October 4, 2022

TO:

Lauren Roth
Associate Commissioner for Policy
The US Food & Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20903

CITIZEN PETITION

The American College of Obstetricians and Gynecologists submits this petition on behalf of itself and 48 other organizations listed below pursuant to 21 C.F.R. § 10.30 to request that the Food & Drug Administration (FDA) ask Danco Laboratories, LLC ("Danco") – the holder of the approved new drug application for Mifeprex (mifepristone)—to submit a Supplemental New Drug Application (sNDA) that seeks to add miscarriage management as an indication to the drug's label and to eliminate or modify mifepristone's Risk Evaluation and Mitigation Strategy (REMS) so that it is not unduly burdensome for that use.[1] In the meantime, Petitioners also request that FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the REMS.[2]

[1] There is precedent for such a request. In 1997, the FDA issued a notice encouraging the manufacturers of certain contraceptives to submit a New Drug Application that would modify the dose and use of its product for postcoital emergency contraception (1). The FDA found that this use was safe and effective, that postcoital emergency contraception was important for public health, and that manufacturers should make this product available. In this case, we are asking the FDA to request the manufacturer to submit an sNDA, as opposed to an NDA, because it is more efficient and the medication abortion drug dosages are identical to the miscarriage management protocol, which was not true in the emergency contraception example.

[2] There also is precedent for FDA to exercise enforcement discretion with respect to REMS requirements when they are seriously affecting patient access to important drugs, as it did last year, for example, with respect to the Clozapine REMS (2). Of course, FDA also exercised enforcement discretion with respect to part of the mifepristone REMS itself in order to facilitate patient access during the COVID-19 public health emergency (3).

Mifepristone, in combination with misoprostol, is the most effective regimen for medical management of miscarriage,[3] but patient access to this regimen is currently limited both because the drug lacks FDA approval for this indication and because the REMS limits clinicians' ability to use the drug for miscarriage management. We urge the FDA to request Danco to seek FDA approval of a miscarriage management indication for mifepristone because it is a safe and essential part of the most effective regimen for miscarriage management. With this new indication on the labeling, the REMS must be eliminated or modified so that it does not unduly burden access to the drug for this use and so that it accurately reflects the approved indications for mifepristone.

ACTION REQUESTED

Petitioners request that the FDA ask Danco to submit an sNDA to add miscarriage management as an indication to the mifepristone label and to modify the REMS so that it does not unduly burden its use for miscarriage management. While the FDA is considering these changes, Petitioners request that FDA state that it will exercise enforcement discretion with respect to the use and distribution of mifepristone consistent with the requested indication and REMS modifications.

STATEMENT OF GROUNDS

Miscarriage is common, has significant physical, psychological, and social sequelae, and is a contributor to—and result of— racial health inequities. Miscarriage describes the spontaneous

[3] HHS Secretary Becerra called mifepristone the "gold standard for care when someone who's pregnant experiences a miscarriage" (4). Indeed, the American College of Obstetricians and Gynecologists recommends using mifepristone in combination with misoprostol whenever available, citing studies we discuss below (5). Nevertheless, the REMS's restrictions have made it difficult for this best practice for miscarriage care to become the standard of care as it ought to be, for reasons we explore in more depth below.

loss of a pregnancy prior to 20 weeks' gestation (6). Miscarriage is most common early in pregnancy (7,8). While 1 in 6 recognized pregnancies ends in miscarriage worldwide (7), it is likely that miscarriage also occurs in some early, unrecognized pregnancies. When accounting for unrecognized pregnancies, the miscarriage rate is estimated to be around 25% (8). Miscarriage affects people of every age, race/ethnicity, and socioeconomic status, but is more common among groups negatively impacted by societal dynamics of power and oppression, such as pregnant people[4] who are Black, poor, or exposed to environmental pollutants (7). These risk factors have compounding effects when it comes to health equity, as people of color are both more likely to be exposed to pollution and more likely to live in poverty (9,10).

Miscarriage can also levy a heavy psychological toll, and the burdens of these negative mental health sequelae further exacerbate health inequities. In a recent prospective study in the United States, 1 in 4 people who experienced miscarriage were at risk for major depression 30 days after their loss, according to their scores on a widely used and validated screener (11). Among participants in this study, people who identified as Black had significantly higher odds than people who identified as non-Black of being at risk for major depression following miscarriage, after adjusting for potential confounding medical and demographic differences (aOR 2.48; 95% CI 1.28-4.81) (11). Miscarriage is also stigmatized in many societies and social groups, meaning people who experience pregnancy loss are socially marked as inferior and may be treated poorly or suffer lower self-esteem (12).

