UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF LOUISIANA

THE STATE OF LOUISIANA, *et al.*, *Plaintiffs*, *v.* U.S. FOOD AND DRUG ADMINISTRATION, *et al.*, *Defendants*.	Case No. 6:25-cv-01491-DCJ-DJA

BRIEF OF FORMER COMMISSIONERS AND ACTING COMMISSIONERS OF THE U.S. FOOD AND DRUG ADMINISTRATION AS *AMICI CURIAE* OPPOSING PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION

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INTERESTS OF *AMICI*

Amici served as commissioners and acting commissioners of the U.S. Food and Drug Administration (FDA or the Agency) and place a high value on the regulatory framework that provides patients access to critical drugs and vaccines. During their time leading the Agency, *Amici* oversaw the complex, evidence-based drug approval process that led to the approval of mifepristone, its "risk evaluation and mitigation strategy" (REMS), subsequent modifications of those REMS, and the regulation of mifepristone after it was approved. As experts in the drug approval process, *Amici* are qualified to explain (i) how the Agency's close examination of mifepristone's safety profile informed each action its taken with respect to the drug from 2000 through the 2023 REMS modification and was consistent with sound science, and (ii) how the FDA Adverse Event Reporting System (FAERS) operates to ensure the safety of a drug and adopting Plaintiffs' incorrect arguments with respect to FAERS data would create serious consequences that would affect the entire drug approval system.

Amici are:

- **David A. Kessler, M.D.**, Commissioner (1990–1997)
- **Jane E. Henney, M.D.**, Commissioner (1999–2001)
- **Margaret Hamburg, M.D.**, Commissioner (2009–2015)
- **Robert M. Califf, M.D.**, Commissioner (2016–2017, 2022–2025)
- **Michael A. Friedman, M.D.**, Acting Commissioner (1997–1999)
- **Joshua M. Sharfstein, M.D.**, Acting Commissioner (2009)
- **Stephen Ostroff, M.D.**, Acting Commissioner (2015–2016, 2017)
- **Norman E. "Ned" Sharpless, M.D.**, Acting Commissioner (2019)
- **Janet A. Woodcock, M.D.**, Acting Commissioner (2021–2022)

BACKGROUND

A. Congress Granted FDA Authority to Engage in an Evidence-Based Process to Approve Drugs.

FDA is the agency that Congress has tasked with reviewing and approving drugs according to established scientific principles. FDA reviewers include physicians, pharmacologists, chemists,

biologists, and statisticians—all with advanced degrees in their respective disciplines—who review every aspect of a New Drug Application (NDA) submitted by a sponsor. Through FDA's consideration of each NDA, its reviewers make hundreds of scientific judgments that lead the Agency to an ultimate decision whether to approve or deny the application. Further, once an NDA is approved, the Agency continues to monitor the drug's safety and efficacy.

The Agency's drug approval process requires rigorous review of available scientific evidence. In order for a new drug to be approved, the Federal Food, Drug, and Cosmetic Act (FDCA) directs FDA to determine whether the sponsor's application contains evidence demonstrating that the drug is safe and effective for its intended use, based on "adequate and well-controlled investigations." 21 U.S.C. § 355(d); *see* 21 C.F.R. §§ 314.50, 314.105(c). FDA has promulgated regulations describing the requirements for clinical investigations that meet the statutory standard and the labeling requirements for approved drugs. *See* 21 C.F.R. §§ 201.56, 201.57, 314.50, 314.126. Congress requires that FDA conduct a careful risk-benefit analysis in considering each NDA "to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs." 21 U.S.C. § 355(d)(7); *see also Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013) ("In order for the FDA to consider a drug safe, the drug's 'probable therapeutic benefits must outweigh its risk of harm.'") (internal citation omitted).

