Nos. 23-235 & 23-236

In the Supreme Court of the United States

U.S. FOOD & DRUG ADMINISTRATION, ET AL.,
Petitioners,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

DANCO LABORATORIES, L.L.C.,
Petitioner,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

On Petitions for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

BRIEF FOR FOOD AND DRUG LAW SCHOLARS AS *AMICUS CURIAE* IN SUPPORT OF PETITIONS FOR WRIT OF CERTIORARI

Lewis A. Grossman
Denise Esposito
Robert A. Long
Counsel of Record
Julia F. Post
Beth Braiterman
Guillaume A. Julian
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
RLong@cov.com
(202) 662-6000

Counsel for Amici Curiae

October 12, 2023

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Statutes

Regulations

Congressional Materials

Regulatory Materials

Other

INTEREST OF THE *AMICI CURIAE*[1]

Amici curiae are U.S. food and drug law scholars from academic institutions across the United States.[2] A full list of *amici* is included as an Appendix to this brief. *Amici* have expertise in food and drug law, including the drug approval process. They also have an interest in the proper interpretation of the Federal Food, Drug, and Cosmetic Act (FDCA). *Amici* submit this brief to address important issues raised by this case concerning the authority of the U.S. Food & Drug Administration (FDA or the Agency) to regulate prescription drugs.

SUMMARY OF ARGUMENT

In the Federal Food, Drug, and Cosmetic Act, Congress created a comprehensive process under which FDA must review and approve new drugs, and major changes to approved new drug applications, before such products may be introduced into interstate commerce. FDA will approve a new drug marketing application only if it determines, based on the full record before the Agency, that the product is safe and

---

[1] No party or counsel for a party authored this brief in whole or in part, and no person other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief. The parties were timely notified that *amici curiae* intended to file this brief.

[2] The views expressed in this brief are those of the *amici* in their individual capacities and do not necessarily represent the views of their respective institutions.

effective for the proposed conditions of use. That determination requires the review of scientific evidence that sponsors[3] submit in support of their applications. In certain circumstances, the FDCA authorizes FDA to impose additional elements to assure a drug's safe use, but the statute requires the Agency to minimize the burdens of such elements on patient access and, to the extent practicable, the healthcare system.

Pursuant to these statutory processes, FDA approved mifepristone in 2000 with use and distribution restrictions. In 2016, after more than 15 years of approved use, FDA concluded that certain of these restrictions should be eliminated or modified and that the approved conditions of use should be amended. In 2021, FDA announced that further changes to the use and distribution restrictions should be made. These FDA actions were science-based, well-documented, and lawful.

As discussed below, the Fifth Circuit's order rests on critical misunderstandings of federal food and drug law, the regulatory history of mifepristone, and the evidence relied on by FDA. Contrary to the Fifth Circuit's conclusion, FDA had *far more* evidence than was statutorily necessary to support the changes to mifepristone's conditions of use and restrictions on use and distribution.

If allowed to stand, the Fifth Circuit's decision will erode the drug regulatory system established by Congress in the FDCA and implemented by FDA through

---

[3] For the purposes of this brief, we use the term "sponsors" to refer to marketing applicants and marketing application holders.

regulations, guidance, and well-established practice. This Court should grant the petitions for certiorari.

ARGUMENT

I. Congress Has Granted FDA Broad Authority to Approve and Regulate Prescription Drugs.

Congress has established a comprehensive statutory process under which new drugs must be reviewed and approved by FDA before they may be lawfully introduced into interstate commerce. *See* 21 U.S.C. §§ 331(d), 355(a). Prior to marketing a new drug, a sponsor must file a New Drug Application (NDA) under section 505(b) of the FDCA. *Id.* § 355(b). Under section 505(d), FDA may not approve a drug if the NDA contains insufficient evidence to demonstrate safety or lacks substantial evidence of effectiveness. *Id.* §§ 355(d)(4), (5); *see also* 21 C.F.R. § 314.125(b). FDA's rigorous review and approval process includes not only a clinical assessment of the drug itself, but also, among other things, the "labeling proposed to be used for such drug." 21 U.S.C. § 355(b)(1)(vi).[4]

