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Students for Life of America
1000 Winchester Street, Suite 301
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January 15, 2025

Re: Docket No. FDA-2022-P-2872

Dear Ms. Hawkins and Ms. Hamrick:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA, Agency, or we) on November 15, 2022, on behalf of Students for Life of America and other signatories (Petition). Your Petition asserts that "the Medical Waste from Mifepristone usage is transmitted directly into the wastewater system when the patient completes the Mifepristone and associated misoprostol Regimen," which the Petition contends is "harmful to drinking water sources, groundwater sources, and any other sources of water that are touched by wastewater."[1] Based on these concerns, the Petition requests that FDA "modify the Risk Evaluation and Mitigation Strategy (REMS) regarding mifepristone (Mifeprex® or RU-486) (hereinafter, "Mifepristone") to require prescribers to include a Medical Waste bag and Catch-Kit with all Mifepristone prescriptions."[2]

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is denied.

I. BACKGROUND

A. Summary of Drug Product History

On September 28, 2000, FDA approved Mifeprex (mifepristone) Tablets, 200 mg for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under title 21, part 314, subpart H of the Code of Federal Regulations (CFR); specifically, 21 CFR 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 21 CFR 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.[3] Those restrictions included, among other things, a requirement that mifepristone be dispensed to patients only

[1] Petition at 1.
[2] Petition at 1.
[3] See FDA approval letter for Mifeprex, dated Sep 28, 2000, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2000/20687appltr.pdf.

in certain healthcare settings, specifically clinics, medical offices, and hospitals (commonly referred to as the *in-person dispensing requirement*).

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.[4] 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. The approval included, among other things, changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol; and the interval between taking Mifeprex and misoprostol). The approval also expanded 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 a generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 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.[5]

At the same time that FDA approved the generic version of Mifeprex in 2019, FDA approved a modification to the 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 a modification to the Mifepristone REMS Program to remove the in-person dispensing requirement and to add a pharmacy certification requirement.

B. Environmental Assessment, Finding of No Significant Impact, and Claim of Categorical Exclusion

In 1996, the applicant for NDA 020687 submitted an environmental assessment (EA) in support of its application pursuant to 21 CFR 25.31(a) and in accordance with applicable National Environmental Policy Act (NEPA) requirements (the 1996 EA).[6] The 1996 EA evaluated the potential environmental

[4] 73 FR 16313 (Mar. 27, 2008).

[5] 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 early pregnancy, unless otherwise noted.

[6] See Environmental Assessment and Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets (March 1, 1996), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

impacts of the manufacture of the drug product, use of the drug product by patients (i.e., excretion by patients), and disposal of pharmaceutical waste. In the 1996 EA, disposal of pharmaceutical waste is addressed in section 4.e "Disposal Sites," and excretion by patients is addressed in section 6.e.i "Expected Introduction Concentration from Use."[7] Regarding disposal of pharmaceutical waste, section 4.e addresses disposal of "rejected, expired, returned or waste drug products," and describes an expectation for disposal to follow Centers for Disease Control Guidelines and the use of incineration or grinding and landfill. Regarding excretion by patients, the applicant calculated a projected environmental introduction concentration (EIC) into the aquatic environment from use (i.e., excretion by patients) of less than 1 part per billion (ppb)[8,9] using default, conservative screening-level assumptions that: all drug substance produced is used, there is even distribution throughout the United States per day, and there are no metabolism or depletion mechanisms.[10,11] The applicant submitted a *Tier 0* EA in accordance with Agency regulations and consistent with guidance that existed at that time (specifically the *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (November 1995) (1995 EA Guidance)).[12,13] As the 1995 EA Guidance explains, a Tier 0 EA is recommended when the EIC is estimated to be less than 1 ppb because FDA "has routinely found that drugs at concentrations less than 1 ppb have no significant effect on relevant

[7] See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, at 2 and 4, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[8] See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, at 4, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf. We note that these calculations from the applicant are generally considered confidential commercial information and in the 1996 EA were provided in a confidential appendix. See id.

[9] FDA noted the EIC was "much less than [(redacted)] ppb even without consideration of metabolism." See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, at 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[10] The *Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements* (November 1995) (1995 EA Guidance) at 14 explains that the calculation of the EIC entering into the aquatic environment from patient use may include consideration of metabolism to less pharmacologically active or inactive compounds and environmental depletion mechanisms that occur in the waste treatment process if the information is available, but the default calculation provided by the guidance assumes no metabolism or depletion mechanisms. See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, at 4, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[11] See 1995 EA Guidance at 14.

[12] We note that FDA's regulations at 21 CFR 25.31 have been revised multiple times. The 1996 CFR containing Title 21 section 25.31 is available at https://www.govinfo.gov/content/pkg/CFR-1996-title21-vol1/pdf/CFR-1996-title21-vol1.pdf.

[13] The 1995 EA Guidance was replaced in July 1998 by the guidance for industry *Environmental Assessment of Human Drug and Biologics Applications* (1998 EA Guidance) (see 63 FR 40127). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. Under the President's reinventing government initiatives, announced in April 1995, FDA reevaluated and revised its environmental regulations to reduce the number of EAs required to be submitted by industry and, consequently, the number of findings of no significant impact prepared by the Agency under NEPA. As part of this initiative, FDA issued the 1998 EA Guidance to provide information on when an EA should be submitted. For your convenience, we have enclosed a copy of the 1995 EA Guidance.

standard test organisms, and, therefore, are unlikely to have a significant effect on the environment."[14,15] Additionally, the Material Safety Data Sheet in the 1996 EA noted that mifepristone is "[b]iodegradable in natural media."[16,17]

During its consideration of the application, FDA reviewed the 1996 EA provided by the applicant and made a finding of no significant impact (FONSI) in July 1996.[18] As explained in the FONSI, FDA "carefully considered the potential environmental impact of [approving this application] and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement [(EIS)] therefore will not be prepared."[19] In reaching this conclusion, FDA considered that "[m]ifepristone may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites."[20] FDA found that there was no information that indicated that extraordinary circumstances existed that would warrant the submission of additional environmental information by the applicant[21] and that "[a]dverse effects are not anticipated upon endangered or threatened species."[22]

In support of its application for approval of a generic version of Mifeprex, the applicant for ANDA 091178 claimed a categorical exclusion under 21 CFR 25.31(a) because action on the ANDA did not increase use of the active moiety (i.e., mifepristone). FDA reviewed the application and approved ANDA 091178 in 2019.[23]

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[14] 1995 EA Guidance at 18, see also Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, and Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, at 4, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[15] FDA codified this approach in the final rule "National Environmental Policy Act; Revision of Policies and Procedures," 62 FR 40570 (July 29, 1997) (adding a categorical exclusion from the NEPA's requirement for an environmental impact statement or EA for an action on a drug application or monograph "if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 [ppb]" at 21 CFR 25.31(b)).