FDA imposes complex, rigorous standards in its review of NDAs and requires drug sponsors to demonstrate the drug's safety and efficacy through rigorous scientific studies, including laboratory and pre-clinical testing as well as three separate phases of clinical studies (with the later phase studies usually including several thousand patients). Further, drug sponsors must demonstrate that the methods used in, and the facilities used for, the manufacturing,

processing, and packaging of the drug are adequate to "preserve its identity, strength, quality, and purity." 21 U.S.C. § 355(d)(3). FDA's scientific and medical experts receive information from and confer with the drug sponsor throughout the development and approval process. Because of the meticulous statutory standard, many NDAs are never approved. Industry members and consumers around the world regard FDA's rigorous review of NDAs as the "gold standard" in ensuring drug safety and efficacy.[1] For this reason, FDA's approval of a new drug promotes its uptake and acceptance. Drug companies look to the consistency, clarity, and predictability of FDA's drug review and approval processes to inform future investments in developing new drugs and vaccines.

B. FDA May Modify the Applicable Postmarketing Restrictions, Including By Removing Restrictions, When a Product's Safety Profile Changes.

After a product is approved and used by larger numbers of people, FDA analyzes more data on its use, and its safety profile may change. Accordingly, the NDA sponsor is required to monitor the drug's safety and report adverse events[2] to FDA. *See* 21 C.F.R. § 314.80. Specifically, the drug sponsor "must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, . . . reports in the scientific literature, and unpublished scientific papers." *Id.* § 314.80(b). Further, the regulation requires that the drug sponsor "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA." *Id.* The regulation also requires that sponsors, manufacturers, packers, and distributors report serious, unexpected adverse

[1] *See* Rachel Roubein, Laurie McGinley & David Ovalle, *Abortion Pill Fight May Have Broader Implications for FDA Drug Approval*, Wash. Post (Mar. 15, 2023), https://www.washingtonpost.com/health/2023/03/15/abortion-pill-fda/.

[2] FDA defines "adverse event" as "any untoward medical occurrence associated with the use of a drug product in humans, whether or not it is considered related to the drug product. An adverse event can occur in the course of the use of a drug product; from overdose of a drug product, whether accidental or intentional; from abuse of a drug product; from discontinuation of the drug product (e.g., physiological withdrawal); and it includes any failure of expected pharmacological action." 21 C.F.R. § 251.2.

experiences to FDA within 15 days and submit quarterly adverse drug experience reports. *Id.* § 314.80(c). Thus, the law places considerable responsibility on manufacturers to assure the continued safety of their drugs. *See, e.g.*, 21 C.F.R. § 314.70(c)(6)(iii)(A); *Wyeth v. Levine*, 555 U.S. 555, 562 (2009).

After a drug's approval, FDA continues to monitor safety data and retains the authority to restrict its distribution through REMS. In addition, FDA regularly evaluates the safety reports it receives. Sometimes after reviewing new safety data, FDA requires that a drug be withdrawn from the market. Sometimes (as with mifepristone) the data demonstrates that the drug is safer than initially estimated, so the safety profile of the drug improves.[3]

In 1992, FDA promulgated regulations (21 C.F.R. § 314.500, Subpart H) to impose conditions needed "to assure safe use" of drugs, including distribution restrictions.[4] In 2007, Congress ratified and expanded on Subpart H. Food and Drug Administration Amendments Act (FDAAA) of 2007, 21 U.S.C. § 355-1; *see* FDAAA, Pub. L. No. 110-85, Tit. IX, § 901, 121 Stat. 922. These amendments authorized the Agency to require a REMS when it finds that restrictions on use are necessary to meet FDA's safety and efficacy standards, which apply to every drug. *Id.* REMS may impose Elements to Assure Safe Use (ETASU) such as requiring prescribing providers to have specific training or experience to prescribe the drug; mandating that a drug may only be dispensed in certain settings like hospitals; or subjecting all patients of a drug to monitoring, subject to certain statutory constraints, including that an ETASU not be "unduly burdensome on patient

[3] *See* Rachel K. Jones & Heather D. Boonstra, *The Public Health Implications of the FDA Update to the Medication Abortion Label*, Guttmacher Inst. (June 30, 2016), https://www.guttmacher.org/article/2016/06/public-health-implications-fda-update-medication-abortion-label (explaining that FDA's 2016 changes to mifepristone's conditions of use were supported by substantial evidence gathered since the drug's initial approval in 2000).

[4] Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58942, 58958 (Dec. 11, 1992) (codified at 21 C.F.R. §§ 314.500, 314.520).

access" and that the ETASU be designed to "minimize the burden on the health care delivery system . . . to the extent practicable."[5] *See* 21 U.S.C. § 355-1(f).