In order to add or modify an indication or claim, revise the dosing regimen, or provide for a new route of administration (among other changes), sponsors must apply and receive approval for efficacy supplements. *See* 21 U.S.C. § 505(b); 21 C.F.R. § 314.3(b). The safety and effectiveness standard applies equally

---

[4] Sponsors of generic drugs may file an abbreviated new drug application that relies on the safety and effectiveness data of an already-approved drug. *See* 21 U.S.C. § 355(j).

to NDAs, and to supplemental applications (sNDAs) seeking changes to the conditions of use (known as "efficacy supplements"). *See* 21 U.S.C. § 355(d). The format, content, and review procedures for NDAs and efficacy supplements are identical in all relevant respects. *See, e.g.*, FDA, Ctr. For Drug Eval. & Rsch., MAPP 6020.8 at 2 (June 13, 2016), https://www.fda.gov/media/72739/download.

In the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress granted FDA express authority to impose restrictions on the distribution and use of prescription drugs if necessary to address specific safety concerns, *i.e.*, risk evaluation and mitigation strategies (REMS). *See* Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926–49 (2007) (codified at 21 U.S.C. § 355-1).[5] FDA may impose a REMS *only if* the Agency determines that a REMS is "necessary to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(1). The components of a REMS may include, among other things, elements to assure safe use (ETASU), such as requirements that healthcare providers who prescribe the drug be certified or that the drug be dispensed to patients only in certain settings.

REMS with ETASU are used sparingly, only where necessary to ensure that the benefits of the

---

[5] Prior to the passage of FDAAA, FDA had established a mechanism to impose distribution and use restrictions through regulation at 21 C.F.R. § 314.520, "Approval with restrictions to assure safe use." FDAAA codified and expanded that regulation by creating a statutory REMS framework.

drug outweigh the risk.[6] The statute demands that ETASU be "commensurate" with a "specific serious risk listed in the labeling." 21 U.S.C. § 355-1(f)(1)(A), (f)(2)(A). It requires ETASU to be designed "so as to minimize the burden on the health care delivery system." *Id.* § 355-1(f)(2)(D). And critically, the Act mandates that ETASU "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) . . . and . . . patients with functional limitations." *Id.* §§ 355-1(f)(2)(C)(ii), (iii). In other words, REMS with ETASU must be the *least restrictive necessary* to ensure that the drug's benefits outweigh its risks.

II. The Fifth Circuit Applied the Incorrect Legal Standards When Reviewing the 2016 sNDA Approval.

FDA follows a standard procedure when reviewing an NDA, including an efficacy supplement. First, FDA assembles an internal team of experts, including medical officers, safety officers, chemists, statisticians, and pharmacologists. Next, this internal team reviews the evidentiary record, which often includes only one adequate and well-designed clinical study

---

[6] Of the thousands of prescription drugs FDA has approved, currently there are only 61 REMS with ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last updated Oct. 10, 2023). Certain REMS are applicable to multiple applications. *See id.*

with other confirmatory evidence. *See* Robert M. Kaplan et al., *Review of Evidence Supporting 2022 US Food and Drug Administration Drug Approvals*, 6 JAMA Network Open e2327650, at 2 (Aug. 8, 2023), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2808057 (finding that in 2022, 65% percent of approved novel drugs, *i.e.*, drugs that had not been previously approved for any indication, were supported by one clinical study).[7] Seldom does the record include more than three. *See*, *supra,* Kaplan et al., *Review of Evidence Supporting 2022 US Food and Drug Administration Drug Approvals* (finding that only four out of 37 novel drugs approved in 2022 had more than three adequate and well-controlled studies in their record). FDA will approve an application only if the Agency concludes that the evidentiary record, including the clinical trial data, satisfies the statutory requirements for approval.