[16] See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, Appendix D, Material Safety Data Sheet, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[17] Generally, *biodegradable* refers to the ability of a substance to be broken down physically and/or chemically by microorganisms. See *Guide to Environmental Issues: Glossary of Terms & Acronyms*, U.S. Environmental Agency (EPA), available at https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=Environmental%20Issues%20Glossary. Nonbiodegradable substances can accumulate and persist longer than biodegradable substances. See FDA, guidance for industry *Drug Products, Including Biological Products, That Contain Nanomaterials* (April 2022) at 16. Biodegradable substances are not expected to accumulate in the environment because they break down through the action of microorganisms.

[18] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[19] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[20] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[21] See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, at 1 and 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[22] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[23] See FDA approval letter for ANDA 091178, dated April 11, 2019, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/091178Orig1s000ltr.pdf.

II. Legal and Regulatory Authority

A. Federal Food, Drug, and Cosmetic Act

FDA's regulation of drug products is governed by the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC 301 et seq.) and the Agency's implementing regulations codified in Title 21 of the CFR. The FD&C Act generally makes it unlawful to market a *new drug* without first obtaining an approved NDA or ANDA.[24] Before approving an NDA, FDA must determine that the drug product is both safe and effective for use under the conditions prescribed, recommended, or suggested in the drug product's labeling.[25] The demonstration of effectiveness under this standard requires substantial evidence that the drug product will have the effect it purports or is represented to have.[26] Because all drugs can have adverse effects, the demonstration of safety requires a benefit-risk assessment that shows that the benefits of the drug outweigh its risks.[27]

Only if FDA concludes that the drug product's benefit-risk profile is favorable will the Agency approve an NDA.[28] FDA must approve an NDA unless, among other reasons, there is a lack of substantial evidence that the drug is effective; the results of safety testing fail to show that the drug is safe; or, on the basis of any other information before the Agency, there is insufficient evidence to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling.[29]

To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of its proposed drug product. Instead, an ANDA applicant relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[30] To rely on this finding, an ANDA applicant must provide sufficient information to show, among other things, that its drug product has the same active ingredient(s), conditions of use, route of administration, dosage form, strength, and, with certain permissible differences, labeling as the RLD.[31] An ANDA applicant must also demonstrate that its proposed drug product is bioequivalent to the RLD.[32] FDA must approve an ANDA unless it finds

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[24] Section 505(a) of the FD&C Act (21 USC 355(a)); see also section 301(d) of the FD&C Act (21 USC 331(d)) (prohibiting the introduction into interstate commerce of any article in violation of section 505 of the FD&C Act).
[25] Sections 505(b)(1) and (d) of the FD&C Act (21 USC 355(b)(1) and (d) and 355(d)).
[26] See section 505(d) of the FD&C Act.
[27] See FDA, guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023) at 3.
[28] See 21 CFR 314.105(c), which states "FDA will approve an NDA after it determines that the drug meets the statutory standards for safety and effectiveness." The information required to satisfy this requirement includes not only comprehensive safety and efficacy data, but also "an integrated summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling" (21 CFR 314.50(d)(5)(viii)).
[29] Sections 505(d)(1), (d)(2), (d)(4), and (d)(5) of the FD&C Act.
[30] An RLD is "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3(b)). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (commonly known as the Orange Book), available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm.
[31] See sections 505(j)(2)(A) and (j)(4) of the FD&C Act.
[32] See section 505(j)(2)(A)(iv) of the FD&C Act. *Bioequivalence* is "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical

that, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug product are inadequate to assure and preserve its identity, strength, quality, and purity.[33]

Section 505-1 of the FD&C Act authorizes FDA to require a REMS if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. A REMS is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. FDA may require Elements to Assure Safe Use (ETASU) as part of a REMS under certain circumstances.[34] FDA can require a REMS at the time of initial approval of an NDA or after the drug has been approved if FDA becomes aware of new safety information[35] about a drug and determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks.[36] When an RLD is subject to a REMS, an ANDA referencing that drug product is subject to certain elements of the REMS including ETASU.[37]

An application holder may propose a REMS modification at any time. In addition, FDA has the authority to require the application holder to submit a proposed modification to a REMS under section 505-1(g)(4)(B) of the FD&C Act when FDA determines that a modification of the REMS is necessary to (1) "ensure that the benefits of a drug outweigh the risks of the drug"; (2) "minimize the burden on the health care delivery system of complying with the [REMS]";[38] or (3) "accommodate different, comparable aspects of the [ETASU] for a drug that is the subject of an application under section 505(j), and the applicable listed drug."

B. National Environmental Policy Act

The National Environmental Policy Act of 1969 (NEPA) (42 USC 4321 et seq.) is a procedural statute that requires each Federal agency to assess the environmental impacts of its actions and ensure that the public is informed of these analyses.[39] FDA's regulations in 21 CFR part 25 implement the portions of NEPA that are relevant to the Agency in a manner that is consistent with FDA's authority under the FD&C Act and the Public Health Service Act. Part 25 also sets forth regulations to supplement the procedural regulations established by the Council on Environmental Quality under 40 CFR parts 1500 to 1508.[40]

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alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" (21 CFR 314.3(b)).

[33] See section 505(j)(4) of the FD&C Act.

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

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

[36] Section 505-1(a) of the FD&C Act.

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

[38] FDA also considers, among other things, the potential burden of ETASU on the health care delivery system and patient access. See sections 505-1(f)(2)(C) and (D) of the FD&C Act.

[39] See 42 USC 4332(2)(C); 21 CFR 25.1.

[40] The Council on Environmental Quality (CEQ) was established within the Executive Office of the President by NEPA (42 USC 4344). Federal agencies are required to develop methods and procedures to implement NEPA in consultation with CEQ (42 USC 4332(2)(B)). The D.C. Circuit recently ruled that CEQ lacks authority to issue binding NEPA regulations. *Marin Audubon Society v. FAA*, No. 23-1067 (D.C. Cir. Nov. 12, 2024); *but see Andrus v. Sierra Club*, 442 U.S. 347, 358 (1979) (CEQ's regulations under NEPA are "entitled to substantial deference"). Both parties in the *Marin Audubon Society* case have since petitioned for *en banc* review in the D.C. Circuit. The

NEPA directs Federal agencies, including FDA, to issue an EIS for a proposed agency action "that has a reasonably foreseeable significant effect on the quality of the human environment."[41] NEPA further directs Federal agencies to prepare an EA for a proposed agency action "that does not have a reasonably foreseeable significant effect on the quality of the human environment, or if the significance of such effect is unknown, unless the agency finds that the proposed agency action is excluded pursuant to one of the agency's categorical exclusions . . . ."[42] NEPA explains that an EA "shall be a concise public document prepared by a Federal agency to set forth the basis of such agency's finding of no significant impact or determination that an environmental impact statement is necessary."[43]

Under FDA's NEPA regulations, proposed actions that require at least the preparation of an EA include, but are not limited to, the approval of an NDA, ANDA, and certain supplements to these applications,[44] unless the action qualifies for a categorical exclusion.[45] An EA adequate to support the approval of an application is one that contains sufficient information to enable the Agency to determine whether the proposed action may significantly affect the quality of the human environment.[46] Under FDA's NEPA regulations, FDA must prepare an EIS for a proposed action when evaluation of data or information in an EA or otherwise available to the Agency leads to a finding by FDA that the action may significantly affect the quality of the human environment.[47] If FDA determines that an action will not have significant effects on the quality of the human environment, the Agency will prepare a FONSI in accordance with 21 CFR 25.41(a).[48]

III. Discussion

status of the CEQ regulations does not need to be resolved in this CP response. Because FDA has validly promulgated its own NEPA-implementing regulations in consultation with CEQ, FDA cites to the statute and its own regulations.