The risks and negative outcomes associated with miscarriage are mitigated when health care teams support patient autonomy in selecting a management strategy when appropriate (13).

[4] Women are not the only people capable of becoming pregnant and not all women are capable of pregnancy. To be inclusive of the diversity of pregnancy-capable individuals, including girls, non-binary people, and trans men, we use gender neutral language in this petition whenever appropriate. However, when referring to studies that only included (presumably cisgender) women or when discussing the gendered impact of regulations, we use gendered language.

Miscarriage management options are particularly important for patients who experience missed or incomplete miscarriage, where the body has not expelled all of the pregnancy tissue on its own. Without proper care and intervention when needed, miscarriage carries risks of hemorrhage, sepsis, and death (14). Second trimester miscarriage (14 weeks 0 days through 19 weeks 6 days gestation) can carry significant medical risks, and expectant management is not routinely recommended (5). However, for the estimated greater than 80% of miscarriages occurring in the first trimester (8), several management strategies may be appropriate. In general, there are three options for miscarriage management: expectant management, where no interventions are initiated immediately but patients are actively monitored for symptoms indicating that intervention could be needed (e.g., infection); medical management, where medications are used to help the body start or complete the miscarriage process; and surgical management, where a procedure is used to empty the uterus. (5,14) Each option has its own unique risks and benefits, and patients often have strong preferences on which option they prefer. Widely accepted and used clinical guidelines support engaging uncomplicated patients who are experiencing miscarriage in a shared decision-making process, wherein clinicians educate patients on available treatment options so they may make informed choices aligned with their values and preferences (5).

Some patients prefer active intervention because both medical and surgical management on average lead to a faster completion of the pregnancy loss and involve fewer unplanned procedural interventions compared to expectant management. While expectant management can take up to 8 weeks to result in complete miscarriage, many observational studies and randomized trials affirm that medical management of miscarriage results in markedly faster resolution of the pregnancy, often within a few hours and usually not more than a few days after initiating treatment (15, 16, 17, 18). People who start medication treatment are also less likely to require a subsequent

uterine evacuation to complete their miscarriage compared to those who pursue expectant management. For example, in a randomized controlled trial of 1,200 pregnant patients, individuals who were randomized to expectant management were more likely to need unplanned surgical intervention to complete their miscarriage (44%) compared to those randomized to medical treatment of miscarriage (13%) (15). Some patients might also prefer active miscarriage management for psychosocial reasons, including an ability to have some control over an unexpected, and often disheartening, bodily process (7,13). In a randomized controlled trial of people experiencing miscarriages, pregnant individuals who were allocated to expectant management were significantly less likely to state they would choose this method again, compared to those allocated to intervention (18). This trial suggests that the experience of expectant management is on average less acceptable compared to intervention to empty the uterus.

Qualitative research also suggests that choice of management strategy is paramount in driving patient satisfaction with miscarriage care. In a 2017 qualitative study, Wallace and colleagues found that women who had recently experienced miscarriage expressed a strong preference for informed choice among multiple options rather than being prescribed a single option by their health care team (19). The induced abortion patient population, though not perfectly analogous, also provides additional context, with similar findings about the value of method choice across multiple studies. Abortion patients hold strong preferences for method of termination. A 2006 review of the global literature on abortion method preference found that in most settings and across multiple studies, the predominant reasons patients provide for choosing medication abortion are to avoid surgery and anesthesia, the (incorrect) perception that it is safer than procedural abortion, and the perception that is more natural compared to procedural abortion (20).

Importantly, surgical options are not always available to all patients. Rural patients in particular can struggle to access surgical management of miscarriage due to the lack of trained clinicians in rural communities, meaning that medical management is their only alternative to expectant management (21, 22). The literature is therefore clear that patients value and deserve a choice between expectant management, medical management, and surgical management in the context of miscarriage.

To ensure access to the safest and most effective treatments for miscarriage, and to preserve patient choice in miscarriage management and equitably confer the benefits of that choice irrespective of geographic location, race/ethnicity, and socioeconomic status, it is imperative to promote access to evidence-based medical management of miscarriage, which includes access to mifepristone. To achieve this goal, Danco should request, and FDA should approve, a miscarriage management indication for mifepristone, and the REMS should be revised accordingly. Because the public health needs are urgent, FDA should immediately state that it will exercise enforcement discretion until this process is completed.