---

[7] *See also* FDA, *Draft Guidance: Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* 1–3 (Sept. 2023) (explaining that one "adequate and well-controlled study" can be sufficient to warrant approval with other confirmatory evidence), https://www.fda.gov/media/172166/download; FDA, *Draft Guidance: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry* 3–4, (Dec. 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products (same)).

In May 2015, Danco Laboratories, LLC (Danco) submitted an efficacy supplement with REMS modifications to FDA for mifepristone, which had been on the market since 2000. C.A. Add. 777. For 10 months, FDA's experts combed through Danco's extensive evidentiary record in support of the proposed changes. They analyzed 54 unique studies;[8] 15 years of adverse event reporting and regulatory filings, including two in-depth REMS assessment reports, C.A. Add. 789; 34 articles, filings, and online sources—in addition to the aforementioned 54 studies—in support of the clinical review, C.A. Add. 751–58; three letters supporting the proposed changes from academic and professional organizations, including the American College of Obstetricians and Gynecologists, C.A. Add. 683; and new information adding or clarifying details from previously submitted data across five different amendments to the application. C.A. Add. 680. These sources provided FDA's expert teams with unusually extensive data and information to evaluate Danco's proposal.

FDA's review considered the "interrelated" impact of the sNDA's multiple changes, noting that "in some cases data from a given study were relied on to provide evidence to support multiple changes." C.A. Add. 781. In particular, one randomized controlled trial and

---

[8] The studies included 15 randomized controlled trials or equivalents, and other interventional, observational, retrospective, and prospective trials, as well as systematic reviews and literature reviews of clinical studies.

three observational studies closely mirrored the overall changes proposed in the sNDA. These studies evaluated "the exact proposed dosing regimen through 70 days gestation [and] . . . had a primary objective of evaluating medical abortion provision by non-physicians." FDA, *Cross Discipline Team Leader Review* 9 (2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf. Based on these and other sources, FDA approved the sNDA in 2016, modifying both mifepristone's prescribing information and its REMS.

As part of its approval, FDA published multiple review memoranda explaining the scientific rationale for its decision. The explanation was meticulous and extensive, spanning close to 500 pages. *See generally,* FDA, *Mifeprex 2016 sNDA Review* (2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm. The memoranda demonstrate that the Agency comprehensively assessed the relative risk of adverse events when using the new dosing regimen of mifepristone in combination with misoprostol (the risk was low); evaluated whether the changes would negatively impact mifepristone's efficacy (they would not—the new dosing regimen was *more* effective); and analyzed whether the modified REMS would ensure that the benefits of the drug would outweigh its risk (they would).

Despite this robust and well-documented record, the Fifth Circuit concluded that FDA's approval was likely arbitrary and capricious because the Agency failed "to seek data on the cumulative effect" of the

proposed changes or explain why it did not do so. U.S. Pet. App. 45a. In so ruling, the court brushed away tens of thousands of pages of supporting evidence and hundreds of pages of administrative record and made demands that go beyond what the FDCA requires.

A. The Fifth Circuit's "Cumulative Effect" Requirement Is Inconsistent with FDCA Section 505-1.

Several of the 2016 changes—including allowing some non-physician healthcare providers to prescribe and dispense mifepristone,[9] and eliminating the requirement for prescribers to report non-fatal adverse events to Danco—were REMS modifications made under section 505-1. The Fifth Circuit's determination that FDA must "seek data" concerning "cumulative effect," or expressly explain why it did not do so, would add a new evidentiary requirement that does not appear in the statute or FDA's regulations. Its inclusion would disrupt the statutory REMS framework by interfering with Congress's command to balance the specific risks of a drug against the burdens that restrictions on distribution or use would impose on patient access and on the healthcare delivery system. 21 U.S.C. § 355-1(f)(2). Furthermore, acceptance of

---

[9] Previously, only physicians could become certified prescribers, but advanced practice clinicians with state-law prescribing authority could prescribe "under the supervision of" a physician who was a certified prescriber. *See* FDA, *NDA 20-687 MIFEPREX (mifepristone) Tablets, 200 Mg: Risk Evaluation and Mitigation Strategy (REMS)* 2 (2011), https://www.fda.gov/media/164648/download?attachment.

the Fifth Circuit's approach would calcify unduly burdensome restrictions on drug use, undermining the REMS framework that Congress intended to be used narrowly and only where necessary to ensure that the benefits of a drug outweigh the risks.

i. The Statute Does Not Require Any Particular Type of Evidence to Impose, Modify, or Remove REMS Elements.