[41] See 42 USC 4336(b)(1). For the purposes of this response, FDA assumes that the *reasonably foreseeable* environmental effects of a drug approval extend to downstream effects that are not regulated by FDA and would not provide a basis for FDA to deny the application. We note that the Supreme Court granted certiorari in *Seven County Infrastructure Coalition v. Eagle County, Colorado*, No. 23-975 (June 24, 2024), to determine whether NEPA requires an agency to study environmental impacts beyond the proximate effects of the action over which the agency has regulatory authority. The Supreme Court has explained previously that NEPA is governed by a "rule of reason" limiting the extent of review required when the potential new information is not useful to the decisionmaking process. *Department of Transportation v. Public Citizen*, 541 U.S. 752, 767 (2004).

[42] See 42 USC 4336(b)(2).

[43] See id.; 21 CFR 25.40(b).

[44] See 21 CFR 25.20.

[45] Certain classes of actions that the Agency has determined normally do not, individually or cumulatively, have a significant effect on the quality of the human environment are ordinarily – or categorically – excluded from the requirement to prepare an EA or EIS (see 42 USC 4336e(1); 42 USC 4336(b)(2); 21 CFR 25.15(c)). However, FDA will require "at least an EA for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment" (21 CFR 25.21). Examples of extraordinary circumstances include actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Flora and Fauna to be endangered or threatened or wild flora or fauna that are entitled to special protection under some other Federal law (see 21 CFR 25.21).

[46] 42 USC 4336(b)(2); 42 USC 4336e(4); 21 CFR 25.15(a).

[47] See 21 CFR 25.22(b).

[48] Under 42 USC 4336e(7), the term *finding of no significant impact* means a determination by a Federal agency that a proposed agency action does not require the issuance of an environmental impact statement.

A. The FD&C Act Contains No Standard for Balancing the Benefits of a Drug Against Potential Environmental Impact

In the Petition, you ask FDA to modify the Mifepristone REMS Program to require prescribers to include a "Medical Waste bag and Catch-Kit" with all mifepristone prescriptions.[49] Your Petition states that "Medical Waste from Mifepristone usage is transmitted directly into the wastewater system when the patient completes the Mifepristone and associated misoprostol regimen" and "[t]his is harmful to drinking water sources, groundwater sources, and any other sources of water that are touched by wastewater."[50] In your Petition, you claim that "a requirement from the FDA" that "all prescriptions of Mifepristone be accompanied by a Catch-Kit and Medical Waste Bag" can address the introduction of bodily fluid from mifepristone use into the wastewater system because the patient's bodily fluid can "be deposited in a Medical Waste bag and Catch-Kit and returned to the institution that provided the Mifepristone."[51]

FDA's decision about whether a human drug product has been shown to be safe and effective depends on the benefits and risks of the product in the diagnosis, cure, mitigation, treatment, or prevention of a disease or condition under the intended conditions of use. The Agency's benefit-risk assessment is a case-specific determination that requires a thorough assessment of the evidence submitted by a sponsor in an application, as well as a thorough understanding of any data gaps. It also requires careful consideration of a complex set of factors, including the nature and severity of the condition the drug is intended to treat or prevent, the benefits and risks of other available therapies for the condition, and any risk management tools that might be necessary to ensure that the benefits of the drug outweigh its risks.[52]

The FD&C Act contains no standard for balancing the benefits of a drug to a human population against possible environmental impacts. For example, humans using a drug generally will excrete some amount of the drug or its metabolites into wastewater. Even assuming that this excretion could be classified as an environmental impact, it is not among the criteria that the FD&C Act requires FDA to consider in drug approval decisions, including REMS decisions.[53]

B. The Petition Does Not Provide Evidence of Harm to the Environment From Patient Use of Mifepristone

The Petition offers only conjecture that remnants of Mifepristone in the nation's water system are "causing unknown harm to citizens and animals alike."[54] Specifically, the Petition provides no evidence

[49] Petition at 1.
[50] Petition at 1.
[51] Petition at 10.
[52] See sections 505 and 505-1 of the FD&C Act; see also FDA, guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023) at 4.
[53] We note that FDA understands its obligations under NEPA to be procedural in nature. *Natural Resources Defense Council. v. EPA*, 822 F.2d 104, 129 (D.C. Cir. 1987) ("NEPA, as a procedural device, does not work a broadening of the agency's substantive powers."). Where a categorical exclusion does not apply, the preparation of an EA is required to aid in the Agency's consideration of the environmental impacts of its actions, to help it determine whether to prepare an EIS or a FONSI, and to ensure that the public is informed of the analysis.
[54] Petition at 9.

showing that bodily fluid from patients who have used mifepristone (a one-time, single-dose drug product) is causing harm to the nation's aquatic environment.

The Petition cites 29 references across six categories: articles, student papers, government reports, web pages, brochures, and books. Mifepristone or its metabolites[55] are mentioned or discussed in only eight of these references, and of these:

- Two, "Medication Abortion Now" and "Medication Abortions Are Increasing," describe increasing use of mifepristone to terminate early pregnancy in the United States.[56] Neither of these references addresses mifepristone or its metabolites in water or harm caused by mifepristone or metabolites to the nation's aquatic environment.
- One, "The Need for a National Abortion Reporting," according to an abstract, "focuses on the status of abortion reporting in the United States and how current data is inadequate." The reference is no longer available, but an abstract indicates that the reference does not address mifepristone or its metabolites in water or their environmental effects.[57]
- One, "Medical Abortion Ratios," assesses the association between ratios of abortion using medication and gender equality in Europe and finds that abortion using medication was more frequent relative to surgical abortion in countries with higher levels of gender equality.[58] This reference does not provide any information on environmental effects from mifepristone or its metabolites in water.
- One, "The Life of the Abortion Pill," mentions that adverse effects can occur in people and test animals that consume mifepristone at therapeutic, and higher, doses while pregnant. This

[55] Drugs entering the body undergo biotransformation through chemical reactions into metabolites (i.e., molecules capable of being excreted from the body more easily). See guidance for industry *Safety Testing of Drug Metabolites* (March 2020), at 2. Metabolites may be less pharmacologically active than the drug or inactive. (See the 1998 EA Guidance at 5.) However, for purposes of this response, we assume that the pharmacological activity of the mifepristone metabolites is the same as the drug itself to help ensure that FDA has considered the greatest possible potential for environmental impact. For the same reason, we consider all excretions from a patient that may contain mifepristone or its metabolites to be relevant and have the potential to contribute to environmental impact. We note that the *Pharmacokinetics* (12.3) subsection of the prescribing information for Mifeprex explains that the drug is is "accounted for by the feces [83%] and 9% by the urine." See Mifeprex (NDA 020687/supplement 26) prescribing information at 11, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf.