I. Miscarriage Management Should be Approved as an Indication for Mifepristone Through the First Trimester of Pregnancy

Miscarriage management should be added to the mifepristone label because it is the most effective regimen for medical management of miscarriage. Published research demonstrates that mifepristone is safe and effective for this use throughout the first trimester (13 weeks and 6 days of pregnancy) (23,24). Indeed, it is as safe or safer than alternatives for miscarriage management and the most effective medical option to manage miscarriage. Patients choosing medical

management of miscarriage should have access to the most effective protocol, which is mifepristone in combination with misoprostol.

A. A Combination of Mifepristone and Misoprostol for Miscarriage is the Most Effective Protocol for Medical Management of Miscarriage

Because of the onerous restrictions currently in place on mifepristone in the United States, the most commonly used medical protocol for miscarriage management today is misoprostol alone. However, leading professional organizations encourage the use of adjunctive mifepristone whenever possible.[5] For example, based on a systematic review of the literature on miscarriage management with misoprostol, and on a large, randomized trial of a misoprostol-only regimen, the American College of Obstetricians and Gynecologists (ACOG) recommends an initial dose of 800 micrograms of misoprostol administered vaginally, with a repeat dose administered in the same quantity and route as needed, when utilizing misoprostol alone for miscarriage management (5,17,25,26). However, ACOG further advises that "[t]he addition of a dose of mifepristone (200 mg orally) 24 hours before misoprostol administration may significantly improve treatment efficacy" (5). Clinical experts in internal medicine also endorse mifepristone use for miscarriage management (27). These recommendations stem from the growing evidence that the mifepristone-misoprostol regimen has superior efficacy for the treatment of miscarriage, compared to misoprostol alone.

In the past decade, two large, randomized trials have augmented the observational literature to definitively prove that misoprostol with adjunctive mifepristone is superior to misoprostol alone

[5] ACOG's practice bulletin notes that "the availability of mifepristone is limited by U.S. Food and Drug Administration Risk Evaluation and Mitigation Strategy restrictions," which makes it inaccessible for miscarriage management in many places (5).

to treat miscarriage (23,24,27). Schreiber and colleagues found that 200 milligrams of oral mifepristone followed by 800 micrograms of vaginal misoprostol is more effective (complete expulsion of pregnancy after the initially prescribed regimen = 83.8%; 95% CI 76.8 to 89.3) compared to 800 micrograms of vaginal misoprostol alone (complete expulsion = (67.1%; 95% CI, 59.0 to 74.6) (23). Moreover, the need for uterine aspiration was much lower in the mifepristone-misoprostol group in this trial compared to misoprostol alone (8.8% vs. 23.5%; relative risk, 0.37; 95% CI, 0.21 to 0.68). A separately conducted randomized controlled trial through 14w0d of pregnancy replicated these results, with patients who received mifepristone and misoprostol having a lower risk of not passing their pregnancy within 7 days ([RR] 0.73, 95% CI 0.54-0.99) and a lower risk of needing surgical intervention to empty the uterus ([RR] 0.71, 95% CI 0.53-0.95), compared to misoprostol alone (24).[6] Having enrolled a diverse combined sample of over 1,000 participants across 30 hospitals in the United States and the United Kingdom, together these trials provide excellent evidence of the superiority of the mifepristone-misoprostol regimen compared to misoprostol alone.

B. A Combination of Mifepristone and Misoprostol for Miscarriage is Safe

Medical management of miscarriage has a comparable or superior safety profile than alternatives for miscarriage management. For the context of this discussion, we compare interventions based on the prevalence of (1) transfusion, (2) sepsis, (3) hospitalization, (4)

[6] Chu and colleagues did not directly compare the efficacy of the two originally administered regimens in their trial. Instead, they compared complete miscarriage at 7 days regardless of how many additional doses of misoprostol individuals received on top of the original 800 microgram dose. The difference in completion by 7 days between mifepristone plus a single dose of misoprostol, vs a single dose of misoprostol alone, would likely be larger in magnitude (24).

infection without sepsis, and (5) hemorrhage. These serious adverse events are substantially similar to the "serious adverse events" on the mifepristone label for abortion.[7]

When mifepristone and misoprostol was compared to misoprostol alone for first trimester miscarriage, there were no differences in safety outcomes. In two randomized trials that assigned pregnant people to misoprostol alone vs mifepristone with adjunctive misoprostol, there was no difference in the rate of blood transfusions or any other safety outcome (23,24). In a randomized trial including 300 individuals, Schreiber et al reported a serious adverse event (defined as bleeding resulting in transfusion or pelvic infection) rate of 3.4% for mifepristone and misoprostol combined vs 2.0% for misoprostol alone (p=0.47) (23). In a subsequent placebo-controlled trial that enrolled 711 individuals, Chu and colleagues found no difference in bleeding patterns between groups, and a rate of inpatient treatment for infection of 1% among both the misoprostol alone and mifepristone and misoprostol combined groups (24).