Under the FDAAA, any conditions needed "to assure safe use" established under Subpart H were automatically converted to a REMS with the same restrictions. *Id.* § 909(b), 121 Stat. at 950-51 (21 U.S.C. § 331 note). When FDA determines that new requirements are needed to assure safe use or that existing requirements are no longer necessary or should be modified to reduce the burdens of an ETASU, FDA may modify a drug's approved REMS. 21 U.S.C. §§ 355-1(f), (g), (h).

ARGUMENT

A. FDA Was Extremely Cautious In Approving Mifepristone And Subsequently Modifying Its REMS.

1. After Careful Review Confirming the Safety and Efficacy of Mifepristone, FDA Approved the Drug in 2000.

In 2000—after an intensive review spanning more than four years, at least 92 submissions by the drug sponsor, and a unanimous advisory committee vote in favor of approval—FDA approved mifepristone (under the brand name Mifeprex®) as safe and effective to terminate pregnancy through the first seven weeks of gestation. *See* ECF No. 1-24. Mifepristone is used with the drug misoprostol to terminate early pregnancy. Pursuant to its authority under Subpart H, FDA placed restrictions on the drug's distribution, including a requirement that mifepristone be dispensed in person by or under the supervision of a physician with specified qualifications. *Id.*

Mifepristone's approval complied with the statute's evidentiary standard. FDA scientific and medical experts comprehensively reviewed the totality of scientific evidence and concluded that, with those distribution restrictions in place, the benefits of mifepristone clearly outweighed its risks. In reaching this conclusion, FDA experts performed an exhaustive review of large

[5] U.S. Food & Drug Admin., *What's in a REMS?*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/whats-rems.

volumes of clinical trial data across three rounds of review over the course of more than four years.[6] Mifepristone's approval was carried out using the process FDA has been using since enactment of the FDCA more than 60 years ago. If anything, the external pressure and sensitivity surrounding the approval of mifepristone resulted in FDA taking particular care because the Agency knew that the drug's approval would face scrutiny.[7] In 2008, the U.S. Government Accountability Office (GAO) confirmed that FDA's review and approval of mifepristone was consistent with the processes for other Subpart H drugs, recognizing that the details of FDA's approval depended on the unique risks and benefits of each drug.[8]

In its initial review, FDA compared the results of three mifepristone clinical trials—two from France and one from the United States—to reliable, well-documented data on pregnancy, including rates of miscarriage.[9] These trials included more than 4,000 patients across the different studies.[10]

FDA also convened an advisory committee of reproductive health drug experts to evaluate the data on mifepristone.[11] That committee voted six to zero, with two abstentions, that the benefits

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6 *See generally* U.S. Gov't Accountability Off., *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751 (Aug. 2008) (GAO-08-751).

7 FDA was correct to assume that its approval of mifepristone would be scrutinized. Immediately after the 2000 Approval, several groups filed a citizen petition seeking reversal of the decision. GAO-08-751 at 4. In 2006, there was a Congressional hearing on the approval. *See* U.S. Gov't Publ'g Off., *RU-486: Demonstrating a Low Standard for Women's Health?: Hearing Before the Subcomm. on Crim. Just., Drug Pol'y, & Hum. Res. of the H. Comm. on Gov't Reform*, 109th Cong. (2006). In 2008, the U.S. Government Accountability Office, at the request of members of Congress, issued its comprehensive review of the 2000 approval and oversight of mifepristone, concluding that there were no irregularities. *See* GAO-08-751.

8 GAO-08-751 at 6.

9 *Id.* at 15–16. By the time FDA approved mifepristone in 2000, the drug had already been approved for use in many other countries. Mifepristone had been approved in France, China, and the United Kingdom in the late 1980s and early 1990s, and by 1999, nearly a dozen more countries had followed suit. Today, mifepristone is available in at least 95 other countries. *See* Gilda Sedgh & Irum Taqi, *Mifepristone for Abortion in a Global Context: Safe, Effective and Approved in Nearly 100 Countries*, Guttmacher Inst., https://www.guttmacher.org/2023/07/mifepristone-abortion-global-context-safe-effective-and-approved-nearly-100-countries.

