Nos. 23-235 and 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 Writs of Certiorari to the United States Court of Appeals for the Fifth Circuit

MOTION FOR LEAVE TO FILE BRIEF AND BRIEF AS *AMICI CURIAE* OF FORMER COMMISSIONERS OF THE U.S. FOOD AND DRUG ADMINISTRATION IN SUPPORT OF PETITIONERS

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Supreme Court of the United States

No. 23-235

U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,

PETITIONERS

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,

No. 23-236

DANCO LABORATORIES, L.L.C., ET AL., PETITIONER

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,

MOTION FOR LEAVE TO FILE BRIEF OF FORMER FDA COMMISSIONERS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

Former commissioners and acting commissioners of the U.S. Food and Drug Administration (Former FDA Commissioners)[1] respectfully request leave to submit a brief as *amici curiae* in support of Petitioners.

Although Former FDA Commissioners recognize that such motions are not favored, proposed *Amici* respectfully submit that the unusual circumstances here merit the Court's consideration. Pursuant to

[1] Former FDA Commissioners are: David A. Kessler, M.D.; Jane E. Henney, M.D.; Margaret Hamburg, M.D.; Michael A. Friedman, M.D.; Joshua M. Sharfstein, M.D.; Stephen Ostroff, M.D.; and Norman E. "Ned" Sharpless, M.D.

Supreme Court Rule 25.1, Petitioners' merits briefs were due on January 29, 2024, meaning that *amicus* briefs supporting Petitioners would have been due on February 5 if Petitioners had filed on the deadline. See S. Ct. R. 37.3. However, Petitioners filed their briefs six days early, on January 23, and counsel for *Amici* did not become aware of this until January 31, 2024. While counsel for other *amici* who filed briefs during the Court's consideration of the petitions for writs of certiorari received electronic notice of the filing of Petitioners' briefs, Former FDA Commissioners did not file a brief as *amici curiae* before the merits stage, and accordingly, counsel did not receive such electronic notice. The Court's acceptance of Former FDA Commissioners' *amicus* brief also will not prejudice any party, as this proposed brief is filed just two days after it was due under the Court's Rules, giving Respondents ample time to respond to any point raised in the *amicus* brief.

Further, Former FDA Commissioners' proposed brief draws on their expertise and provides important information about FDA's role in monitoring the safety and efficacy of drugs to help inform the Court's consideration of the merits. Former FDA Commissioners are uniquely positioned to explain the onerous requirements imposed on manufacturers seeking to market new drugs as well as FDA's nuanced approach to considering New Drug Applications and subsequent modifications to conditions of use. As physicians, Former FDA Commissioners are also qualified to explain why FDA's rigorous scientific review of mifepristone's initial approval and subsequent modifications to its conditions of use merit deference. Additionally, the *amicus* brief of Former FDA Commissioners sets forth the potential

catastrophic consequences to public health that would ensue if the Fifth Circuit's decision were upheld.

Accordingly, Former FDA Commissioners respectfully ask the Court to grant them leave to file this brief as *amici curiae*.

Respectfully submitted,

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February 1, 2024

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BRIEF OF FORMER FDA COMMISSIONERS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

INTERESTS OF THE *AMICI CURIAE*[1]

Amici served as commissioners and acting commissioners of the U.S. Food and Drug Administration (FDA or the Agency) and place a high

[1] Pursuant to Supreme Court Rule 37.3, counsel for *Amici* certify that: No party's counsel authored this *amicus* brief in whole or in part; no party or party's counsel contributed money that was intended to fund preparing or submitting this *amicus* brief; and no person or entity, other than *Amici* or their counsel, contributed money intended to fund the preparation or submission of this *amicus* brief. This brief represents the views of the individual *Amici* and not necessarily of their organizations.

value on the regulatory framework that provides patients access to critical drugs and vaccines. By second-guessing FDA's evaluation of scientific data, the Fifth Circuit's decision threatens to undermine the complex, evidence-based drug approval process that *Amici* oversaw during their time leading the Agency and that exists today. As experts in the drug approval process, *Amici* are qualified to explain how the Fifth Circuit fundamentally misunderstood the science of FDA's approval and subsequent actions with respect to mifepristone. *Amici* will also describe how the Fifth Circuit's decision, if allowed to stand, would harm patients that rely on FDA-approved drugs to treat serious diseases by allowing courts to second-guess FDA's evaluation of scientific evidence supporting the approval of new drug applications or modifications of those approvals.