C. Abortion Bills are Targeting Mifepristone, Potentially Limiting Access to the Drug for Miscarriage Management and Harming Public Health

Based on the evidence and clinical guidance cited above, clinicians with the political freedom to make evidence-based choices regarding miscarriage treatment are increasingly using mifepristone. For example, in a survey of Massachusetts obstetrician-gynecologists, Neill and colleagues found that 63% use mifepristone to treat miscarriages (29). However, clinicians in areas where abortion is highly stigmatized and legally scrutinized face many more barriers to this evidence-based best practice. Now that the Supreme Court has overturned *Roe v. Wade*, some

[7] The only serious adverse event on the mifepristone label that we did not include is Emergency Room (ER) visits. ER visits are not a good indicator of safety in the miscarriage population because these patients often first seek care in the ER.

states are moving quickly to limit access to drugs that can induce abortion. These efforts have collateral consequences that harm all aspects of reproductive health, including miscarriage management.

The fact that mifepristone is only approved to terminate a pregnancy—even though it is used and is recommended for use off-label for miscarriage management-–has made it vulnerable to wholesale bans on the drug. For instance, in the last legislative session, Alabama legislators introduced Alabama H261, which made it "unlawful for any person or entity to manufacture, distribute, prescribe, dispense, sell, or transfer the 'abortion pill,' otherwise known as RU-486, Mifepristone, Mifegyne, or Mifeprex, or any substantially similar generic or non-generic abortifacient drug in Alabama" (30). A nearly identical bill was also introduced in Arizona (H2811) and other states (31). These are wholesale bans on mifepristone for any use and, if enacted, will prevent clinicians from providing the gold standard miscarriage care in their communities of practice, harming public health. Even without a wholesale ban on mifepristone, clinicians in states that ban abortion may be hesitant to prescribe a drug that has only been approved for abortion even for a legal, off-label use, like miscarriage management (32). Adding miscarriage management to the label would legitimize this important use and potentially hamper legislative efforts to ban the drug so patients have greater access to the most effective medical tool for miscarriage care.

Media reports affirm that out of an abundance of caution, in the wake of *Dobbs v. Jackson Women's Health Organization,* some pharmacies are creating barriers to accessing drugs that can cause or treat pregnancy loss but are prescribed for other uses, such as methotrexate for rheumatic diseases or mifepristone or misoprostol for miscarriage (33,34,35). Moving forward, regulators and the pharmacy community must work to clarify and educate the field on professional

responsibility of pharmacists—by law and by oath—to serve their patients' medical needs and comply with federal law.[8] In this context, including the indication of miscarriage management on the mifepristone label may help to clear up confusion or anxiety about legal compliance in a rapidly evolving legal landscape.

II. The Mifepristone REMS Must Be Eliminated Because it is Not Necessary for the Drug's Benefits to Outweigh its Risks and is Unduly Burdensome for this New Use

If miscarriage management is added as an indication to the mifepristone label, then changes to the mifepristone REMS would also be needed to ensure that it is not unduly burdensome for this new use. Section 505-1(f)(2) of the Federal Food, Drug, and Cosmetic Act states that an Element to Assure Safe Use (ETASU) may "not be 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)." 21 U.S.C. § § 355–1(f)(2). The statute also only permits the imposition of a REMS where it is "necessary to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(1). And finally, each ETASU must "conform with elements to assure safe use for other drugs with similar, serious risks." 21 U.S.C. § § 355–1(f)(2)

Each element of the mifepristone REMS imposes unique burdens on accessing mifepristone for miscarriage management and is unnecessary to ensure mifepristone's benefits for miscarriage management outweigh its risks. Furthermore, as described below, the misoprostol-only alternative has lower efficacy and similar risks but is not subject to an ETASU (or any REMS at all). As a result, the REMS burdens the equally safe and more effective

[8] HHS Secretary Becerra recently issued a guidance document stating that a pharmacy's refusal to dispense mifepristone for miscarriage management due to its concern for abortion laws constituted unlawful sex discrimination (36).

miscarriage management protocol, making it harder for patients, especially poor and rural patients, to access it. Accordingly, a REMS with ETASU is inappropriate for a miscarriage management indication for mifepristone and should therefore be eliminated.