By Congress's direct instruction, REMS are not intended to be static. All REMS require the submission of "assessments" at certain regular intervals, and FDA may require additional assessments at any other time it needs one to evaluate whether to modify a REMS. 21 U.S.C. § 355-1(d), (g)(2)(B), (g)(2)(C). Additionally, when a sponsor submits an sNDA seeking approval of a new indication for a drug subject to a REMS, it must include an assessment of the approved REMS with its application. *Id.* § 355-1(g)(2)(A). An assessment must include, "with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified." *Id.* § 355-1(g)(3).

In reviewing REMS assessments and proposed modifications, FDA has broad latitude in determining the types of data and information that would support a modification to the program.

Although FDA did, in fact, examine numerous clinical trials when it approved the 2016 REMS modifications for mifepristone, nothing in the FDCA requires that clinical trial data be included in a REMS assessment or provide the basis for a REMS modification. "Assessment" simply means "the action or instance of making a judgment about something." *Assessment*, Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/assessment. It does not imply any particular degree of rigor, and in the context of REMS, Congress requires that a sponsor provide only a mere "adequate rationale" to support a proposed modification. 21 U.S.C. § 355-1(g)(4)(a). It also does not require any particular method of analysis. By contrast, when Congress *requires* an FDA decision (such as the approval of a drug) to be based on clinical investigations, it is explicit on the point. *See* 21 U.S.C. § 355(d) (requiring "adequate and well-controlled investigations, including clinical investigations" to demonstrate a drug's effectiveness); *see also id*. § 355a(a) (defining "pediatric studies" to mean "at least one clinical investigation").

Through guidance and precedent, FDA has made clear that clinical trial data are not required for REMS assessments or modifications. In providing examples of acceptable sources of data to include in a REMS assessment, FDA does not even mention data from additional clinical trials. *See* FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting* 7–12 (Jan. 2019), https://www.fda.gov/media/119790/download. Instead, the Agency expects such assessments—and the resulting REMS modifications—to be based on "a combination of qualitative

and quantitative information about the REMS" derived from sources such as company databases, stakeholder surveys, drug utilization data, post-marketing adverse event data, observational data, epidemiological data, and "stakeholder outreach." *Id.* at 7–12. Such data are to be used both to assess the effectiveness of the REMS and "the impact of the program on the healthcare delivery system and on patient access to the drug." *Id.* at 12.

As a matter of practice, FDA regularly makes modifications to ETASU without *any* clinical trial data at all. For example, since the establishment of the procedure in 2007, FDA has fully removed 208 REMS—including ten REMS with ETASU.[10] In none of these ten instances did FDA's public memoranda cite a controlled clinical study comparing the safety of the drug without any ETASU in place against safety under the then-current regime. Nor did FDA in any of these instances announce that it was reviewing the "cumulative effect" (or explain why it was not doing so), even in instances where FDA removed multiple ETASU at once.[11]

---

[10] *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/dfa2f0ce-4940-40ff-8d90-d01c19ca9c4d/state/analysis (last updated Oct. 10, 2023).

[11] *See, e.g.*, FDA, *Lotronex (alosetron hydrochloride) Information*, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information ("Evidence to Support Eliminating the Lotronex and Alosetron REMS").

Adopting the Fifth Circuit's "cumulative effect" requirement could result in stringent restrictions being kept in place even after FDA has acquired sufficient information demonstrating that the restrictions (1) are no longer necessary to ensure that the benefits of the drug outweigh the risk, or (2) are imposing undue burdens on patient access or the healthcare system. In short, it could ossify and burden drug regulation, harming the very patients that a REMS is intended to protect.

ii. FDA Had More Than Enough Data and Information to Modify the Mifepristone REMS in 2016.

