcomes in Ontario, Canada, among all surgical and medical abortions that were provided before the introduction of mifepristone in the province (2012 through 2016), after the introduction but with Risk Evaluation and Mitigation Strategy (REMS)–like restrictions (January 1, 2017, through November 6, 2017), and after a regulatory change to remove restrictions, which made mifepristone available by normal prescription (November 7, 2017, through March 15, 2020). Panel A shows the percentage of all abortions that were performed medically at any gestational age. Panel B shows the annual abortion rate among female residents between the ages of 15 and 49 years per 1000 female residents in the same age group in the population. Panel C shows the percentage of second-trimester abortions (≥14 weeks of gestation) among all abortions. In Panels B and C, the insets show the same data on an expanded y axis; shading indicates 95% confidence intervals. The expected outcomes if mifepristone had not been available were estimated from segmented mixed-effects models (log binomial regression in Panels A and C and Poisson regression with population offset in Panel B) and smoothed with the use of a 6-month moving-average function.

The proportion of all abortions that were medical increased by an adjusted risk difference of 28.8 percentage points (95% CI, 28.0 to 29.7). The rate of second-trimester abortions showed a stable, continuous decline (adjusted risk difference, −0.22 percentage points; 95% CI, −0.63 to 0.19). Abortion safety outcomes were materially stable, with an adjusted risk difference of 0.01 percentage points (95% CI, −0.06 to 0.03) for severe adverse events and 0.06 percentage points (95% CI, −0.07 to 0.18) for complications. The rate of subsequent uterine evacuation increased modestly, with an adjusted risk difference of 1.1 percentage points (95% CI, 0.91 to 1.3), and the rate of ongoing intrauterine pregnancy that continued until delivery increased by 0.08 percentage points (95% CI, 0.04 to 0.10). The rate of ectopic pregnancy that was detected after abortion was materially stable, with an adjusted risk difference of −0.03 percentage points (95% CI, −0.19 to 0.09).

Interrupted time-series graphs from generalized least-squares regression with the use of

aggregated monthly data showed the robustness of the findings to modeling specification (Figs. S2, S3, and S4). Changes in outcome incidences and trends after mifepristone availability with a normal prescription were consistent for all outcomes except for the percentage of second-trimester abortions, for which aggregated models indicated a slight reduction (−0.92 percentage points; 95% CI, −1.40 to −0.48).

OUTCOMES AFTER FIRST-TRIMESTER ABORTION

Outcome incidences among all first-trimester abortions are presented in Tables S3 and S4 and Figures S5, S6, and S7; outcomes among first-trimester medical abortions are provided in Tables S5 and S6. The percentage of first-trimester abortions that were performed medically increased from 1.6% before mifepristone was available to 32.4% after mifepristone was available without restrictions. Severe adverse events were rare among first-trimester medical abortions (<6 events per 25,744 abortions [too infrequent to report exact incidence]), the incidence of abortion complications was 0.76%, and the incidence of subsequent uterine evacuation was 4.5%. Similarly, ongoing intrauterine pregnancy was uncommon, with 0.13% continuing to delivery. Ectopic pregnancy detected after abortion that occurred with any severe adverse event was also rare (<6 per 314,859 abortions).

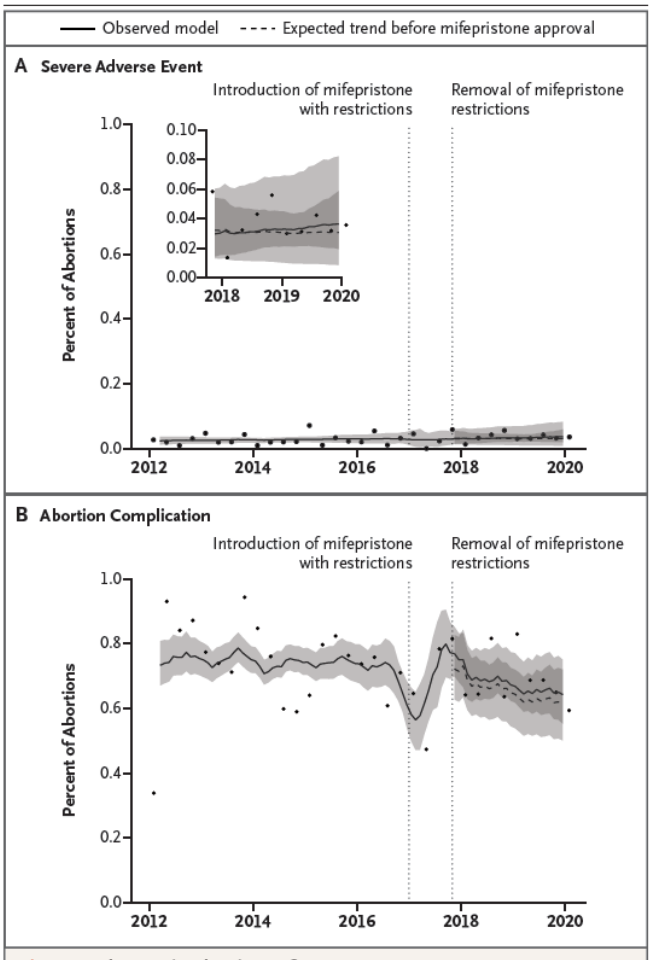

Figure 2. Changes in Abortion Safety Outcomes.

Shown are the results of interrupted time-series analyses of the level and trend of abortion safety in Ontario, Canada, among all surgical and medical abortions provided during the study period. Panel A shows the incidence of severe adverse events, which included any blood transfusion, abdominal surgery (laparotomy, laparoscopy, or hysterectomy), admission to an intensive care unit, or sepsis that occurred during a hospitalization associated with an abortion-complication code. Panel B shows abortion complications, which included genital tract or pelvic infection, hemorrhage, embolism, shock, renal failure, damage to pelvic organs or tissues, venous complications, and other or unspecified abortion complications. In Panel A, the inset shows the same data on an expanded y axis; shading indicates 95% confidence intervals.

DISCUSSION

We comprehensively examined changes in abortion use, safety, and effectiveness during the period when mifepristone had become available without REMS-like restrictions in a population-based cohort of abortion service users in Ontario, Canada. We found that after mifepristone had become available with a normal prescription dispensed by pharmacists and taken at user discretion, abortion rates were materially stable, medical abortion uptake was rapid, and abortion-related adverse events and ectopic pregnancy remained rare, as compared with before mifepristone had been available.