A. The Patient Agreement Form is Not Necessary for the Benefits of Mifepristone to Outweigh the Risks and Unduly Burdens Access to the Drug

We recommend that the Patient Agreement Form be removed entirely because it is medically unnecessary and repetitive of informed consent, as a previous review conducted by CDER determined in 2016.[9] As a result, the Form does nothing to ensure the benefits of the drug outweigh the risks. Moreover, for miscarriage management, there is an additional concern: the medical alternative (misoprostol alone) does not require patients to sign any form, and therefore the mandated Patient Agreement Form adds an administrative and logistical burden that disincentivizes the most effective protocol for medically managing miscarriage at the health systems level. It should therefore be removed for that reason.

If the Patient Agreement Form is retained, however, it at least minimally needs to be amended to reflect the new indication or separate forms should be used for the separate indications. The current Form makes people attest that they are ending a pregnancy, which is not accurate for the indication of miscarriage, in which the loss of the pregnancy has already occurred or is already in process. Asking a miscarriage patient to attest to having an abortion will confuse patients at best, but due to the prevalence of abortion stigma, it might also add emotional harm to their miscarriage experience (38).

[9] These recommendations were ultimately rejected by Dr. Janet Woodcock, who decided to retain this element of the REMS (37).

B. The Provider Self-Certification Process for Mifepristone is Not Necessary for the Benefits of Mifepristone to Outweigh the Risks and Unduly Burdens Access to the Drug

Second, the Certified Provider Requirement serves no benefit to patient safety, especially in the miscarriage population. In this population, the pregnancy has already been confirmed and diagnosed as a miscarriage. Moreover, clinicians prescribing mifepristone for miscarriage know how to date a pregnancy, diagnose an ectopic pregnancy, and treat complications that arise (or refer to someone who could). Clinicians who commonly provide early pregnancy loss care, such as emergency medicine specialists, obstetrician-gynecologists, family physicians, women's health nurse practitioners, and certified nurse midwives, receive training in pregnancy dating, ectopic risk factors,[10] and care coordination (40,41). As a result, the certification is redundant and unnecessary to prove that mifepristone's benefits outweigh its risks for this indication.

The negligible or non-existent benefits of provider self-certification are vastly outweighed by the impediments to accessing mifepristone that result from this requirement. This requirement creates an administrative burden that discourages clinicians from using the drug. First, social science research demonstrates in other contexts that an opt-in requirement generally disincentivizes participation (42). The certification process therefore presents an administrative burden that busy clinicians may be unable or unwilling to fulfill without institutional support or technical assistance.

In addition to the administrative burden, clinicians might also be particularly wary about undergoing the certification process for mifepristone given its relationship to abortion. Even before

[10] Recent studies have suggested that mifepristone use is safe even for pregnancies of unknown location (PUL). In a 2022 retrospective cohort study of 432 abortion patients with a PUL and no ectopic risk factors, Goldberg and colleagues report that individuals had a faster time to rule out ectopic pregnancy when they were treated with mifepristone immediately, rather than delaying initiation of mifepristone until after pregnancy location was diagnosed (39).

Roe v. Wade was overturned, abortion providers have consistently faced risks of violence and harassment unlike any other field of medicine (43). For that reason, clinicians might have reasonable reservations about opting into a prescription system that could, if their certification were leaked, suggest they were an abortion provider and open them up to violence and harassment (42). In recent qualitative studies in Illinois and Massachusetts, researchers found this fear was present even among physicians who personally only plan to prescribe mifepristone for miscarriage care (29,44). It is likely that clinicians' reservations will increase in states that have moved to ban abortion care since the *Dobbs* decision, further compounding the effects of abortion stigma (45). Research has shown that without certification, more clinicians would prescribe mifepristone. In qualitative studies in Massachusetts, Illinois, Alabama, and with a national sample, both generalist obstetrician-gynecologists and primary care providers described the REMS as a barrier to integration of mifepristone use in their practice (29,44,45,46).