10 GAO-08-751 at 15.

11 *Id.* at 16–17.

of mifepristone outweigh its risks and seven to zero, with one abstention, that mifepristone is safe.[12]

As is often the case, FDA did not approve mifepristone after the sponsor's initial submission. Instead, FDA denied approval twice to require and evaluate additional data and information from the drug sponsor. After completing those evaluations, FDA concluded, based on its own comprehensive review of the data and the advisory committee's recommendations, that mifepristone was safe and effective for use in terminating early-stage pregnancies subject to certain distribution restrictions.

2. Consistent With the FDCA and FDA Regulations and Mifepristone's Improved Safety Profile, FDA Amended the Drug's Postmarketing Restrictions in 2016.

The subsequent modifications to mifepristone's approved conditions of use were also driven by a straightforward and thorough application of the expert scientific review process that Congress entrusted to FDA. In May 2015, Danco Laboratories, L.L.C. ("Danco"), the drug's sponsor, submitted a supplemental new drug application proposing changes to mifepristone's conditions of use, which were approved by the Agency in March 2016, following a comprehensive scientific review by numerous FDA scientific and medical experts who examined 16 years of experience with mifepristone, guidelines from professional organizations here and abroad, and clinical trials that had been published in the peer-reviewed medical literature since the drug's approval. ECF No. 1-11.

Relying on safety and efficacy data from more than 20 studies, FDA increased the gestational age limit from seven to ten weeks. *Id.* at 4, 8. Relying on additional studies, FDA also reduced the number of in-person clinical visits from three to one. *Id.* at 8. Based on four studies

[12] *Id.*

including more than 3,000 patients, in 2016 FDA also modified the REMS to allow the sponsors to distribute the drug to a broader set of healthcare providers, rather than only physicians, to prescribe and dispense mifepristone. *Id.* at 25.

Finally, in that same year FDA modified a prior requirement that prescribers of mifepristone report certain non-fatal adverse events such as hospitalizations and blood transfusions to Danco. *Id.* at 28. After considering 15 years of adverse event reporting across more than 2.5 million patients since mifepristone's approval in 2000, which consistently demonstrated the drug's safety, FDA found that the reporting of serious adverse events other than death could instead be collected in the periodic safety update reports and annual reports submitted by the drug's sponsor to FDA as it generally requires for other prescription drugs. *Id.* at 28. FDA based its conclusion on studies showing that serious adverse events occurred very rarely, in less than 1% of cases. ECF No. 1-11 at 12–13. This change did not impact reporting requirements for Danco, which remain the same, *supra* Part A; instead it eliminated some, but not all, of the reporting requirements for prescribers, which typically are not required for prescription drugs. *Infra* Part B.

3. Based On 20 years of Adverse Event Reporting and a Thorough Review of the Literature, FDA Amended the Drug's Postmarketing Restrictions in 2021 and 2023.

In April 2021, during the COVID-19 pandemic public health emergency, after conducting a thorough review of the relevant data, FDA exercised its enforcement discretion with respect to the in-person dispensing requirement in mifepristone's REMS. FDA determined that the available data and information, including studies regarding the use of telehealth, supported modification of

the REMS to reduce the burden on the health care delivery system and to ensure that the benefits of the product outweighed its risks.[13]

Then, following another thorough review by multiple scientists, FDA amended mifepristone's REMS on January 3, 2023 to remove the in-person dispensing requirement.[14] To support the 2023 REMS modification, FDA undertook a thorough assessment of the relevant evidence, including a literature review of 646 unique publications from the period from March 29, 2016 to July 26, 2021. ECF No. 1-50 at 65–81. Of those publications, 15 assessed safety outcomes from various mifepristone delivery models in countries around the world, including prescribers sending mifepristone by mail; prescribers delivering mifepristone by courier; partner entities dispensing mifepristone; and pharmacies dispensing mifepristone in person or through the mail. *Id.* FDA found that these studies confirmed that no significant safety concerns would result from removal of the in-person dispensing requirement.