The modestly slower decline in the abortion rate, relative to the expected decline based on the trend before mifepristone had become available, may be due in part to the provision of abortion earlier in pregnancy. Since 4 to 7% of pregnancies per week in the first trimester[27] end in

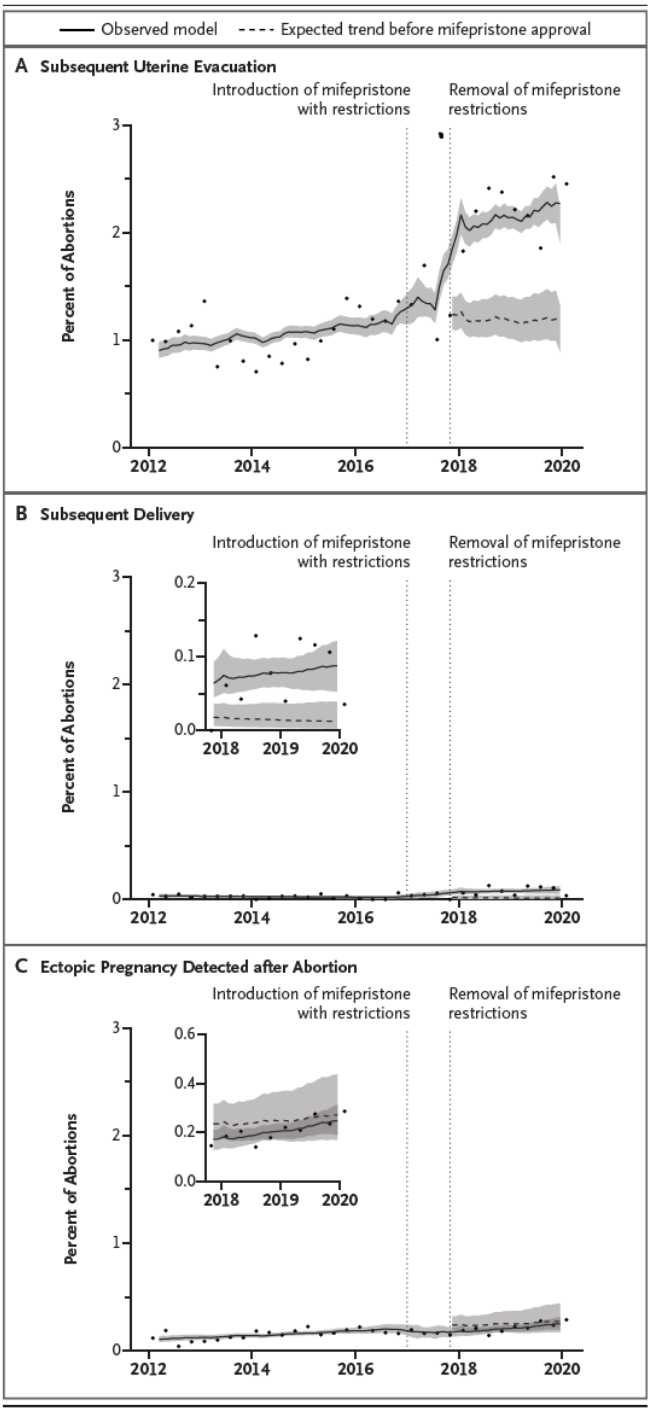

Figure 3. Abortion Effectiveness and Ongoing Pregnancy Outcomes.

Shown are the results of interrupted time-series analyses of the level and trend of ongoing pregnancy outcomes among all surgical and medical abortions provided during the study period. These outcomes include the incidences of uterine evacuation after abortion (Panel A), ongoing intrauterine pregnancy continuing until delivery (Panel B), and ectopic pregnancy detected after abortion (Panel C). Shading indicates 95% confidence intervals.

spontaneous abortion, the availability of abortion at earlier gestational ages would increase the abortion rate by enabling termination of pregnancy before the occurrence of miscarriage, even in the absence of a true increase in demand for abortion. The availability of mifepristone without restrictions may have slowed the decline in the abortion rate through improved abortion access, a hypothesis that is consistent with findings that restrictive policies regarding the prescription of mifepristone worsen access to abortion[28] and that abortion rates increase when access improves.[29] Because we did not measure pregnancy intention in our study, we cannot differentiate trend changes in unintended pregnancy from changes in the fraction of pregnancies that were terminated. Our findings indicate that improved abortion access was not associated with a material increase in the abortion rate.

The uptake of mifepristone for medical abortion under Canada's unrestricted regulations was faster than reported in settings with restrictive regulations. Although more than one third of abortions in Ontario were medically induced 2 years after mifepristone had been available as a normal prescription, 5.2% of abortions in the United States were medically induced 2 years after mifepristone availability, with the percentage slowly increasing to 39.0% 17 years after availability.[2] Similarly slower uptake has been reported in European settings that have mifepristone restrictions, even among those where mifepristone had been introduced long after best practice guidelines had been established.[30]

Our findings indicate that abortion remained safe and ongoing pregnancy remained infrequent after unrestricted access to mifepristone.

Without observed administration, some patients with a prescription for mifepristone may have never used it.[9] However, the infrequent occurrence of ongoing intrauterine pregnancy indicates that patients who received mifepristone most often correctly used the medication without supervision.[31] Our abortion safety and effectiveness findings are consistent with the results of recent studies examining patient-reported outcomes during the coronavirus disease 2019 pandemic, when REMS-like restrictions were temporarily removed in some settings.[9,32,33] A study involving 52,142 patients in the United Kingdom showed no material differences in success rates or serious adverse events between abortions provided under REMS-like restrictions and a telemedicine-hybrid model with investigations such as ultrasonography performed only when indicated.[33]

The small increase in the incidence of ectopic pregnancy that was detected after unrestricted access to mifepristone was consistent with the increasing trend before the availability of mifepristone, which indicated no increase over the expected incidence. A 2012 cross-sectional survey of abortion providers in the United States and Canada showed that more than 90% of providers routinely performed ultrasonography before abortion,[34] even though the value of such imaging in the absence of known ectopic risks or symptoms had not been shown.[2,35] Ectopic pregnancy is more likely to be detected after abortion that is provided at earlier stages of gestation before a clinical or ultrasonographic diagnosis. Because undiagnosed ectopic pregnancy can lead to tubal rupture and death,[36] identifying ectopic pregnancy before the onset of complications with the use of clear clinical protocols[2,4] is essential, although such procedures do not need to be performed before the initiation of medical abortion.[33]

Our safety and ongoing pregnancy findings among first-trimester medical abortions during the period after unrestricted access to mifepristone were consistent with reports from other settings with restricted access.[2,4] In settings with REMS-like restrictions, first-trimester medical abortions resulted in major adverse events in 0.3 to 0.5% of women[2,4,31] and blood transfusion in 0.04 to 0.10%.[4,31] Among medical abortions performed up to 63 days after the last menstrual period, subsequent uterine evacuation occurred in 2.0 to 4.8% of patients and ongoing intrauterine pregnancy in 0.5 to 2.0%.[2,4] In our study among first-trimester abortions, severe adverse events were too infrequent to report an incidence value, 0.04% of the patients underwent blood transfusion, 4.5% underwent uterine evacuation, and 0.13% had an ongoing pregnancy continuing to delivery. Although the incidence of uterine evacuation was increasing before mifepristone had become available, the expected incidence trend after the availability of mifepristone leveled off because of the more rapid increase in the number of abortions (the denominator). Because subsequent uterine evacuation is substantially more frequent after medical abortion than after surgical procedures (<3.0%),[4,37] a practice shift to more medical abortions is expected to increase the incidence of this outcome.