The result is that only the limited number of clinicians who have already navigated mifepristone REMS compliance to provide abortion care are prepared to prescribe mifepristone for miscarriage. And those clinicians are almost always located in cities (47,48), meaning that rural residents will disproportionately lack access to certified providers who can prescribe mifepristone as part of a medical miscarriage protocol. Moreover, rural residents are more likely to lack access to OBGYNs (21), meaning that surgical management is also less likely to be an option. Thus, rural residents will only have access to a less effective medical protocol for managing miscarriage or may be forced to complete their miscarriage without active measures.

This certification barrier has devastating effects for the miscarriage population, who may only be able to access the most effective medical miscarriage management protocol if their hospital or provider group has an abortion provider on staff. And these burdens fall disproportionately on

poor and rural women, contrary to goals of the REMS statute. Because the misoprostol-only alternative does not require certification despite being less effective and having a similar risk and safety profile, the certified provider requirement again burdens the more effective protocol and makes it much harder to access the best medical treatment for miscarriage.

C. The Certified Pharmacy Requirement is Not Necessary for the Benefits of Mifepristone to Outweigh the Risks and Unduly Burdens Access to the Drug

Though the details of the new pharmacy certification requirement have yet to be finalized, research also suggests that the pharmacy requirement is unnecessary to ensure that mifepristone's benefits outweigh its risks and unduly burden access. A preliminary trial of pharmacy dispensing of mifepristone conducted by Grossman and colleagues in California and Washington state suggests that pharmacies are already equipped to dispense the drug without special certification. In this trial of 266 individuals, which was halted early due to the COVID-19 pandemic, rates of non-serious adverse events following pharmacy dispensing were extremely low (1.5%) and no higher than rates from studies of in-clinic dispensing, and satisfaction was high, with 65.4% of patients very and 19% somewhat satisfied. Though the pharmacies in this study partnered with prescribers, there is no reason to think the results would be different with retail pharmacies, especially in light of the Canadian data discussed in the next section (49).

The pharmacy certification requirement is also expected to create similar barriers to care for the miscarriage population as the provider certification. The extra administrative burden will disincentivize participation and the fact that pharmacies are businesses, not people, exacerbates this concern. Unlike clinicians, who may endure the obstacles of certification out of a moral

conviction or professional obligation to provide the best reproductive healthcare, pharmacies will engage in a business decision where they will evaluate whether the financial gain in distributing the drug is worth the costs and risks (42). Moreover, given that the antiabortion movement is known for boycotts, pharmacies will also likely weigh the risks associated with their status as a certified pharmacy becoming public. Walgreens already indicated that it will not seek certification, and many large retail pharmacies may follow suit (42). People will therefore be dependent on online pharmacies to access mifepristone—even for miscarriage management.

As with the certified provider requirement, the burdens associated with the certified pharmacy requirement will also fall disproportionately on poor and rural women, contrary to the REMS statute. Most Americans rely on neighborhood retail pharmacies to obtain their prescription drugs, and retail pharmacy distribution of drugs can increase access for rural residents (42). For instance, when the government in Australia started allowing retail pharmacies to dispense mifepristone, access to the drug increased, especially in rural areas (43). If only online pharmacies become certified to dispense mifepristone, then it might harm those with less digital literacy, who may have more difficulty interfacing with online pharmacies after their clinicians prescribe mifepristone for miscarriage. This might be especially true for patients struggling to process their loss, who have little emotional capacity to set up an account and learn a new pharmacy's online interface. Moreover, adults who are not digitally literate are disproportionately less educated and more likely to be Black, Hispanic, or foreign born, meaning that these groups would likely be the most adversely impacted if mifepristone is available solely through online pharmacies (50). Given that the misoprostol-only alternative can be accessed at any pharmacy, the pharmacy certification requirement therefore incentivizes the less effective protocol for medical miscarriage management and will limit access to the most effective protocol.

D. Existing Data Demonstrate that a Removal of All REMS Requirements Will Not Harm Patient Safety

After Canada removed all restrictions on prescribing mifepristone for abortion, thereby allowing it to be prescribed and dispensed like any other drug ("normal prescribing"), there was no increase in complications from mifepristone use (51). In a 2022 study, Schummers and colleagues used multiple sources of medical and administrative data to create a linked dataset containing information on Ontario residents receiving abortion care through Canada's universal, single-payer health system from 2012 through 2020 (total n=314,859 abortions). They found no difference in the rate of any complication (0.67% vs. 0.69%) or in the rate of serious adverse events (0.03% vs. 0.04%) between the ten-month period when mifepristone was distributed with REMS-like restrictions and the twenty-eight-month period of normal prescribing after all such restrictions were lifted and mifepristone was prescribed with no special self-certification and dispensed routinely from pharmacies (52). We expect the same results in the miscarriage population given the similarity in regimens when using mifepristone for abortion and miscarriage.