In 2016, FDA "determined that the approved REMS for Mifeprex should be modified to continue to ensure that the benefits of Mifeprex outweigh its risks and to minimize the burden on the healthcare delivery system of complying with the REMS." C.A. Add. 769. In doing so, FDA considered evidence that far exceeded the "adequate rationale" statutory threshold.

For example, although clinical trials are not necessary to support a REMS modification, Danco nonetheless provided data from over 3,200 women in randomized controlled trials and data on 596 women in prospective studies comparing medical abortion care by physicians versus nurses or nurse midwives. C.A. Add. 739. These studies found *no statistically significant differences* in serious adverse events, ongoing pregnancy, or incomplete abortion (or in efficacy). *See id.*

FDA also determined that the REMS requirement that prescribers report non-fatal adverse events to Danco was "not warranted." C.A. Add. 856. Previously, certified prescribers needed to sign an agreement indicating that they would report ongoing pregnancies, hospitalizations, transfusions, or other serious adverse events to Danco. In 2016, the prescriber agreement form was amended to require such reporting only of fatal adverse events.[12]

FDA had an ample evidentiary basis to support this change. As FDA documented, "[t]he safety profile of Mifeprex [was] well-characterized over 15 years of experience, with known risks occurring rarely; the safety profile [had] not changed over the period of surveillance." C.A. Add. 800.[13] Moreover, when approving the modification, FDA explained that adverse event information regarding, among other things, transfusions, serious infections or sepsis, and hospitalizations due to complications, no longer needed to be included because "[t]his information is being submitted to the Agency through other pathways including spontaneous adverse event reporting

---

[12] Prescribers were never required to report such data to FDA. The Fifth Circuit's contrary statement, *see* U.S. Pet. App. 46a, is incorrect.

[13] According to the Fifth Circuit, FDA's decision "failed to account for the fact" that the modifications to the conditions of use might "alter the risk profile" of the drug. U.S. Pet. App. 46a. But, in approving the sNDA, FDA concluded that these modifications would *not* meaningfully affect the benefit-risk profile. *See* U.S. Pet. 24.

and the annual report." FDA, *REMS Modification Review* at 10, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RiskR.pdf. In other words, FDA's standard adverse event reporting infrastructure[14] was *already* capturing the adverse events the heightened reporting requirements were designed to ascertain. Given the undeniable burdens of reporting for physicians, once FDA concluded that ongoing required reporting of non-fatal adverse events was not necessary to meet a specific risk, the Agency was *required* to amend the prescriber agreement accordingly.

Even following the 2016 REMS revision, mifepristone remains subject to a more rigorous adverse event reporting regime than the vast majority of other drugs. The prescriber agreement continues to state that prescribers must report any patient deaths to the sponsor. Only 32 REMS programs currently require prescriber reporting of adverse drug experiences.

---

[14] For adverse drug experiences that are both serious and unexpected, FDA requires the NDA holder to submit a report to the Agency "as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant." 21 C.F.R. § 314.80(c)(1)(i). The applicant must then "promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports" and must submit follow-up reports to the Agency. *Id.* § 314.80(c)(1)(ii). FDA also has an extensive infrastructure for voluntary reporting, including by healthcare professionals and patients. *See* FDA, *Reporting Serious Problems to FDA* (May 18, 2023), https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda.

B. The Fifth Circuit's "Cumulative Effect" Requirement Is Inconsistent with FDCA Section 505.

When FDA was considering the proposed changes to mifepristone's conditions of use in 2016, the Agency reviewed an enormous amount of clinical data. In support of the dosage modifications for mifepristone and misoprostol, FDA examined 22 different studies analyzing the effects of the proposed dosing regimen on over 35,000 women. C.A. Add. 689–91. To change the indicated gestational age to 70 days, FDA relied on eight unique studies which enrolled more than 4,000 women. C.A. Add. 695–97. Further, as previously noted, FDA reviewed multiple studies that closely mirrored the overall changes proposed in the sNDA. Together, this evidence was more than sufficient to satisfy the legal requirements to modify mifepristone's prescribing information.