[56] The shortened titles, "Medication Abortion Now" and "Medication Abortions Are Increasing," refer to the following references from the Petition: Jones RK et al., February 24, 2022, Medication Abortion Now Accounts for More Than Half of All US Abortions, Guttmacher Institute, available at https://www.guttmacher.org/article/2022/02/medication-abortion-now-accounts-more-half-all-us-abortions and Miller CC and Sanger-Katz M, June 27, 2022 (updated), Medication Abortions Are Increasing: What They Are and Where Women Get Them, New York Times, available at https://www.nytimes.com/2022/05/09/upshot/abortion-pills-medication-roe-v-wade.html.

[57] The shortened title, "The Need for a National Abortion Reporting," refers to the following reference from the Petition: "The Need for a National Abortion Reporting Requirement: Why Both Sides Should Be in Support of Better Data," by J. Hill (2014), originally available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2306667. An abstract of this reference is available at https://www.researchgate.net/publication/274879976_The_Need_for_a_National_Abortion_Reporting_Requirement_Why_Both_Sides_Should_Be_in_Support_of_Better_Data.

[58] The shortened title, "Medical Abortion Ratios," refers to the following reference from the Petition: Miani C, 2021, Medical Abortion Ratios and Gender Equality in Europe: An Ecological Correlation Study, Sex Reprod Health Matters, 29(1):1985814. doi: 10.1080/26410397.2021.1985814.

reference does not discuss mifepristone or its metabolites in patient excretion or the potential for environmental impact from excretion.[59]

- One, "Aftercare Instructions," provides aftercare instructions for patients undergoing an abortion using mifepristone.[60] This reference states that most patients pass "some blood clots in the toilet and the pregnancy is often one of those clots," but it does not address mifepristone or its metabolites in patient excretion or the potential for environmental impact from excretion.
- One, "Abortion Statistics," provides statistics about abortion in the United States and other matters not relevant to the Petition, such as business revenue.[61] This reference does not provide any data on the presence, amount, or impact of excretions related to the use of mifepristone.
- One, the 1996 EA, is the only one of these eight references, and indeed the only one of the 29 references that the Petition cited in total, that addresses the potential environmental impact from mifepristone in the waters of the United States. However, following review of the 1996 EA, FDA concluded that the drug "will not have a significant effect on the quality of the human environment."[62]

It is well known that patients using a drug likely will excrete some amount of the drug or its metabolites in their urine or feces; this is generally addressed in the *Pharmacokinetics* (12.3) subsection of the prescribing information under the Excretion heading.[63] While patient excretions are expected to enter the wastewater treatment system, the occurrence and concentrations of pharmaceuticals in the environment vary widely and can depend on many factors, including the physical, chemical, and pharmacological characteristics of a drug (e.g., water solubility, metabolism), production and sales volumes, removal efficiency of the wastewater treatment plants (WWTP) through which the waste stream flows, and the characteristics of the receiving body of water. For these reasons, FDA generally takes a commonly used tiered approach that starts with conservative assumptions when calculating the

[59] The shortened title, "The Life of the Abortion Pill," refers to the following reference from the Petition: Hogan JA, The Life of the Abortion Pill in the United States, Harvard Law School Student Papers, 2000 Third Year Student Paper, available at https://dash.harvard.edu/handle/1/8852153.

[60] The shortened title, "Aftercare Instructions," refers to the following reference from the Petition: Comprehensive Women's Health Center, Aftercare Instructions: Medication Abortion, web page available at https://cwhccolorado.com/services/medication-abortion/aftercare-medication-abortion/index.html.

[61] The title, "Abortion Statistics," refers to the following reference from the Petition: "Abortion Statistics," All American Life League, available at https://all.org/abortion/abortion-statistics.

[62] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[63] See, e.g, 21 CFR 201.57(c)(13)(i)(C) requiring the labeling for human prescription drug and biological products to "describe the clinically significant pharmacokinetics of a drug or active metabolites, (i.e., … metabolism, and excretion parameters)" and the guidance for industry *Pharmacokinetics in Patients With Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* (March 2024), at 2, explaining that the kidneys are involved in the elimination of many drugs and impaired renal function typically decreases renal excretion of the drug or its metabolites.

concentration of the substance of interest in the effluent (i.e., water exiting the treatment plant) to determine whether a categorical exclusion applies to an Agency action.[64,65]

Specifically, the 1995 and 1998 EA Guidances recommend a default calculation to use for estimating the EIC of pharmaceuticals at the point of entry into the aquatic environment when information is unavailable regarding metabolism and environmental depletion mechanisms that occur in the wastewater treatment process.[66] This default calculation is scientifically appropriate to use for purposes of determining whether the 1 ppb categorical exclusion would apply. The 1995 and 1998 EA Guidances recommend that the default calculation be made using certain assumptions[67] to provide for a conservative estimate. As such, factors such as the metabolism of the drug by the human body, the anticipated dilution of the drug, and the ability of WWTPs to remove pharmaceuticals from wastewater generally are not considered when calculating the estimated EIC of a pharmaceutical at its entry into the environment.

We interpret the concern you raised that "remnants of Mifepristone are in the nation's water system, causing unknown harm to citizens and animals"[68] to indicate concerns that the drug is not fully metabolized and is not fully degraded by WWTPs such that active drug compounds are leaving the WWTPs. However, these concerns are fully accounted for by the calculations outlined in the 1995 and 1998 EA Guidances. The assumptions described in these guidances are designed to ensure that the default calculation is based on conservative estimates – as if every molecule of the pharmaceutical produced enters the WWTP in influent (water entering the treatment plant) without being metabolized by the patient, is discharged in effluent without being degraded or removed, and is not diluted upon release into the receiving water.[69]

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[64] See, e.g., 1998 EA Guidance at 13 (stating "[t]he Centers encourage the use of a logical, tiered approach") and *Exposure Assessment Tools by Tiers and Types - Screening-Level and Refined* (stating "EPA's Exposure Assessment Guidelines recommend completing exposure assessments iteratively using a tiered approach"), EPA, available at https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-screening-level-and-refined (last updated May 6, 2024).

[65] We note that the Petition provided nine references about estrogen; however, mifepristone is a synthetic steroid with antiprogestational effects, not an estrogen. Because mifepristone is not an estrogen, we interpret these references to communicate a general concern about pharmaceuticals in the environment. See Mifeprex (NDA 020687/supplement 26) prescribing information, section 11 "Description," at 10, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf.