III. FDA Should Immediately State That it Will Exercise Enforcement Discretion Until This Process is Completed

As just discussed, clinicians who treat miscarriage and their patients have an urgent need to address increasing barriers to accessing mifepristone. While we urge both FDA and Danco to act expeditiously on our requests, we recognize that submission and review of an sNDA and corresponding REMS changes will take time. Thousands of patients suffering miscarriages will be adversely affected during this period. We therefore request that FDA immediately announce that it will exercise enforcement discretion to permit the use and distribution of mifepristone consistent

with the requested miscarriage indication and changes in the REMS for this indication. The public health needs for this safe and effective treatment are substantial. Just last year, FDA exercised enforcement discretion with respect to certain pharmacy and wholesale distribution requirements under the Clozapine REMS because they had frustrated patients' ability to access a needed drug. FDA explained that its "highest priorities" are "[c]ontinuity of care, patient access . . ., and patient safety" (2). Patient access to the gold standard of miscarriage care, which is being significantly restricted due to the mifepristone REMS, and patient safety weigh heavily in favor of exercising enforcement discretion here as well. There is, of course, precedent for FDA to exercise enforcement discretion specifically with respect to the mifepristone REMS as well, as it did last year during the COVID-19 public health emergency (3). Enforcement discretion will ensure patients have access to the most effective regimen for miscarriage management while Danco submits, and FDA reviews, the sNDA.

ENVIRONMENTAL IMPACT

The proposed action is exempt from the requirement of an environmental impact statement under 21 C.F.R. § 25.24(c)(2).

ECONOMIC IMPACT

No information required at this time.

CERTIFICATION

The petitioners certify that, to the best of our knowledge and belief, this petition includes all information and views on which the petition relies. The petitioners know of no data unfavorable to the opinion.

Signed:

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Together with:

Advancing New Standards in Reproductive Health
All Families Healthcare
American Academy of Family Physicians
American Civil Liberties Union
American College of Nurse-Midwives
American Humanist Association
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American Medical Women's Association
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SisterReach
Society for Academic Specialists in General Obstetrics and Gynecology
Society for Maternal-Fetal Medicine
Society of Family Planning
UCSF Bixby Center for Global Reproductive Health

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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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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.

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January 3, 2023

Re: Docket No. FDA-2022-P-2425

Dear Dr. Phipps:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on October 4, 2022, on behalf of the American College of Obstetricians and Gynecologists and 48 other organizations (Petition). In the Petition, you request that FDA:

(1) Ask Danco Laboratories, LLC, the holder of the approved new drug application (NDA) for Mifeprex (mifepristone) (NDA holder), to submit a supplemental new drug application (sNDA) that seeks to add miscarriage management as an indication to the drug's labeling, and to eliminate or modify mifepristone's risk evaluation and mitigation strategy (REMS) so that it is not unduly burdensome for that use

(2) Immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the REMS

We have carefully considered the Petition and other information available to us. For the reasons stated below, the Petition is denied.

I. BACKGROUND

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (NDA 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H); specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[1]

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect

[1] See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.

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elements to assure safe use.[2] Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the NDA holder. The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective (through 70 days gestation), as well as the process for follow-up after administration of the drug.

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 milligrams (mg) (abbreviated new drug application 091178). As required by 21 CFR 314.94(a)(8), the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex.[3]

At the same time that FDA approved the generic version of Mifeprex in 2019, FDA approved a supplemental new drug application for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In January 2023, FDA approved another supplemental new drug application, approving modifications to the Mifepristone REMS Program to remove the requirement that mifepristone be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the in-person dispensing requirement) and to add a pharmacy certification requirement.

II. DISCUSSION

A. Adding a New Indication to Mifeprex

In your Petition, you request that the Agency ask the NDA holder for Mifeprex to submit an sNDA that seeks to add miscarriage management as an indication to the drug's labeling (Petition at 1).[4]

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[2] 73 FR 16313 (Mar. 27, 2008).