Changes to a drug's prescribing information (*e.g.*, the indication or dosing regimen) submitted in an efficacy supplement are subject to a higher statutory standard than modifications to a REMS. Under section 505, FDA can approve an efficacy supplement only after determining that the drug, when used according to the new conditions of use, is both safe and effective. *See generally*, 21 U.S.C. § 355(d). Effectiveness must be established by "substantial evidence," which is defined as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience

> to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

21 U.S.C § 355(d).

Because each drug and intended use presents their own specific issues, the Agency determines, on a drug-by-drug basis, what data are necessary to meet the "substantial evidence" standard. In 1997, Congress expressly confirmed FDA's longstanding flexible approach to determining if "substantial evidence" had been demonstrated, amending the FDCA to codify FDA's discretion to rely on data from a single adequate and well-controlled clinical investigation along with confirmatory evidence from other sources.[15] The new language was intended to "guard against [a] rote requirement" for the data and evidence necessary to obtain marketing approval. *See* 143 Cong. Rec. S8163 (July 28, 1997) (statement of Sen. Jeffords). Applying

---

[15] Section 115(a) of the Food and Drug Administration Modernization Act of 1997 amended section 505(d) of the FDCA to state: "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." Pub. L. No. 105-115, § 115, 111 Stat. 2296, 2313 (1997) (codified at 21 U.S.C. § 355(a)).

this more flexible approach, FDA has in many instances approved a drug or use based on a single study with other confirmatory evidence.[16] The Fifth Circuit's requirement that FDA expressly consider and discuss "cumulative effect" in its efficacy supplement decision-making, is inconsistent with the evidentiary flexibility that FDA has exercised for decades under section 505(d)—flexibility that Congress expressly endorsed and codified.

The Fifth Circuit's imposition of a "rote requirement" also calls into question other aspects of FDA's flexible, drug-by-drug assessment practices. Based on reasonable clinical predictions, FDA frequently extrapolates the findings of a drug's pivotal trial to support approval for different indications and conditions of use than those used in the trial itself. *See* Daniel Feldman et al., *Use of Extrapolation in New Drug Approvals by the US Food and Drug Administration*, 5 JAMA Network Open e227958, (Apr. 19, 2022), https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2791292. Extrapolation can be vital to ensuring access to critical treatments for certain patient groups for whom it is either impractical or impossible to conduct meaningful and representative clinical studies. For example, FDA has

---

[16] *See* FDA, *Guidance for Industry on Providing Clinical Evidence of Effectiveness of Human Drugs and Biological Products* (May 1998), https://www.fda.gov/media/71655/download; *see also* Use of Advisory Committees by the Food and Drug Administration: Hearings Before the Subcomm. of the House Comm. On Gov't Operations, 93d Cong., 2d Sess. 122 (1975) (Statement of Peter Barton Hutt) (explaining that FDA has never treated a two-study standard as a "rigid requirement").

interpreted the "substantial evidence" standard to allow for the approval of drugs designed to treat exposure to certain toxic biological, chemical, radiological, or nuclear substances, based on extrapolation from animal studies. *See* 21 C.F.R. § 314.600 *et seq*.; 64 Fed. Reg. 53960, 53964 (Dec. 20, 1999). Similarly—and as codified by Congress—FDA may rely on adequate and well-controlled studies in adults to approve certain drugs for pediatric use. *See* 21 U.S.C. § 355c(B) (allowing pediatric efficacy to be supported by efficacy data in adult trials with sufficient safety data).

In short, the Fifth Circuit's approach goes beyond the standards Congress set for FDA in section 505(d). If allowed to stand, it would undermine the Agency's ability to undertake the flexible, case-by-case assessment of each drug that is central to the regulatory system Congress designed.