[66] See 1995 EA Guidance at 14 and 1998 EA Guidance 17-18.

[67] The assumptions recommended at the time that the 1996 EA was completed were: "all drug substance produced is used, even distribution throughout the U.S. per day, and no metabolism or depletion mechanisms" (1995 EA Guidance at 14). These assumptions were changed slightly when the 1995 EA Guidance was replaced in 1998: "All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system," "Drug product usage occurs throughout the United States in proportion to the population and amount of wastewater generated," and "There is no metabolism" (1998 EA Guidance at 4). As described in both guidances, factors such as the metabolism of the drug by the human body, the anticipated dilution of the drug, and the ability of WWTPs to remove pharmaceuticals from wastewater are generally not considered. And, as also described in both guidances, the calculation may be appropriately weighted using certain information about depletion mechanisms as well as metabolism when that information is known and the metabolite is known to be less metabolically active or inactive. If the information about metabolism has not been established, the entire quantity of the active moiety should be used. See 1995 EA Guidance at 14 and 1998 EA Guidance at 5.

[68] Petition at 9.

[69] To the extent a pharmaceutical and its metabolites are active when they enter the WWTP and are not degraded in the WWTP, they will exit the WWTP in effluent. In actuality, however, pollutants remaining in the effluent,

In the 1996 EA, the projected EIC from patient use of mifepristone was much less than 1 ppb.[70] The EIC was calculated using the conservative, default calculation in the 1995 EA Guidance, which did not consider metabolism of the drug by the human body, the anticipated dilution of the drug, or the ability of WWTPs to remove pharmaceuticals from wastewater, to generate a conservative estimate of the amount of mifepristone that could enter the aquatic environment. Further, the Material Safety Data Sheet in the 1996 EA noted that mifepristone is "[b]iodegradable in natural media."[71] This means that mifepristone is not expected to accumulate in the environment because it will break down through the action of microorganisms. The calculations conducted as part of the 1996 EA, then, along with FDA's finding that the drug "will not have a significant effect on the quality of the human environment,"[72] show that "remnants of mifepristone" are not causing harm to the environment and to people through environmental pathways, and also show, by extension, that metabolites from patients using mifepristone have not been "causing teratologic repercussions or congenital anomalies in animals like birth defects."[73]

The assumptions underlying the 1996 EA are conservative because, among other reasons, they do not account for any treatment at a WWTP, which is designed to reduce or remove pollutants from wastewater. A particular active pharmaceutical ingredient or its metabolites may undergo many processes within a WWTP, including full or partial degradation, mineralization, sorption into organic fractions, incorporation into biomass, and deconjugation.[74] Furthermore, there are a variety of WWTP designs, and these differences may have an impact on the degradation and activity profiles. All of these processes can affect the extent of pharmaceutical degradation and the percentage of active drug compound that enters the environment.

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including pharmaceuticals, are expected to be significantly diluted after exiting the WWTP, and this dilution will reduce the pharmaceutical's exposure concentration and the potential for negatively impacting ecological species. See letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Nicholas J. Schroek and Thomas Cmar, February 22, 2013, Docket No. FDA-2010-P-0377 (referencing Oulton R, T Kohn and D Cwiertny, 2010, Pharmaceuticals and Personal Care Products in Effluent Matrices: A Survey of Transformation and Removal During Wastewater Treatment and Implications for Wastewater Management, J Envt'l Monit, 12:1956-1978), and more recent literature, e.g., Rout PR, Zhang TC, Bhunia P, Surampalli RY, 2021, Treatment Technologies for Emerging Contaminants in Wastewater Treatment Plants: A Review, Sci Total Environ, 753:141990.

[70] See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, at 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[71] See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, Appendix D, Material Safety Data Sheet, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[72] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[73] Petition at 9 and 2.

[74] See letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Nicholas J. Schroek and Thomas Cmar, February 22, 2013, Docket No. FDA-2010-P-0377.

The Petition raises the possibility that mifepristone causes teratogenic harm, citing two references: the 1996 EA[75] and a student paper.[76,77,78] Teratogenicity (the ability to cause defects in a developing embryo) is addressed in these references in the context of people or animals that consumed much higher doses of the drug while pregnant rather than being exposed to water containing the much lower EIC calculated in the 1996 EA, which FDA concluded "will not have a significant effect" on the quality of the human environment. The Petition has not provided, and FDA is not aware of, evidence suggesting that environmental exposure to mifepristone at the levels estimated to be introduced into the aquatic environment (as calculated in the 1996 EA) is teratogenic or otherwise harmful.

It is unclear whether the Petition is asserting a harm from "fetal remains" separate from the alleged harm from mifepristone residues from excretions.[79] If the argument is that "fetal remains" contain mifepristone or its metabolites, which causes harm, then, as discussed above, FDA's analysis accounted for all expected mifepristone discharges. To the extent the Petition is asserting a separate harm from "fetal remains,"[80] the Petition does not provide any evidence to support this assertion. FDA is not aware of any evidence suggesting that products of conception pose an environmental hazard to the water supply. Nor is FDA aware of any evidence suggesting that products of conception from induced abortions differ from the naturally occurring products of conception from spontaneous abortions (commonly known as miscarriages).

In sum, the information provided to support the Petition fails to include evidence of harm to the environment from the use of Mifeprex and the generic version of the drug.

C. Default EIC and Expected Environmental Concentration Calculations Based on Current Use

Notwithstanding the above conclusion that the Petition does not provide evidence of harm, FDA reviewed publicly available data on current usage rates of mifepristone in consideration of the Petition's concern about increasing rates of use of the drug and the asserted potential negative environmental impact of any such increase. We have applied the default environmental calculations described in our

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[75] The Material Safety Data Sheet included in the 1996 EA says, "embryolethal in rat, mice, rabbit per oral route," "[n]ot teratogenic in surviving rat and mice foetuses," "[t]eratogenic effects have been seen in rabbit foetuse (undirect action, at low frequency.)" See Environmental Assessment for NDA 20-687 Mifepristone Tablets, March 1, 1996, Appendix D, Material Safety Data Sheet, at 87, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[76] See Hogan JA, The Life of the Abortion Pill in the United States, Harvard Law School Student Papers, 2000 Third Year Paper, available at https://dash.harvard.edu/handle/1/8852153.

[77] The Petition includes one additional reference associated with its concern about teratogenic harm, but this reference is not about mifepristone: Gonsioroski A, Mourikes VE, Flaws JA. *Endocrine Disruptors in Water and Their Effects on the Reproductive System*. Int J Mol Sci. 2020 Mar 12;21(6):1929. doi: 10.3390/ijms21061929. PMID: 32178293; PMCID: PMC7139484. Petition at 2. While this reference discusses the well-known fact that some pharmaceuticals are present in wastewater and receiving waters, it makes no mention of mifepristone or any specific drug product. Rather, this reference discusses the occurrence of endocrine disrupting chemicals in water such as "disinfection byproducts, fluorinated compounds, bisphenol A, phthalates, pesticides, and estrogens." See id. The reference does not identify mifepristone as an endocrine disruptor.