Our study has several potential limitations. The fundamental assumption underlying the validity of interrupted time-series analysis is that outcome trends before the exposure of interest would have continued if the exposure had not occurred. This assumption does not hold if other policy, practice, or contextual changes that may have an effect on outcome incidence occur concurrent to the exposure of interest.[20] However, this analytic approach is robust with respect to changes in the individual-level characteristics of patients or provider practices that accrue gradually over the study period, since such changes are accounted for in trend regression terms during the period before mifepristone had become available. Careful review of policies, academic literature, practice guidelines, and media output that are related to abortion during the study period identified no concurrent changes that would have invalidated our analytic approach. Practitioner fees, training programs, administrative data codes, and cost coverage for the drug were stable during the study period. Surveys and interviews among practitioners indicate that initial mifepristone restrictions were barriers to broad adoption of this practice.[13,38] The short period during which mifepristone was available in Canada with REMS-like restrictions (January 1 to November 6, 2017) precludes a formal analysis of mifepristone

availability with restrictions as compared with such availability without restrictions. The unrestricted availability of mifepristone appears to be the fundamental factor associated with changes in our study outcomes.

Our prescription database universally captured mifepristone prescriptions that were dispensed after August 10, 2017 (when a universal no-cost subsidy was introduced) but only captured mifepristone prescriptions from January to August 9, 2017, among patients with income-based prescription subsidies and those under 25 years of age. These factors may have contributed to an underestimation of early mifepristone uptake. However, this limitation was mitigated by our identification of medical abortions using data regarding practitioner payments, procedures, and prescriptions, along with our exclusion of these months from our time-series analysis. Our population-based data comprehensively captured all abortions among Ontario residents, as well as all subsequent hospital or health service events, even if such services were not provided by the same provider or facility that provided the initial care. Therefore, loss to follow-up was minimal since it involved only patients who had moved out of the province within 6 weeks after the abortion or during the current pregnancy. However, since linkages across databases are possible only for residents who are eligible for provincial health insurance, we excluded the 397 abortions (0.1%) that were provided to nonresidents. Because of lags in availability of cause-of-death data, we could not report the incidence of abortion-related deaths. However, surveillance by the U.S. Centers for Disease Control and Prevention indicates that death is a very rare outcome (2 deaths among 609,095 abortions in 2018).[39] Although minimal data were missing for gestational trimester, we did not have data regarding specific gestational ages in weeks, which prevented an evaluation of changes to abortion timing within trimesters.

When mifepristone became available as a normally prescribed medication in Canada, the frequency of medical abortion rose substantially as compared with the frequency during the period before mifepristone became available, even though the rate of abortion remained materially stable. The incidences of serious adverse events and complications remained materially unchanged, and uterine evacuation and ongoing pregnancy remained infrequent.

Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health and the Canadian Institute for Health Information. The analyses, conclusions, opinions, and statements expressed in this article are solely those of the authors and do not reflect those of the funding or data sources.

Supported by a grant (PJT-168964) from the Canadian Institutes of Health Research and by a grant from the Women's Health Research Institute of the Provincial Health Services Authority of British Columbia.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank staff members at ICES, which is supported by the Government of Ontario Ministry of Health and the Ministry of Long-Term Care, for their assistance with data management; staff members at IQVIA Solutions Canada for use of their Drug Information File; and our fellow members of the Canadian Contraception and Abortion Research Team for their contributions to the study.

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Center for Drug Evaluation and Research (CDER)

(b)(6)/PPI

Memorandum to File

NDA	020687
Reviewer Names	(b)(6)/PPI
(b)(6)/PPI	
Date of Memorandum	December 30, 2022
Subject	Referenced Publications

On December 16, 2021, FDA sent REMS Modification Notification letters to Danco Laboratories, LLC (Danco) and GenBioPro, Inc. (GBP) (collectively the Applicants) regarding the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program), which was approved on April 11, 2019 and last modified on May 14, 2021. The December 16, 2021 letters explained that, in accordance with section 505-1(g)(4)(8) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA had determined that the 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. The letters also noted that the determination was based on a review of published literature, safety information collected during the COVID-19 Public Health Emergency (PHE), FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

FDA is reviewing Danco's supplemental new drug application (sNDA) and GBP's supplemental abbreviated new drug application (sANDA), which were submitted on June 22, 2022, in response to the December 16, 2021 letters. The REMS modification supplemental applications propose revisions to the Mifepristone REMS Program that, consistent with the December 16, 2021 REMS Modification Notification letters, 1) remove the REMS requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber (known as the "in-person dispensing requirement") and 2) add a new REMS requirement for pharmacy certification. The supplemental applications also include proposed changes

to, among other things, the REMS document and REMS materials, to align with the removal of the in-person dispensing requirement and the addition of pharmacy certification.

(b)(6)/PPI was notified that the publications listed below were attached to the Complaint recently filed in a lawsuit (Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration, No. 2:22-cv-00223-Z (N.D. Tex.)):

1. Studnicki et al., 2021: "A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999–2015"[1]
2. Studnicki et al., 2022: "A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization"[2]
3. Rafferty et al., 2020: "#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives"[3]
4. Aultman et al., 2019: "Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019"[4]
5. Cirucci et al., 2021: "Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act"[5]

(b)(6)/PPI has reviewed these five publications for the limited purpose of determining whether they contain information relevant to our review of the REMS modifications proposed in the pending sNDA and sANDA, applying the same approach described on pages 11-12 of the December 16, 2021 REMS Modification Rationale Review prepared jointly by (b)(6)/PPI As described on pages 11-12 of the REMS Modification Rationale Review, (b)(6)/PPI approach to the literature review for the Agency's December 16, 2021 REMS modification determination focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS elements to assure safe use (ETASUs). We excluded systematic reviews and meta-analyses because these publications did not include original safety data related to the outcomes of medical abortion.

We applied the same approach that was used for the literature search for the December 16, 2021 review to these five articles, which were not studies focused on in-person dispensing or pharmacy certification. We conclude that the five publications listed above do not include safety data relevant to

[1] Studnicki J, Harrison DJ, Longbons T, et al. A Longitudinal Cohort Study of Emergency Room Utilization Following Mifepristone Chemical and Surgical Abortions, 1999–2015. Health Services Research and Managerial Epidemiology. 2021;8. doi:10.1177/23333928211053965.

[2] Studnicki J, Longbons T, Harrison DJ, et al. A Post Hoc Exploratory Analysis: Induced Abortion Complications Mistaken for Miscarriage in the Emergency Room are a Risk Factor for Hospitalization. Health Services Research and Managerial Epidemiology. 2022;9. doi:10.1177/23333928221103107.

[3] KA Rafferty and T Longbons. #AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives. Health Communication 2020; 36:12, 1485-1494.

[4] Aultman K, Cirucci CA, Harrison DJ, et al. Deaths and Severe Adverse Events after the use of Mifepristone as an Abortifacient from September 2000 to February 2019. Issues Law Med. 2021;36(1):3-26.

[5] Mifepristone Adverse Events Identified by Planned Parenthood in 2009 and 2010 Compared to Those in the FDA Adverse Event Reporting System and Those Obtained Through the Freedom of Information Act. Health Serv Res Manag Epidemiol. 2021 Dec 21;8:23333928211068919. doi: 10.1177/23333928211068919. eCollection 2021 Jan-Dec.

the Applicants' proposed modifications to the REMS ETASUs (i.e., removal of the "in-person dispensing requirement" or the addition of a new requirement for pharmacy certification).

