Maureen G. Phipps, MD, MPH, FACOG
American College of Obstetricians and Gynecologists
409 12th Street SW
Washington, DC 20024

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.

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

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Date: 2023.01.03 18:47:23 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research