[78] Petition at 7.

[79] See Petition at 5 ("[C]hemical abortion caused by Mifepristone creates more harmful byproducts, along with the expected fetal remains, because it includes the remains of Mifepristone itself.").

[80] See Petition at 6.

current environmental guidance (the 1998 EA Guidance)[81] to estimates of current use rates[82] in order to characterize the current expected level of exposure of mifepristone and potential for effects on the environment. As explained in detail below, these calculations, which are based on conservative estimates, show a mifepristone exposure level that is so low that it is predicted to have no effect on the environment.

Even though the Petition raises a concern about environmental impact only from mifepristone's use for medical termination of early pregnancy, we looked at current estimated use rates for the two approved indications for mifepristone products in order to provide a fuller picture of potential environmental impact.[83] In consideration of the Petition's concern about mifepristone in the "waters of the United States,"[84] we calculated both the EIC at the point of entry into the aquatic environment (i.e., effluent leaving WWTPs) and the expected environmental concentration (EEC) (the concentration of mifepristone that organisms would be exposed to in the environment (e.g., surface water throughout the United States)).[85] The EEC for the aquatic environment is generally expected to be significantly less than the EIC after consideration of factors such as dilution or degradation.[86]

[81] See 1998 EA Guidance at 4 for the default EIC calculation and at 19 for the default expected environmental concentration calculation.
[82] We used estimates of current use from public sources because production rates are considered confidential commercial information and because these estimates are more responsive to the Petitioner's concerns related to current use rates and their potential impact on the environment.
[83] See footnote 5 for information on mifepristone products approved for use in patients with endogenous Cushing's syndrome.
[84] Petition at 1.
[85] While EAs are not required to include both the EIC and the EEC, applicants may choose to examine both values and some have done so (e.g., Aleve PM (NDA 205352) Environmental Assessment, at 9, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205352Orig1s000EA.pdf; Nexlizet (NDA 211617) Product Quality Review(s), Chapter III: Environmental, at 3, at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211617Orig1s000ChemR.pdf; Tazverik (NDA 211723) Product Quality Review(s), Chapter III: Environmental, at 64, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211723Orig1s000ChemR.pdf; and Steglatro (NDA 209803), Steglujan (NDA 209805), and Segluromet (209806) Chemistry Reviews, Product Quality Reviews, Chapter III, Environmental Analysis, at 1 and FONSI at 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209803,209805,209806Orig1s000ChemR.pdf). We note that what we are referring to in this response as "EEC" may also be referred to as "maximum expected environmental concentration (MEEC)" as was done in some of the reviews referenced here.
[86] 1998 EA Guidance at 19.

Indication	**EIC (ng/L)[87,88]**	**EEC (ng/L)[89]**	**EEC Risk Quotient[90,91]**
Medical termination of early pregnancy	2.8[92]	0.28	0.028
Cushing's syndrome	7.0[93]	0.70	0.070
Total	9.8	0.98	0.098

[87] Consistent with the 1998 EA Guidance, EIC = A x B x C x D where A = kilograms (kg)/year produced for direct use (as active moiety), B = 1/liters per day entering WWTPs, C = year/365 days, and D = 10^9 micrograms (µg)/kg (conversion factor). See 1998 EA Guidance at 4.

[88] As used in this response, the abbreviation *ng/L* means nanogram per liter and 1,000 ng/L equals 1 microgram per liter (µg/L) or 1 ppb.

[89] Consistent with the 1998 EA Guidance, EEC = EIC/10. To calculate the EEC, we applied a dilution factor of 10. See 1998 EA Guidance at 19.

[90] A risk quotient (RQ) is calculated by dividing a point estimate of exposure by a point estimate of effects. An RQ greater than or equal to 1 indicates the estimated exposure could result in adverse effects, and an RQ less than 1 indicates the estimated exposure will not result in adverse effects, including for threatened and endangered species. To calculate the EEC RQ, we divided the EEC by the predicted no-effect concentration (PNEC). See *Technical Overview of Ecological Risk Assessment: Risk Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk and *Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs: Endangered and Threatened Species Effects Determinations*, EPA, available at https://www.epa.gov/sites/default/files/2014-11/documents/ecorisk-overview.pdf. *PNEC* refers to the concentration of a substance in an environment below which adverse effects will most likely not occur during long-term or short-term exposure. The PNEC for mifepristone was obtained from Fass, 2020, Mifepristone Linepharma: Environmental Information, available at https://www.fass.se/LIF/product?userType=2&nplId=20100302000013; this source used a standard assay approach to determine the PNEC. For your convenience, we have enclosed a copy of this reference containing the PNEC for mifepristone.

[91] Although not at issue in this response, we note that an RQ of greater than or equal to 1 does not immediately indicate that exposure will result in adverse effects because the default calculations for producing these estimates include conservative assumptions that generate exposure estimates that are higher than what is likely present in the environment. The 1998 EA Guidance accounts for this by recommending a logical, tiered approach so that adequate information is available to assess the potential environmental impact of pharmaceuticals while minimizing cost to industry (see 1998 EA Guidance at 13). Under certain circumstances, the 1998 EA Guidance recommends the use of higher tier approaches (e.g., Tier 2 or Tier 3) in order to generate more specific data regarding environmental impact by using testing and consideration of depletion mechanisms (see 1998 EA Guidance at 13-26).

[92] This is equivalent to 0.0028 ppb. The EIC for medical termination of early pregnancy was calculated using the following: A = 131 kg/year; B = 1/(1.21 x 10^{11} liters per day entering treatment plants); C = year/365 days; and D = 10^{12} ng/ kg. Instead of relying on confidential production rates, see footnote 82 above, FDA based its determination of A (kg/year produced for direct use as active moiety, per the 1998 EA Guidance) on a dose of 200 mg/use (0.0002 kg/use) and figures from the Guttmacher Institute, from which we estimated that 653,300 medication abortions occurred in the United States in 2023. See "Fact Sheet Abortion in the United States," Guttmacher Institute, June 2024, available at https://www.guttmacher.org/fact-sheet/induced-abortion-united-states.

[93] This is equivalent to 0.007 ppb. The EIC for Cushing's syndrome was calculated using the following: A = 328 kg/year; B = 1/(1.21 x 10^{11} liters per day entering treatment plants); C = year/365 days; and D = 10^{12} ng/ kg. Instead of relying on confidential production rates, see footnote 82 above, FDA based its determination of A (kg/year produced for direct use as active moiety, per the 1998 EA Guidance) on a dose of 300 mg/day for 3,000 Cushing's syndrome patients with type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery, as indicated, based on (1) a high-end estimate of Cushing's syndrome prevalence of close to 40 per million (Castinetti, F., Morange, I., Conte-Devolx, B. et al. 2012, Cushing's Disease, Orphanet J Rare Dis, 7:41) and (2) a high-end assumption of 25 percent use within this population to account for only that fraction of Cushing's syndrome patients that would (a) have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery, as indicated, and (b) use Korlym instead of other preferred medications or no medications (Ibid.).