III. FDA Had an Adequate Basis to Determine that the In-Person Dispensing Requirement Should Be Removed.

In April 2021, FDA announced that it would not enforce the in-person dispensing requirement for mifepristone during the COVID-19 public health emergency if the other requirements of the REMS were met. *See* Janet Woodcock, FDA Acting Commissioner, Letter to Am. Coll. Of Obstetricians & Gynecologists and Soc'y for Maternal Fetal Med. (Apr. 12, 2021). In December 2021, FDA reiterated its position that "mifepristone may be safely used without in-person dispensing" and directed Danco and the generic sponsor to initiate the process of modifying the

REMS. C.A. Add. 863; *see* 21 U.S.C. § 355-1(g)(4)(B). In January 2023 FDA approved the sponsors' applications to remove the in-person dispensing requirement from the REMS while adding a new requirement for pharmacy certification. *See* FDA, *Risk Evaluation and Mitigation Strategy (REMS) Single Shared System for Mifepristone 200 mg* (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf.[17]

FDA's determination was both lawful and well-documented. As discussed above, FDA makes REMS modifications based on a flexible "combination of qualitative and quantitative information," including "post-marketing adverse event data." FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting* 7–12 (Jan. 2019), https://www.fda.gov/media/119790/download. Here, in addition to the submitted shared REMS assessment, FDA relied on FDA Adverse Event Reporting System (FAERS) reports, safety information submitted to FDA during the public health emergency, published clinical data, and information provided by advocacy groups, individuals, and the plaintiffs in separate ongoing litigation. C.A. Add. 841–42.

The Fifth Circuit nevertheless held that FDA's determination was likely arbitrary and capricious because FDA "gave dispositive weight" to adverse

---

[17] Plaintiffs have not challenged FDA's 2023 sNDA approval, and the Fifth Circuit does not address the merits of that decision. We have focused our discussion here on FDA's announcement that it would require a REMS modification, rather than the approval of the REMS modification.

event data in the FAERS database "despite the uncontested limitations of doing so," and because the "literature did not affirmatively support [FDA's] position." U.S. Pet. App. 49a, 51a. These conclusions are without merit.

As an initial matter, FDA did not give "dispositive weight" to the data in the FAERS database. FDA also reviewed other sources of postmarketing safety data, including data published in the medical literature and data submitted by sponsors. C.A. Add. 863. The Agency used this data to compare time periods when in-person dispensing was and was not enforced, concluding that "there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced." *Id.* at 862; *see id.* 861–64.

Taken to its logical conclusion, the Fifth's Circuit's reasoning would preclude FDA from ever relying on the FAERS database (or other sources of adverse event data that are not 100% comprehensive), as "many adverse events will go unreported." U.S. Pet. App. 50a. FDA routinely relies on the FAERS database and other postmarketing safety data to support a host of regulatory actions, including modifying or releasing REMS, updating a product's labeling information, communicating new safety information

to the public, and even requesting that a company remove the product from the market.[18]

The Fifth Circuit also pointed to "significant limitations" of the published literature that FDA reviewed. U.S. Pet. App. 52a. It bears repeating that *no* clinical trials are required to modify a REMS under section 505-1 (21 U.S.C. § 355-1). Here, FDA considered clinical data from three studies evaluating retail pharmacy dispensing, three studies evaluating mail order dispensing, five studies evaluating clinic dispensing by mail, and one study evaluating clinic dispensing by courier, among others. C.A. Add. 865–70.[19] FDA acknowledged limitations in the published

---

[18] *See, e.g.*, FDA, *Lotronex (alosetron hydrochloride) Information*, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information (citing as support for removing the REMS that reporting of adverse events in FAERS "has been stable since 2002 and an increase in severe outcomes has not been observed"); Chisato Fukazawa et al., *Factors Influencing Regulatory Decision-Making in Signal Management: Analysis Based on the Signals Identified from the FAERS*, 55 Therapeutic Innovation & Regul. Sci. 685 (Mar. 2021) (analyzing regulatory actions taken based on signals FDA identified from FAERS, including labeling changes, REMS modifications, product recall, and withdrawal).