FDA also considered drug safety information collected during the COVID-19 Public Health Emergency, FAERS reports, REMS assessments, and information provided by advocacy groups, individuals, the plaintiffs in ongoing litigation, and the manufacturers of mifepristone and its generic equivalent. *Id.* In its analysis of U.S. postmarketing data, FDA divided the FAERS data into time periods when FDA enforced the in-person dispensing requirement versus when FDA did not enforce the in-person dispensing requirement. FDA analyzed a total of eight cases of reported adverse events from January 2020 to April 2021. Based on its analysis of the postmarketing data

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[13] Ex. 1, Memorandum from Dr. Patricia Cavazzoni to Dr. Janet Woodcock re: In-Person Dispensing Requirement in Mifepristone REMS Program During the COVID-19 Public Health Emergency Reference: NDA # 020687 (Apr. 12, 2021).

[14] *See* U.S. Food & Drug Admin., *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.

and those cases, FDA did not identify any new safety concerns resulting from the removal of the in-person dispensing requirement.

B. Disregarding FAERS Data Would Upend FDA's Gold-Standard, Science-Based Drug Approval System.

Plaintiffs' argument about the unreliability of FAERS data is wrong. FAERS was launched in 2012 to succeed the legacy Adverse Event Reporting System, which had been established in 1969.[15] In general, FDA relies on two types of reporting to FAERS for prescription drugs: (i) from manufacturers, which are required to report deaths and serious adverse events irrespective of a drug's REMS, and (ii) from prescribing physicians, who voluntarily report adverse events to the system. For virtually all of the 20,000 drugs approved by FDA,[16] physicians' reporting to FAERS remains voluntary.

FDA uses FAERS as the sole source of adverse event reporting for virtually all drugs. Although, as the Agency has long acknowledged, FAERS is not designed to capture every single adverse event, a feature which FDA keeps that in mind as it regulates all drugs. FAERS also operates to improve data access and transparency to the general public. Like all other FDA-approved drugs, pursuant to FDA regulations, mifepristone's REMS still require mandatory reporting of adverse events by the manufacturers as well as mandatory reporting by prescribers when a fatality occurs. 21 C.F.R. §§ 314.80, 314.81 (imposing reporting requirements on

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[15] Archived Reports | Potential Signals of Serious Risks/New Safety Information Identified from the FDA Adverse Event Reporting System (FAERS) (formerly AERS), https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/archived-reports-potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event#:~:text=Reporting%20System%20(FAERS)-,Archived%20Reports%20%7C%20Potential%20Signals%20of%20Serious%20Risks/New%20Safety%20Information,(FAERS)%20(formerly%20AERS)&text=The%20following%20reports%20list%20potential,archived%20reports%20on%20this%20page.

[16] U.S. Food & Drug Admin., *FDA At a Glance: Regulated Products and Facilities* (Nov. 2020), https://www.fda.gov/media/143704/download#:~:text=%E2%80%A2%20FDA%20is%20responsible%20for,%E2%80%A2.

manufacturers). FDA routinely relies on data reported through the FAERS system to support its decision to modify or remove REMS or labels of other drugs.[17]

If Plaintiffs' position were adopted, it would upend FDA's rigorous, well-established system for drug approvals, which relies on voluntary reporting by prescribing physicians for almost all drugs. *See, e.g.*, *FCC v. Prometheus Radio Project*, 592 U.S. 414, 427 (2021) (explaining that an agency need not have perfect data to support its decisions). FDA has used adverse event reporting data in some form to inform its assessments of drug safety for almost half a century. In its expert judgment, FDA has determined that it is appropriate to only require mandatory reporting from manufacturers—not physicians—for the vast majority of approved drugs because this system generates sufficient data to inform the Agency about the safety profile of approved drugs. The orderly system that Congress and FDA have established would screech to a halt if litigants could weaponize the limitations of FAERS data to support successful challenges to drug approvals.

[17] U.S. Food & Drug Admin., Lotronex sNDA Approval 2 (Sept. 8, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/021107s030ltr.pdf.

CONCLUSION

For the foregoing reasons, *Amici* respectfully request that the Court deny Plaintiffs' motion for preliminary injunction.

Dated: February 20, 2026

Respectfully submitted,

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