The EIC and EEC default calculations provide conservative estimates that are higher than the concentration of a drug that is likely to be in the environment. Consistent with the Agency's current guidance, we assumed that all of the estimated mifepristone used by patients in a year for both indications entered the WWTP system, and was released into the receiving waters without reduction from human metabolism or depletion mechanisms to calculate a conservative EIC.[94]

To assess ecological risk, we used a standard three-step analysis: (1) characterizing ecological effects (i.e., how toxic a substance is); (2) characterizing exposure (i.e., environmental exposure estimate); and (3) comparing ecological effects level to environmental exposure.[95] For the first step (ecological effects), we obtained mifepristone's predicted no-effect concentration (PNEC), which is the concentration of a substance in an environment below which adverse effects will most likely not occur during long term or short-term exposure. The PNEC for mifepristone is 10 nanograms (ng)/liter (L)[96] For the second step (exposure), the total EIC (9.8 ng/L) and EEC (0.98 ng/L) were estimated as discussed in footnotes 92 and 93. For the third step (comparing ecological effects to environmental exposure), the risk quotient (RQ) method for examining environmental exposure is used to identify high and low risk situations. An RQ of greater than or equal to 1 indicates the estimated exposure could result in adverse effects, and an RQ of less than 1 indicates the estimated exposure will not result in adverse effects, including for threatened or endangered species.[97] To do this, we followed the steps outlined by EPA for estimating RQs and comparing the EEC to the PNEC.[98] The total EEC RQ is 0.098. Therefore patient use of mifepristone across both indications is predicted to have no adverse effects on the environment.[99]

In sum, not only does the Petition provide no evidence of harm to the environment, but the Agency's conservative calculations using estimates of current use rates of mifepristone also show an exposure

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[94] 1998 EA Guidance at 4.

[95] See *Technical Overview of Ecological Risk Assessment - Analysis Phase: Ecological Effects Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-0 and *Technical Overview of Ecological Risk Assessment: Risk Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk.

[96] See Health and Medical Care Administration, Region Stockholm, 2020, Mifepristone, available at https://janusinfo.se/beslutsstod/lakemedelochmiljo/pharmaceuticalsandenvironment/databaseenven/mifepristone.5.30a7505616a041a09b062f91.html, which provides a no-observed effects concentration (NOEC) of 100 ng/L, and its reference, Fass, 2020, Mifepristone Linepharma: Environmental Information, available at https://www.fass.se/LIF/product?userType=2&nplId=20100302000013, which provides the corresponding PNEC of 10 ng/L. We consider the PNEC of 10 ng/L for mifepristone appropriate for use in this response because it was derived by using a standard assay approach.

[97] See *Technical Overview of Ecological Risk Assessment - Analysis Phase: Ecological Effects Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-0 and *Technical Overview of Ecological Risk Assessment: Risk Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk.

[98] *Technical Overview of Ecological Risk Assessment: Risk Characterization*, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk.

[99] Technical Overview of Ecological Risk Assessment: Risk Characterization, EPA, available at https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk.

level that is so low that it is predicted to have no effect on the environment, including threatened and endangered species.[100] Accordingly, there is no environmental harm that needs to be addressed.

D. The EA Completed in 1996 Complied With NEPA and Applicable Regulations

In your Petition, you claim that the 1996 EA "only reviewed the impact that packaging, partially empty packaging, production waste, and pharmaceutical waste would have on the environment, and underestimated the impact the excretion of Mifepristone would have on the environment."[101] Further, you claim "[t]here was not any evaluation of Mifepristone's effect on the water supply or pollution for the people or animals who consume that water."[102] Finally, you claim that "FDA reported that there would be high standards for disposal related to Mifepristone. This has not been the case."[103] FDA disagrees with these claims because the 1996 EA reviewed patient use of mifepristone in section 6.e.i "Expected Introduction Concentration from Use," which assessed potential impact on water from patient use caused by patient excretion entering the wastewater treatment system. The 1996 EA estimated an EIC into the aquatic environment from patient use of less than 1 ppb, which FDA concluded would not have a significant effect on the quality of the human environment. Section 4.e "Disposal Sites," which addressed the standards for disposal of pharmaceutical waste, did not consider or set a standard for excretions from patient use.

Regarding the format and content of the 1996 EA, the 1996 EA used the term *disposal* to address the disposal of "rejected, expired, returned, or waste drug products" (at 3), which did not include patient excretion of mifepristone or its metabolites, because excretion was addressed separately as "excretion" or "use." The format of the 1996 EA, including its separate sections for disposal of waste drug product (section 4.e "Disposal Sites") and the EIC from patient use (section 6.e.i "Expected Introduction Concentration from Use"), was consistent with Agency guidance and regulations that existed at that time.

Specifically, FDA's 1995 EA Guidance provided recommendations on how to prepare an EA for submission to FDA. As explained in the 1995 EA Guidance, the EA "should describe the method(s) of disposal of rejected, expired, returned or waste drug substance."[104] Section 4.e of the 1996 EA addressed disposal of pharmaceutical waste through incineration, grinding, and landfill, which are typical disposal methods for pharmaceutical waste and align with the 1995 EA Guidance.[105]

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[100] Because the EEC RQ of 0.098 is less than one tenth of an EEC RQ of 1, the usage across both indications could increase tenfold and the exposure level would still be predicted to have no adverse effects on the environment, including threatened and endangered species.

[101] Petition at 1.

[102] Petition at 3.

[103] Petition at 3.

[104] 1995 EA Guidance at 9. We note that the recommendation to describe the methods for disposal of pharmaceutical waste from the 1995 EA Guidance was not included in the 1998 EA Guidance. In the 1998 EA Guidance, FDA explained that the Agency would no longer routinely request submission of manufacturing and disposal information in an EA. The 1998 EA Guidance explains that FDA has found that regulated articles produced and disposed of in compliance with all applicable emission requirements do not significantly affect the environment and has determined it is unnecessary to review a company's compliance with Federal, State, and local environmental laws. See 1998 EA Guidance at 9.