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12/30/2022 10:49:21 AM

Center for Drug Evaluation and Research (CDER)

(b)(6)/PPI

Memorandum to File

NDA	020687
Reviewer, (b)(6)/PPI (b)(6)/PPI	(b)(6)/PPI
Date of Memorandum	January 3, 2023
Subject	Referenced Publication

On December 16, 2021, FDA sent REMS Modification Notification letters to Danco Laboratories, LLC (Danco) and GenBioPro, Inc. (GBP) (collectively the Applicants) regarding the single, shared system Risk Evaluation and Mitigation Strategy (REMS) for mifepristone 200 mg (hereafter referred to as the Mifepristone REMS Program), which was approved on April 11, 2019 and last modified on May 14, 2021. The December 16, 2021 letters explained that, in accordance with section 505-1(g)(4)(B) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA had determined that the 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. The letters also noted that the determination was based on a review of published literature, safety information collected during the COVID-19 Public Health Emergency (PHE), FDA Adverse Event Reporting System (FAERS) reports, REMS assessment reports, and information provided by advocacy groups, individuals, the Applicants, and plaintiffs in ongoing litigation.

FDA is reviewing Danco's supplemental new drug application (sNDA) and GBP's supplemental abbreviated new drug application (sANDA), which were submitted on June 22, 2022, in response to the December 16, 2021 letters. The REMS modification supplemental applications propose revisions to the Mifepristone REMS Program that, consistent with the December 16, 2021 REMS Modification Notification letters, 1) remove the REMS requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber (known as the "in-person dispensing requirement") and 2) add a new REMS requirement for pharmacy certification. The supplemental applications also include proposed changes to, among other things, the REMS document and REMS materials, to align with the removal of the in-person dispensing requirement and the addition of pharmacy certification.

(b)(6)/PPI received notification through a weekly email listing the table of contents for the Annals of Internal Medicine that a large clinical study, Liu N, Ray JG., 2023 "Short-term Adverse Outcomes After

Mifepristone–Misoprostol Versus Procedural Induced Abortion," was published in Annals of Internal Medicine on January 3, 2023.[1]

(b)(6)/PPI have reviewed this publication for the limited purpose of determining whether it contains information relevant to our review of the REMS modifications proposed in the pending sNDA and sANDA, applying the same approach described on pages 11-12 of the December 16, 2021 REMS Modification Rationale Review prepared jointly by (b)(6)/PPI As described on pages 11-12 of the REMS Modification Rationale Review, (b)(6)/PPI approach to the literature review for the Agency's December 16, 2021 REMS modification determination focused on publications containing safety data related to outcomes of medical abortion (objective safety data) obtained from our literature search and from the references provided to us relevant to the REMS elements to assure safe use (ETASUs).

We applied the same approach that was used for the literature search for the December 16, 2021 review to this article. We conclude that the findings are not relevant to the Applicants' proposal to remove the "in-person dispensing requirement" or to add a new requirement for pharmacy certification because the study did not evaluate and compare outcomes when the drug is dispensed in person versus a manner other than in person.

[1] Liu N, Ray JG. Short-term Adverse Outcomes After Mifepristone–Misoprostol Versus Procedural Induced Abortion. A population-based propensity-weighted study. Ann Intern Med. 3 January 2023. [Epub ahead of print]. doi:10.7326/M22-2568.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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Exhibit 3

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2019
Drug Safety

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
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Food and Drug Administration
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Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
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Food and Drug Administration
10903 New Hampshire Ave, Bldg. 71, Room 3128
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Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2019
Drug Safety

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary

Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to clarify how the Food and Drug Administration (FDA or Agency) applies the factors set forth in section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) in determining whether a risk evaluation and mitigation strategy (REMS) is necessary to ensure that the benefits of a drug outweigh its risks.[2] This guidance fulfills one of the performance goals that FDA agreed to satisfy in the reauthorization of the Prescription Drug User Fee Act (PDUFA) V.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by the Office of New Drugs, Office of Surveillance and Epidemiology, Office of Medical Policy, and Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

[2] Section 505-1 of the FD&C Act applies to applications for prescription drugs submitted or approved under subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications) of the FD&C Act and to applications submitted or licensed under section 351 (i.e., biologics license applications) of the Public Health Service Act (PHS Act) (42 U.S.C. 262). For the purposes of this document, unless otherwise specified, the term *drug* refers to human prescription drugs, including those that are licensed as biological products (biologics).

[3] Section XI.A.1 of "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017" (PDUFA V), available at http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf.

Contains Nonbinding Recommendations

II. BACKGROUND

The Food and Drug Administration Amendments Act of 2007 (FDAAA)[4] created section 505-1 of the FD&C Act, which establishes FDA's REMS authority. A REMS is a required risk management plan that can include one or more elements to ensure that the benefits of a drug outweigh its risks.[5]

If FDA determines that a REMS is necessary, the Agency may require one or more REMS elements, which could include a Medication Guide,[6] a patient package insert,[7] and/or a communication plan.[8] FDA may also require elements to assure safe use (ETASU) as part of a REMS.[9] ETASU may be required if the drug has been shown to be effective, but is associated with a specific serious risk and can be approved only if, or would be withdrawn unless, such elements are required as part of a strategy to mitigate a specific serious risk(s) listed in the labeling of the drug. ETASU may be required for approved drug products that were initially approved without ETASU when other elements are not sufficient to mitigate a serious risk.

Specifically, ETASU may include one or any combination of the following requirements[10]:

- Health care providers who prescribe the drug have particular training or experience, or are specially certified;
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified;
- The drug be dispensed to patients only in certain health care settings, such as hospitals;
- The drug be dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results;
- Each patient using the drug be subject to monitoring; or
- Each patient using the drug be enrolled in a registry.

If a REMS includes certain ETASU, the REMS may also include an implementation system to enable the applicant to monitor, evaluate, and improve the implementation of the elements (e.g., development of a REMS specific Web site or call center to facilitate enrollment; establishment of electronic databases of certified health care settings).[11]

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[4] Public Law 110-85.

[5] See section 505-1(e) of the FD&C Act and section 505-1(f) of the FD&C Act.

[6] See Section 505-1(e)(2) of the FD&C Act.

[7] Id.

[8] See Section 505-1(e)(3) of the FD&C Act.

[9] See Section 505-1(f) of the FD&C Act.

[10] See Section 505-1(f)(3) of the FD&C Act.

[11] See Section 505-1(f)(4) of the FD&C Act.

All REMS should include one or more overall goals, and if the REMS has ETASU, the REMS must include one or more goals to mitigate a specific serious risk listed in the labeling of the drug and for which the ETASU are required.[12]

Finally, REMS generally must include a timetable for submission of assessments of the REMS.[13] The timetable for submission of assessments of the REMS must include an assessment by the dates that are 18 months and 3 years after the REMS is initially approved, and an assessment in the 7th year after the REMS is approved, or at another frequency specified in the REMS.[14]

FDA can require a REMS before initial approval of a new drug application or, should FDA become aware of new safety information[15] about a drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.[16]

Before FDAAA was enacted, FDA approved a small number of drugs and biologics with risk minimization action plans (RiskMAPs).[17] A RiskMAP is a strategic safety program designed to meet specific goals and objectives in minimizing the known risks of a drug while preserving the drug's benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies that went beyond the provision of FDA-approved labeling, including the prescribing information.[18] In 2005, FDA issued a guidance for industry, *Development and Use of Risk Minimization Action Plans* (RiskMAP Guidance).[19] Many of the principles described in the RiskMAP Guidance are reflected in the REMS provisions set forth in FDAAA[20] and have been incorporated into FDA's REMS decision-making process. The purpose of this new guidance is to explain FDA's current application of previously articulated risk management principles and considerations under the REMS regulatory paradigm.