[19] When FDA initially announced that it would not enforce the in-person dispensing requirement during the COVID-19 public health emergency, it cited four of these studies. "The overall findings from these studies do not appear to show increases in serious safety concerns (such as hemorrhage, ectopic pregnancy, or surgical interventions) occurring with medical abortion as a result of modifying the in-person dispensing requirement during the COVID-19 pandemic." FDA Letter to Am. Coll. Of Obstetricians & Gynecologists and Soc'y for Maternal Fetal Med. 1–2 (Apr. 12, 2021).

literature, but concluded, based on its analysis of the totality of the information before it, that mifepristone would remain safe if the in-person dispensing requirement were removed. *See* C.A. Add. 864. The published literature represented only one part of FDA's review. Even if, as the Fifth Circuit states, the literature "did not affirmatively support [FDA's] position," U.S. Pet. App. 51a, FDA's conclusion that modifications to the REMS should be made was well-supported by the extensive data and information in the regulatory record.

As with the 2016 REMS changes, the Fifth Circuit ignores key statutory requirements guiding FDA's review. Most notably, FDA considered the burdens imposed by the in-person dispensing requirement, a statutory directive the Fifth Circuit does not acknowledge. The in-person dispensing requirement prevented patients from meeting with providers remotely from their homes, thereby imposing on patients costs and logistical burdens associated with travel. *See* Greer Donley, *Medication Abortion Exceptionalism*, 107 Cornell L. Rev. 627, 648, 691 (June 2022). It also forced providers to dispense mifepristone themselves instead of relying on pharmacies, creating logistical barriers associated with establishing and managing drug inventories. *See id.* at 645. The Agency concluded that "the REMS must be modified to remove the in-person dispensing requirement" so as to "render the REMS less burdensome to healthcare providers and patients." C.A. Add. 871.

CONCLUSION

The Court should grant the petitions for certiorari.

Respectfully submitted,

Lewis A. Grossman
Denise Esposito
Robert A. Long*
Julia F. Post
Beth Braiterman
Guillaume Julian
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
RLong@cov.com
(202) 662-6000
**Counsel of Record*

October 12, 2023

Counsel for Amici Curiae

APPENDIX

TABLE OF CONTENTS

Page

APPENDIX A

LIST OF *AMICI* FOOD AND DRUG LAW SCHOLARS

Greer Donley, JD, University of Pittsburgh Law School

Patricia J. Zettler, JD, The Ohio State University Moritz College of Law

R. Alta Charo, JD, University of Wisconsin-Madison

I. Glenn Cohen, JD, Harvard Law School

Marsha N. Cohen, JD, UC Hastings College of the Law, San Francisco

Nathan Cortez, JD, Southern Methodist University, Dedman School of Law

Doron Dorfman, JSD, JSM, LLM, LLB, Seton Hall University School of Law

Rebecca S. Eisenberg, JD, University of Michigan Law School

Henry T. Greely, JD, Stanford Law School

Ralph F. Hall, JD, University of Minnesota Law School (retired)

Joel E. Hoffman, JD, Antonin Scalia Law School of George Mason University (retired) and University of New Hampshire Franklin Pierce School of Law (retired)

George Horvath, MD, JD, University of Akron School of Law

Peter Barton Hutt, LLM, LLB, Harvard Law School

Joan Krause, JD, University of North Carolina School of Law

Holly Fernandez Lynch, JD, MBE, Perelman School of Medicine, University of Pennsylvania

Elizabeth McCuskey, JD, Boston University School of Public Health and School of Law

Jennifer D. Oliva, JD, MBA, Indiana University Maurer School of Law

Jordan Paradise, JD, Loyola University Chicago School of Law

Christopher Robertson, JD, PhD, MA, Boston University Law School and School of Public Health

Joanna Sax, JD, PhD, California Western School of Law

Allison M. Whelan, JD, MA, Georgia State University College of Law

Diana Winters, JD, PhD, MA, UCLA School of Law