[3] We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone – as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

[4] Your reference to FDA's request for submissions of NDAs to add an emergency contraception indication to certain combined oral contraceptives as precedent for FDA requesting that the NDA holder for Mifeprex add a management of miscarriage indication to its labeling is not on point (Petition at 1, footnote 1). The circumstances under which FDA made this request to manufacturers of oral contraceptives – which included unanimous backing by the

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a person seeking to market a new drug, including a new indication for an approved drug, submit an application to FDA for review.[5] To support the addition of a new indication to a drug product's FDA-approved labeling, the holder of the NDA for the drug product would submit a supplemental application requesting a new indication.[6] FDA would approve a supplemental application only if the Agency finds that the drug product is safe and effective for the proposed indication.[7]

Only the holder of an approved application may submit a supplement to an application.[8] Therefore, if the person seeking a new indication for an approved drug product is not the application holder for the drug, that person would need to submit a separate, original application for approval of a new drug with the new indication.[9]

To support a finding of safety and effectiveness for a new indication, FDA would require, among other information, that an applicant provide adequate data and information to support the new indication. The applicant must establish effectiveness of the drug for the proposed indication and the application (whether an original application or a supplemental application) generally would contain data and information adequate to support a determination that the drug is safe and effective under the conditions of use specified in the labeling.

If the NDA holder for Mifeprex chooses to submit an sNDA to add an indication for miscarriage management to the Mifeprex labeling, the Agency will review such application consistent with the FD&C Act, FDA regulations, and our standard process for sNDAs. In addition, any person may submit an original new drug application requesting approval of mifepristone for miscarriage management.[10] As with all products, FDA is open to meeting with interested parties to discuss the potential submission of an application. In addition, it is our understanding that the NDA holder for Mifeprex is aware of your Petition, including the request to add miscarriage management as an indication to the drug's labeling.[11]

For these reasons, we deny your request that we ask the NDA holder for Mifeprex to submit an sNDA that seeks to add miscarriage management as an indication to the drug's labeling.

Advisory Committee for Reproductive Health Drugs in addition to specific findings by FDA based on literature and experience with approved combined oral contraceptive products – do not exist here.

[5] Section 505(a) of the FD&C Act (21 U.S.C. 355(a)) and 21 CFR part 314.

[6] §§ 314.71(b) and 314.50(d)(5). See also FDA final guidance, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (Dec. 2004), at 6. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[7] See section 505(d) of the FD&C Act.

[8] § 314.71(a).

[9] An application submitted under section 505(b)(1) of the FD&C Act, also called a "stand-alone NDA," requires that the application contain, among other information, "full reports of investigations" to show that the drug is safe and effective for its intended use.

[10] See section 505(b)(1) and (2) of the FD&C Act.

[11] See https://www.reuters.com/business/healthcare-pharmaceuticals/doctors-urge-us-fda-add-miscarriage-management-abortion-pill-label-2022-10-04/.

B. Mifepristone REMS Program

In your Petition, you ask that FDA eliminate or modify the Mifepristone REMS Program so that it is not unduly burdensome for a miscarriage management indication (Petition at 1). Because the management of miscarriage is not a currently approved indication for mifepristone, it would be premature for FDA to consider the impact that the addition of this indication would have, if any, on the Mifepristone REMS Program so that it is not unduly burdensome for that use.

For these reasons, we deny your request that we eliminate or modify the Mifepristone REMS Program so that it is not unduly burdensome for a miscarriage management indication.

In your Petition, you also request that FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the REMS (Petition at 1).

The action you seek may not properly be the subject of a citizen petition under FDA's regulations. Under 21 CFR 10.30, a person may petition the Agency to issue, amend, or revoke a regulation or order or to take or refrain from taking any other form of administrative action. FDA regulations in 21 CFR 10.3 define "administrative action" as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner, except that it does not include the referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings or an act in preparation of a referral." Similarly, under 21 CFR 10.30(k), citizen petitions may not be used with respect to "referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence." Agency decisions to take, or to refrain from taking, enforcement action are decisions related to the "referral of apparent violations to U.S. attorneys for the institution of civil or criminal proceedings, or acts in preparation of such referrals" and therefore are not properly the subject of a citizen petition.

For these reasons, your request that FDA immediately exercise enforcement discretion with respect to the use and distribution of mifepristone for miscarriage management without complying with the Mifepristone REMS Program is denied.

III. CONCLUSION

For the reasons explained above, we deny your Petition.

Sincerely,

Patrizia A. Cavazzoni -S

Digitally signed by Patrizia A. Cavazzoni -S
Date: 2023.01.03 18:47:23 -05'00'

Patrizia Cavazzoni, M.D.
Director
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