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[12] See Section 505-1(f)(3) of the FD& C Act.

[13] New Drug Applications (NDAs) and Biologics License Applications (BLAs) must include a timetable for submission of assessments. ANDAs are not subject to the requirement for a timetable for submission of assessments (Section 505-1(i)), but FDA can require any application holder, including ANDA applicants, to submit REMS assessments under Section 505-1(g)(2)(C).

[14] See Section 505-1(d); see also 505-1(g)(2) of the FD&C Act.

[15] Section 505-1(b)(3) of the FD&C Act.

[16] See section 505-1(a)(2) of the FD&C Act.

[17] Some of these drugs were approved pursuant to either subpart H (21 CFR 314.520) or subpart E (21 CFR 601.42) with restrictions on their use or distribution to assure safe use.

[18] A drug's *prescribing information* (PI) contains a summary of the essential scientific information needed for the safe and effective use of the drug. 21 CFR 201.56(a)(1). The PI is updated from time to time to incorporate information from postmarketing surveillance or studies, for example, revealing new benefits or risk concerns.

[19] The RiskMAP Guidance is available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071616.pdf.

[20] See section 505-1(a)(1) of the FD&C Act.

III. MANAGING DRUG RISKS

The statutory standard for FDA approval of a drug is that the drug is safe and effective for its labeled indications under its labeled conditions of use.[21] FDA's determination that a drug is safe, however, does not suggest an absence of risk. Rather, a drug is considered to be safe if the clinical significance and probability of its beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects. In other words, a drug is considered safe if it has an appropriate benefit-risk balance.

Risk management is a key factor in FDA's risk-benefit assessment.[22] As described in previous guidances, risk management consists of both risk assessment and risk minimization: it is an iterative process involving (1) assessing a drug's benefit-risk balance, (2) developing and implementing tools to minimize the drug's risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a drug's life cycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.[23]

IV. THE USE OF REMS IN MANAGING DRUG RISKS

The goal of risk mitigation is to preserve a drug's benefits while reducing its risks to the extent possible. For the majority of drugs, routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks. In some cases, however, FDA may consider whether a REMS would help ensure that the benefits of the drug outweigh its risks.

FDA's determination as to whether a REMS is necessary for a particular drug is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case. In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.

In making these determinations, FDA may take into consideration information from a variety of sources, including FDA's internal and external experts with specialized expertise relevant to a particular risk, input on relevant issues from other centers within FDA, other government

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[21] See section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

[22] Information about FDA's Benefit-Risk Assessment Framework is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm

[23] See the following FDA guidances for industry: *Premarketing Risk Assessment,* available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm072002.pdf; RiskMAP Guidance; and *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment,* available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071696.pdf.

agencies, advisory committee meetings, the Drug Safety Oversight Board, literature, and professional societies. For approved drugs, FDA may also gather information from post-approval adverse event reports and active surveillance, as well as from post-approval clinical trials and other post-approval studies, including epidemiological studies, when evaluating whether a REMS is necessary.

If FDA determines that a REMS is necessary, the Agency considers what the goals of a proposed REMS to address these risks would be and what specific REMS elements, as described above, could help meet those goals. The REMS should be designed to meet the relevant goals, not unduly impede patient access to the drug, and minimize the burden on the health care delivery system to the extent practicable. If FDA believes that the drug's risks would exceed its benefits even if FDA were to require a REMS for the drug, FDA will not approve the drug or may consider seeking withdrawal of the drug if it is already being marketed.

V. APPLICATION OF STATUTORY FACTORS IN REMS DECISION-MAKING

Section 505-1(a)(1) of the FD&C Act, as added by FDAAA, requires FDA to consider the following six factors[24] in making a decision about whether to require a REMS:

- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- The expected benefit of the drug with respect to the disease or condition;
- The seriousness of the disease or condition that is to be treated with the drug;
- Whether the drug is a new molecular entity;
- The expected or actual duration of treatment with the drug; and
- The estimated size of the population likely to use the drug.

These six factors influence FDA's decisions with respect to whether a REMS is required for a particular drug and what type of REMS might be necessary (i.e., what specific elements or tools should be included as part of the REMS). FDA makes decisions about requiring a REMS as part of a benefit-risk determination for a drug after an evaluation that includes integrated consideration of each of the statutory factors. All six factors are considered together to inform FDA's REMS decision making process and no single factor is determinative as to whether a REMS is necessary. The relative importance or weight of each factor is a case specific inquiry. The application of these factors is discussed in the sections below.

[24] The FD&C Act requires that FDA consider these factors in determining whether a REMS is necessary for a new drug. FDA also generally considers these factors in determining whether (based on new safety information) a REMS is necessary for a drug that is the subject of an approved application.

Contains Nonbinding Recommendations

A. Seriousness of Known or Potential Adverse Events That May Be Related to the Drug and the Background Incidence of Such Events in the Population Likely To Use the Drug

The more serious[25] a drug's known or potential associated risks relative to its benefits, the more likely it is that a REMS will be necessary to ensure that the benefits of the drug outweigh its risks. In determining whether to require a REMS, FDA considers the source, nature and reliability of available scientific evidence about the adverse events as well as the characteristics of the risks, including the reversibility, preventability, temporality, frequency, severity, background incidence, and likelihood of occurrence.

For drugs associated with adverse events that are reversible or preventable if particular measures are taken promptly, FDA may consider requiring a REMS to help ensure that such measures are undertaken in a timely manner to minimize or prevent a serious adverse event. For example, for a drug that is associated with hepatotoxicity that is reversible with drug discontinuation, the REMS may require that the patient be monitored through laboratory studies so that the drug can be discontinued if and when hepatic enzyme elevations are observed.

A drug that is associated with a risk of a serious adverse event that is irreversible, such as one that causes a permanent disability or persistent incapacity, may be particularly likely to have a favorable benefit-risk profile only in the presence of a REMS that helps minimize drug exposure and the associated occurrence of the adverse event. In such cases, a REMS may include, for example, a prescriber certification requirement that includes prescriber training and patient counseling on the nature of the associated risk and on the drug's benefit-risk balance to facilitate informed patient and prescriber decisions about treatment with the drug. Such REMS are designed to ensure that patients are fully informed of the serious risk before beginning therapy and may involve patient acknowledgment forms or other methods of documenting that such patient-provider discussions have taken place. This kind of REMS is particularly important for drugs with limited available methods of preventing the actual occurrence of drug-associated adverse events.