[105] Pharmaceutical waste will typically be disposed of in landfills or at incineration facilities that are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation

Consistent with 21 CFR 25.15(a), FDA concluded that the 1996 EA contained sufficient information for the Agency to determine that the approval of the application) would have no significant effect on the quality of the human environment.[106] In reaching this conclusion, FDA considered that "[m]ifepristone may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites."[107] The projected EIC from patient use of the drug product was less than 1 ppb.[108] As noted in the FONSI, FDA had previously found that drug concentrations of less than 1 ppb generally had no effect on relevant standard test organisms, and therefore were unlikely to have a significant effect on the environment.[109] Furthermore, at the time that the applicant developed the 1996 EA, the Agency's policy was that FDA could request additional information from an applicant when sufficient available information suggested that the substance may be toxic to organisms in the environment at the expected levels of exposure.[110] FDA found that there was no information which indicated that extraordinary circumstances[111] existed that would warrant the submission of additional environmental information by the applicant.[112] FDA specifically considered potential impact upon endangered or threatened species and found that "[a]dverse effects are not anticipated upon endangered or threatened species."[113] Finally, FDA's decision to prepare a FONSI and not to prepare an EIS was in full accordance with 21 CFR 25.41 and 25.22 because the Agency determined that there would be no significant effects on the quality of the human environment.[114]

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of these facilities in their licensing process and require controls (e.g., scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. See 1995 EA Guidance at 15. See also 1998 EA Guidance at 18.

[106] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf. See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf

[107] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[108] See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, at 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[109] Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 1, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf; see also 1995 EA Guidance at 18.

[110] 1995 EA Guidance at 3.

[111] *Extraordinary circumstances* are circumstances that "indicate that the specific proposed action may significantly affect the quality of the human environment" (21 CFR 25.21).

[112] See Review of Environmental Assessment for NDA 20-687 Mifepristone Tablets, July 9, 1996, at 1 and 6, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[113] See Finding of No Significant Impact for NDA 20-687 Mifepristone Tablets, July 1996, at 2, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_EA.pdf.

[114] In your Petition, you assert that "[w]hen approving Mifepristone for consumer use in 2000, the FDA did not conduct an environmental study regarding the potential impact Mifepristone could have on the nation's wastewater, nor was a study conducted when REMS were adopted in 2011 or when the REMS were modified in 2016, supplemented in 2019 and modified again in 2021" (Petition at 1). We note that FDA must prepare an EIS only for a proposed action when FDA determines that the action may significantly affect the quality of the human environment (21 CFR 25.22(b)). Prior to approving Mifepristone in 2000, an EA was completed, and FDA concluded that the projected EIC of less than 1 ppb would have no effects on the quality of the human environment; therefore, the threshold triggering the preparation of an EIS was not met. Similarly, the applicant for ANDA 091178 claimed a categorical exclusion under 21 CFR 25.31(a) because the action did not increase use of the active moiety. FDA reviewed and approved ANDA 091178 in 2019. The threshold triggering the preparation of an EIS was not met. Regarding other FDA actions on mifepristone to date and their potential for environmental impact, we note that the calculations above (see section III.C.) demonstrate that, even when conservative assumptions are applied

For these reasons, the 1996 EA was consistent with NEPA and 21 CFR part 25 and demonstrates that FDA appropriately assessed the potential impact on the human environment from excretion by patients who use mifepristone and determined that there would be no significant effects on the quality of the human environment.

E. Concerns Regarding Regulation of Medical Waste Should be Directed to Appropriate Regulators

In your Petition, you say that in terms of regulating medical waste "states lead the way and there is not much that the EPA can do in the realm of Medical Waste."[115] You also say that "EPA has not had authority, specifically [to regulate] medical waste, since the Medical Waste Tracking Act (MWTA) of 1988 expired in 1991."[116] Further, you say that "to require the inclusion of a Catch-Kit and Medical Waste bag in the prescriber requirements is one way to combat the inability of the EPA or FDA to control Medical Waste."[117]

Generally, medical waste is considered a subset of wastes generated at health care facilities, such as hospitals, physicians' offices, dental practices, blood banks, and veterinary hospitals/clinics, as well as medical research facilities and laboratories.[118,119] Such medical waste may be contaminated by blood, body fluids, or other potentially infectious materials and is often referred to as regulated medical waste.[120,121]

We agree with the Petition that medical waste is primarily regulated by state environmental and health departments.[122] We also note that Federal agencies, such as the Occupational Safety and Health

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and the current usage rates of mifepristone for both of its FDA-approved indications are considered, the exposure level of mifepristone in the aquatic environment is so low that it is predicted to have no effect on the environment. These calculations therefore show that none of FDA's other actions on mifepristone would have been expected to have an effect on the environment.

[115] Petition at 6.

[116] Petition at 6.

[117] Petition at 6.

[118] See EPA website on medical waste, available at https://www.epa.gov/rcra/medical-waste#:~:text=Generally%2C%20medical%20waste%20is%20healthcare,to%20as%20regulated%20medical%20waste.

[119] We note that the FD&C Act and FDA have not defined the term "medical waste." We defer to other government agencies on what constitutes "medical waste" under their respective definitions. We note that bodily fluid that enters the wastewater treatment system typically falls under regulations aimed at wastewater treatment and domestic sewage.

[120] See EPA website on medical waste, available at https://www.epa.gov/rcra/medical-waste#:~:text=Generally%2C%20medical%20waste%20is%20healthcare,to%20as%20regulated%20medical%20waste.

[121] The Petition uses the term "pathological waste" (Petition at 6). We note that the FD&C Act and FDA have not defined the term "pathological waste." We interpret the Petition's use of "pathological waste" to refer to a subset of "medical waste." Accordingly, this section of our response on "medical waste" also speaks to the Petition's concerns regarding "pathological waste." The Petition cites the World Health Organization's website on "Health-care waste" on page 6, which describes "pathological waste" as "human tissues, organs or fluids, body parts and contaminated animal carcasses." See https://www.who.int/news-room/fact-sheets/detail/health-care-waste.

[122] Petition at 6 (noting that individuals are encouraged "to contact your state environmental program first when disposing of medical waste" and "[c]ontact your state environmental protection agency and your state health agency for more information regarding your state's regulations on medical waste").

Administration (OSHA) and the Department of Transportation (DOT), have regulations regarding medical waste.[123] We defer to EPA regarding the scope of its authority over medical waste because the EPA is the Federal agency primarily responsible for implementing Federal laws and regulations related to protecting the environment, including water quality.

We suggest you direct concerns regarding the regulation of medical waste to appropriate state and local officials and other Federal agencies in accordance with their respective jurisdictions over relevant issue areas such as water sanitation systems, the environment, and occupational health and safety.

IV. Conclusion

For the reasons explained above, we deny your Petition.

Sincerely,

Patrizia A. Cavazzoni -S

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Patrizia Cavazzoni, M.D.
Director
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Enclosure

[123] See, e.g., OSHA's Bloodborne Pathogens Standard at 29 CFR 1910.1030, available at https://www.osha.gov/laws-regs/regulations/standardnumber/1910/1910.1030, and DOT's Hazardous Materials Regulations at 49 CFR., parts 171-180, available at https://www.ecfr.gov/current/title-49/subtitle-B/chapter-I/subchapter-C. See also, the Centers for Disease Control and Prevention's guidelines for regulated medical waste from the Guidelines for Environmental Infection Control in Health-Care Facilities (2003), available at https://www.cdc.gov/infection-control/hcp/environmental-control/regulated-medical-waste.html#:~:text=Health%2Dcare%20facility%20medical%20wastes,and%20other%20body%2Dfluid%20specimens.