The frequency and severity of adverse events associated with the use of a drug may also affect FDA's determination of whether a REMS is necessary. While a high frequency of adverse events may necessitate a REMS to mitigate this risk, FDA may also require a REMS for an infrequent adverse event, if the adverse event is particularly severe.

As part of its assessment of whether a particular adverse event is drug-associated, FDA examines the rate of the adverse event in individuals exposed to the drug relative to the background incidence of the adverse event in the population likely to use the drug. If an adverse event is determined to be drug-associated, FDA may determine that treatment with the drug unacceptably

[25] Section 505-1(b)(4) of the FD&C Act defines an adverse drug experience as serious if it results in death, immediate risk of death, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (or, based on appropriate medical judgment, may jeopardize the patient and may require a medical or surgical intervention to prevent the above-described outcomes).

increases the frequency and/or severity of the adverse event in the patient population and that this risk needs to be mitigated through a REMS.

As part of its evaluation of the risks associated with the use of a drug, FDA also takes into consideration whether information about managing the particular risk is widely available and whether risk management measures are being widely implemented. FDA may also consider factors such as the specialties of the healthcare providers who may prescribe, dispense or administer the drug and whether approaches to mitigate the risk are standard and well-known by the health care professional or are less familiar to the health care professional when determining whether a REMS is needed. The Agency also takes into account the health care setting(s) in which the drug is used or is likely to be used. For drugs intended for use in an outpatient setting, FDA considers the degree to which patients can be expected to reliably recognize symptoms as being associated with a drug and to take necessary actions to address adverse events. If, for example, FDA expects that a drug will likely be used in a setting where patient monitoring and certain medical equipment are not available, and believes that such measures are needed to mitigate the risks associated with the use of the drug, FDA may require a REMS with ETASU to limit use of the drug to settings in which these measures are available.

B. Expected Benefit of the Drug With Respect to the Disease or Condition

When assessing a drug's expected benefits with respect to a specific disease or condition, FDA may evaluate information about the drug's effectiveness, whether the drug treats a serious disease or condition, whether it fills an unmet medical need, and whether it can cure the disease or alleviate its symptoms. FDA may also consider the extent to which new dosage forms enhance convenience of administration and/or improve adherence to prescribed regimens, and whether new formulations or delivery mechanisms may extend treatment to patient populations who were formerly unable to use the drug.

A drug's expected benefits, however, are not considered in isolation. In determining whether a REMS is necessary, FDA's assessment of a drug's benefit is balanced against consideration of the risks associated with its use. For example, a once-a-month oral dosage form of a drug that was previously only available as a daily oral dosage form may offer a meaningful benefit in terms of convenience to the patient and adherence to medication therapy, but may have a different risk profile (e.g., a new risk associated with the new formulation, or with the longer half-life of the drug) that makes it more likely that FDA would determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.

C. Seriousness of the Disease or Condition To Be Treated

The seriousness of the disease or condition[26] to be treated is a part of FDA's overall analysis of the benefits of a drug: the more serious the disease or condition to be treated, the greater the potential benefit of the drug's measured effect in the benefit-risk assessment. Nevertheless, even for drugs intended to treat serious or life-threatening diseases or conditions, the severity, irreversibility, or duration of an associated risk may weigh in favor of a REMS. For example, if a drug indicated for long-term treatment of an indolent, asymptomatic, or slowly progressing cancer also has a more immediate risk of serious and potentially fatal cardiac arrhythmias, FDA may conclude that, without a REMS, the risk of serious cardiac arrhythmias outweighs the potential benefits of this kind of cancer treatment. In this example, a REMS may be required to educate prescribers about the risk, appropriate monitoring, and management of cardiac arrhythmias to help minimize the occurrence of the adverse event associated with the drug.

D. Whether the Drug Is a New Molecular Entity

For new molecular entities (NMEs)[27] and certain Biologics License Applications (BLAs) licensed under section 351(a) of the PHS Act, available information about the drug can be limited and, as a result, there may be greater uncertainty about risks associated with the use of the drug that might emerge in the post-approval setting. When available safety information about a NME or BLA indicates a serious risk, there may be uncertainties about the nature of the serious risk (e.g., the strength of the association of the adverse event with drug treatment, the likelihood of occurrence of the adverse event, or the accuracy and/or reliability of the data). Depending on the nature of the uncertainties about the risks associated with the use of the drug, FDA may require a REMS to help ensure that the benefits of the drug outweigh its risks.

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[26] FDA has defined *serious disease or condition* as

> "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

(21 CFR 312.300(b)); see also FDA's guidance for industry on *Expedited Programs for Serious Conditions – Drugs and Biologics*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

[27] FDA has defined the term "new molecular entity" as an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act (in any application approved or deemed approved from 1938 to the present), or has been previously marketed as a drug in the United States. See Manual of Policies and Procedures (MAPP) 5018.2 NDA Classification Codes, available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

E. Expected or Actual Duration of Treatment With the Drug

The duration of treatment with a drug and the impact of treatment length on the likelihood and severity of adverse events also affect FDA's decision-making with regard to the need for a REMS. If long-term therapy with a drug appears to increase the likelihood of a serious adverse event, FDA may require a REMS either to limit the duration of treatment or to ensure that patients on long term treatment are monitored, e.g., for liver function if the drug is associated with liver toxicity.

A REMS may also be required for a drug with a relatively short duration of treatment, depending on the nature of the associated risk if, for example, the drug is associated with a serious adverse event that occurs immediately after administration. Such a REMS may require that the drug only be administered in a setting in which monitoring is available to ensure that the adverse event can be appropriately managed or in a setting in which, for example, providers have received particular risk management training. Similarly, a REMS may be required for a drug that is only intended to be administered once or twice if FDA determines that specialized training is necessary to prevent the occurrence of an adverse event associated with improper drug administration. In some cases, serious adverse events may occur even after treatment with a drug has ended. In such cases, FDA may determine that a REMS is required to ensure proper monitoring of patients for a period of time following completion of treatment.

F. Estimated Size of Population Likely To Use the Drug

In considering the estimated size of the population likely to use the drug, FDA considers, among other things, the extent to which that population includes patients expected to use the drug for unapproved uses and the risks associated with those uses. In certain cases, FDA may consider whether a REMS designed to help ensure that a drug's use is limited to its approved indications is appropriate.

VI. ADDITIONAL CONSIDERATIONS: POTENTIAL BURDEN ON THE HEALTH CARE DELIVERY SYSTEM AND PATIENT ACCESS

FDA understands that REMS, particularly those with ETASU, may impose some measure of burden on patients and/or health care providers. When considering this burden on patient access and the health care delivery system, FDA takes into account existing REMS elements for other drugs with similar risks and whether the REMS under consideration can be designed to be compatible with established medical drug distribution, procurement, and dispensing systems. FDA also considers how patients for whom the drug is indicated currently access health care (such as whether patients are in rural or medically underserved areas) and whether the REMS may impose additional access difficulties. FDA also takes into account the consequences of potential treatment interruption or delays, particularly where patients have serious or life-threatening conditions and/or have difficulty accessing health care. In such circumstances, FDA takes steps, to ensure that REMS are designed to minimize delays or interruptions in drug therapy that may have untoward clinical impact. Particularly for a REMS that requires additional procedures and controls in the patient care process, FDA also considers the characteristics,

experience, and size of the likely prescriber population; how the drug will likely be dispensed in the setting in which it will likely be used; and the patient population likely to use the drug.

The selection of REMS elements and tools may be influenced by the extent to which they have already been used in the clinical trials to evaluate the drug's safety and efficacy, and by what is known about the effectiveness of the elements and tools more generally. Selection of risk management elements and tools is also informed by any regulatory precedent for addressing similar risks.[28] For example, if a serious risk is common to all members of a drug class, FDA will consider, as appropriate, how the Agency has previously managed the riskand seek opportunities to standardize the approach to managing that risk. FDA also encourages sponsors to submit REMS proposals that are compatible with established distribution, procurement, and dispensing systems. Following approval of a REMS, FDA continues to evaluate the impact of the REMS on patient access and the health care delivery system.

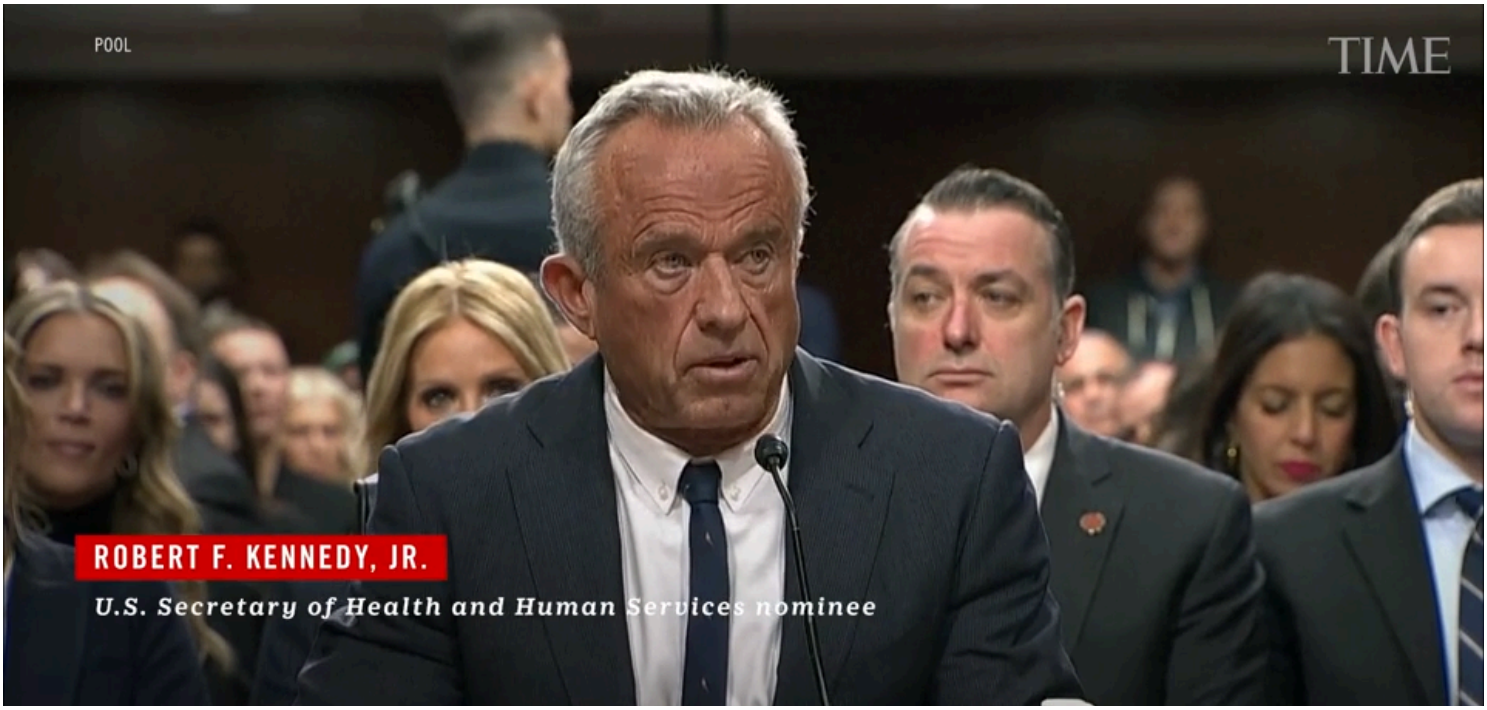
[28] In addition, the elements and tools may be driven by results of previous REMS assessments for REMS designed to address a similar risk, a similar patient population, or a similar drug distribution or dispensing system to the product under review.

Exhibit 4

HEALTH ABORTION

RFK Jr. Says He'll Follow Trump's Lead on Abortion

5 MINUTE READ



BY ALICE PARK

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Robert F. Kennedy Jr., President Trump's pick to lead the U.S. Department of Health and Human Services (HHS), has been tough to tie down to one stance on abortion. For most of his career, he has supported it—in stark contrast to the views of many prominent figures in the current Administration.

But in a Senate confirmation hearing on Jan. 29, Kennedy clarified his position on abortion. “I serve at the pleasure of the President," he said in response to a question about his abortion beliefs. "I’m going to implement his policies.”

The following day, Kennedy further cemented his new position when asked if he was hiring people who are pro-life for his department. "Yes, I am," he said.

Here's what to know about Kennedy's past and current stance on abortion.

What Kennedy has said in the past about abortion

Kennedy, a former Democrat, has long advocated for women's reproductive rights and supported a woman's right to choose whether or not she gets an abortion. As a presidential candidate in May 2024, Kennedy described every abortion as a “tragedy” but said the decision should be left up to women, going as far as to say this freedom to choose should extend to full-term pregnancies.

Shortly after, in a long post on X, he clarified his statement but essentially continued to back abortion. “I support the emerging consensus that abortion should be unrestricted up until a certain point. I believe that point should be when the baby is viable outside the womb. Therefore I would allow appropriate restrictions on abortion in the final months of pregnancy, just as Roe v. Wade did."

Read More: *RFK Jr. Denied He Is Anti-Vaccine During His Confirmation Hearing. Here’s His Record*

In a video he posted to Facebook in June, he further explained that his stance on late-term abortion, in particular, had evolved. He initially believed that the only reason a woman would get an abortion in the third trimester is if the pregnancy put her life at risk or the baby had a fatal condition. “I don’t think a bureaucrat or a judge is better equipped than the baby’s own mother to decide what to do in those circumstances,” he said.

"I had been assuming that virtually all late-term abortions were such cases, but I've learned that my assumption was wrong," he wrote on X. "Sometimes, women abort healthy, viable late-term fetuses. These cases of purely 'elective' late-term abortion are very upsetting. Once the baby is viable outside the womb, it should have rights and it deserves society's protection."

His position on abortion now

At the Jan. 29 confirmation hearing, Kennedy stuck to a different refrain: "I agree with President Trump that every abortion is a tragedy," he said several times. "I agree with him that we cannot be a moral nation if there are 1.2 million abortions a year," he also said. "I agree with him that states should control abortion."

The statements reflect Kennedy's changing position as he attempts to appease Trump's conservative anti-abortion supporters.

Read More: *The Origins of the Anti-Vaccination Movement*

Numerous Democratic senators pointed out his past pro-choice position in the hearing. "I have never seen any major politician flip on that issue quite as quickly as you did when Trump asked you to become HHS Secretary," said Sen. Bernie Sanders of Vermont.

Sen. Catherine Cortez Masto, a Democrat from Nevada, asked if a pregnant woman with a life-threatening bleed should be able to get an emergency abortion even if her state bans them. "You would agree, also as an attorney, that federal law protects her right to that emergency care. Correct?" Kennedy responded after a long pause, "I don't know."

A clash with conservatives and changing stances

Kennedy's views on abortion have put him at odds with more conservative Republicans, who have successfully instituted abortion bans in 13 states. The anti-abortion agenda outlined in Project 2025—from which President Trump

has already drawn for many of actions early in his second term—calls for an end to abortion medications, which is how most women in the U.S. get abortions.

Concerned that new policies could restrict or remove that access, some providers have reported spikes in these requests after Trump was elected President in November.

But Kennedy made it clear that on abortion medication, too, he would defer to Trump to inform his new stance. "President Trump has asked me to study the safety of mifepristone," Kennedy said during the Jan. 29 hearing—despite the fact that the medication has already been reviewed and approved by the U.S. Food and Drug Administration as safe and effective. "He has not yet taken a stand on how to regulate it. Whatever he does, I will implement those policies, and I will work with this committee make those policies make sense."

Exhibit 5

Anti-Abortion Lawyer Pushed Out of F.D.A. After Republican Senator's Pressure Campaign

Hilary Perkins, a career lawyer and a conservative, was targeted by Senator Josh Hawley of Missouri for defending the Biden administration's position on the abortion pill.

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By Devlin Barrett
Reporting from Washington

March 17, 2025

Since 2019, Hilary Perkins had proudly served as a career lawyer for the government. She took seriously a basic tenet of the job, which is to argue the position of the administration, no matter the political stripes of the boss you serve. A Christian conservative hired under President Trump, she went on to defend the availability of the abortion pill under President Biden.

But last week, three days after becoming chief counsel of the Food and Drug Administration, Ms. Perkins abruptly resigned, forced out by a pressure campaign instigated by Senator Josh Hawley, Republican of Missouri. "It turns out this Biden lawyer has argued FOR Biden's outrageous pro-abortion rules in *many* cases," he wrote on social media.

He omitted that Ms. Perkins worked on the opposite side of a case his wife, Erin Hawley, took to the Supreme Court over access to the pill, mifepristone. He also did not mention that, in at least one other instance, Ms. Perkins had worked to keep limits on the drug's availability.

The episode underscored the continuing purge of civil servant attorneys across the government, claiming, in this instance, a conservative casualty. Her ouster, current and former Justice Department lawyers said, is a troubling indication of how the ejections of government attorneys, at a time when the administration is engaged in dozens of high-stakes legal battles, is weakening the department.

“Senator Hawley’s accusations against me are false,” Ms. Perkins told The New York Times. “I am not who he says I am. I am a Christian who is both conservative and pro-life and who simply followed my oath as a Department of Justice career attorney. He should be fighting for me, not against me.”

Asked for comment, a spokeswoman for the senator referred to his previous social media posts. A representative for Ms. Hawley did not immediately comment.

Over two days, Mr. Hawley attacked Ms. Perkins not just as an abortion advocate but also as a lawyer who argued in favor of vaccine mandates. When it became clear that her hiring could threaten the nomination of Dr. Marty Makary as F.D.A. commissioner, Ms. Perkins reluctantly decided to resign.

Lost in the social media scrum about Ms. Perkins was a fundamental principle undergirding the work of Justice Department lawyers. They are obligated to argue legal positions at the direction of their bosses, not based on their personal views, and only in rare instances do such attorneys beg off a case.

A memo issued by Attorney General Pam Bondi emphasized that point, but she went further in suggesting that any lawyer who did not follow orders could be fired. The argument leveled against Ms. Perkins, then, is in effect at odds with Ms. Bondi’s guidance.

At the Justice Department, scores of senior and career lawyers have been demoted, fired or forced to resign as the Trump administration seeks to exert tighter control over the department. Ms. Bondi and others have argued the moves are meant to end what she and the president call the “weaponization” of the legal system. Critics say the administration is undermining the department by stripping away decades of experience and expertise.

Senator Josh Hawley and his wife, Erin Hawley, with their family in January. Alex Wong/Getty Images

Ms. Perkins left her job at the Justice Department to join the F.D.A. Tim Goeglein, the vice president of government affairs at the anti-abortion group Focus on the Family, said time was running out to get “a pro-life F.D.A. chief counsel.” He added, “I have only known Hilary Perkins to be categorically and reliably pro-life.”

Mr. Trump’s former solicitor general, Noel Francisco, praised Ms. Perkins as “a great lawyer” who “vigorously advanced our client’s interests, not her own.” The pair worked together to defend the former governor of Virginia Bob McDonnell, a Republican, in a corruption case that was later tossed out by the Supreme Court.

Mr. McDonnell seconded that assessment, saying, “She’s worked for Republican and Democrat administrations, which is a very positive thing.”

The “rush and crush of the legislative process in Washington” made it hard to get the full story on recent events, he added, saying that Ms. Perkins was a “genuine conservative” who would have done extraordinary work at the F.D.A.

Ms. Perkins worked on a number of cases involving mifepristone.

Like all civil service lawyers in the department, she argued for the government's position. Sometimes that meant seeking to maintain limits on the drug, such as requiring in-person visits to get a prescription, and other times she argued or oversaw legal arguments against imposing additional limits on it.

One case she supervised reached the Supreme Court last year. In that case, the conservative court ruled unanimously in the Biden administration's favor against advocates who wanted to significantly limit the availability of mifepristone.

Ms. Hawley was the lead lawyer in that case representing a group of abortion opponents who claimed that the pill, approved more than two decades ago, is a danger to women.

The senator has made no suggestion that his wife's role as opposing counsel in a case had anything to do with his public campaign against Ms. Perkins, who had already been scrutinized and vetted by the Trump administration before she was offered the F.D.A. job.

But as Mr. Hawley issued a steady drumbeat of criticism against her last week, Trump administration officials began to fear his anger might scuttle Dr. Makary's nomination.

Just before a Senate committee voted on Thursday on Dr. Makary, administration officials were told that the senator planned to vote against him if Ms. Perkins did not leave the agency, according to people familiar with the conversations who spoke on the condition of anonymity to describe private discussions.

At the hearing, the senator said he had decided to vote for Dr. Makary because Ms. Perkins had resigned.

In the end, two Democrats on the panel voted for Dr. Makary, meaning Mr. Hawley's vote might not have been the deciding one. But by then, it was too late.

"I was honored that President Trump appointed me to be F.D.A.'s chief counsel, and I was firmly committed to advancing the administration's priorities," Ms. Perkins told The Times.

Devlin Barrett covers the Justice Department and the F.B.I. for The Times. More about Devlin Barrett

A version of this article appears in print on , Section A, Page 17 of the New York edition with the headline: G.O.P. Senator's Pressure Forces Anti-Abortion Lawyer to Leave F.D.A.