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)
- **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)

SUMMARY OF THE ARGUMENT

For more than 60 years, Congress has trusted FDA to ensure that companies demonstrate the safety and efficacy of new drugs before they reach the market. And for good reason. Congress first passed the Federal Food, Drug, and Cosmetic Act of 1938 after more than 100 people died due to toxic ingredients in elixir sulfanilamide. This tragedy illustrated the dangers of an unregulated drug market and led Congress to empower FDA to serve as a gatekeeper requiring that new drugs be proven safe before they can be marketed.[2] Nearly 25 years later (in 1962) after the drug thalidomide caused serious birth defects, Congress expanded FDA's authority by requiring drug companies to prove to FDA that their drugs are effective.[3]

Today, every FDA decision to approve a drug is supported by hundreds of scientific judgments made by a team of experts, which includes physicians, chemists,

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[2] Paul M. Wax, *Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug and Cosmetic Act*, 122 Annals Internal Med. 456 (1995).

[3] Katie Thomas, *The Unseen Survivors of Thalidomide Want to Be Heard*, New York Times (Mar. 23, 2020), https://www.nytimes.com/2020/03/20/health/thlidomide-surviros-usa.html.

biologists, pharmacologists, and statisticians. To determine whether a drug meets the standard established by Congress, these experts typically must review a massive quantity of data submitted by the sponsor of the New Drug Application (NDA), including complex clinical studies. The Agency's final decision regarding whether to approve any drug results from this careful process—often occurring over several years and always involving numerous scientific judgments by experts. Once a drug is approved, its sponsor and FDA both continue to monitor safety and efficacy data to determine if any changes in the conditions of approval are warranted.

This case does not involve FDA's interpretation of applicable law, and there is no dispute about the legal standard that FDA applied in approving the drug at issue here. Instead, the dispute involves FDA's evaluation of the scientific data submitted to support the approval of a new drug application. As this Court has recognized, judicial review of an administrative agency's action based on the agency's evaluation of technical evidence is extremely deferential, and a court may not second-guess an agency's judgment unless the agency's decision is arbitrary and capricious. In applying this standard, the court's role is to determine whether the agency's decision was "reasonable and reasonably explained." See *FCC v. Prometheus Radio Project*, 592 U.S. 414, 423 (2021); see also *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 579 (2021) (Roberts, C.J., concurring).

In this case, instead of reviewing FDA's 2016 and 2021 modifications to mifepristone's postmarketing restrictions under this firmly established standard, the

Fifth Circuit substituted its own opinions about the scientific data for the expert judgments of FDA clinicians and scientists, and on that basis overturned FDA's reasoned, evidence-based decisions.

This unprecedented decision turns Congress's desired regulatory scheme on its head and opens the door to constant legal challenges of drug approval decisions. If permitted to stand, the Fifth Circuit's approach would allow courts to substitute their lay analysis for FDA's scientific expertise and to overturn the Agency's approval and conditions of use for drugs—even after they have been on the market for decades. The resulting uncertainty would threaten the incentives for drug companies to undertake the time-consuming and costly investment required to develop new drugs and ultimately hinder patients' access to critical remedies that prevent suffering and save lives.

ARGUMENT

I. Congress granted FDA broad authority to approve drugs and to modify the applicable postmarketing restrictions.

FDA is the expert agency that Congress has tasked with reviewing and approving drugs according to established scientific principles. FDA reviewers include doctors, pharmacologists, chemists, biologists, and statisticians—all with advanced degrees in their respective disciplines—who review every aspect of an 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.

A. 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.'").

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). FDA's scientific and medical experts receive information from and confer with the drug sponsor throughout the development and approval process. Because of the high statutory standard, many NDAs are never approved.

Under the FDCA and FDA regulations, the conditions and indications on a drug's approved label are not required to be identical to the conditions under which the drug was studied. Further, as FDA has explained, "[m]any clinical trial designs are more restrictive * * * than will be necessary or recommended in post-approval clinical use; this additional level of caution is exercised until the safety and efficacy of the product is demonstrated." J.A. 265. Consistent with scientific best practices and medical ethics, conditions of use for approved drugs frequently differ from clinical trial protocols. For example, although biopsies were required in clinical trials for menopause hormonal therapy drugs to protect trial participants until safety was established, once FDA approved those drugs as safe and effective, such mandated biopsies were no longer required and would have been impractical. J.A. 265.

Industry members and consumers around the world regard FDA's rigorous review of NDAs as the "gold

standard" in ensuring drug safety and efficacy.[4] 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.

After a product is approved and used by larger numbers of people, its safety profile may change. Accordingly, the NDA sponsor is required to monitor the drug's safety and report adverse events 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 experiences to FDA within 15 days and submit quarterly adverse drug experience reports. *Id.* § 314.80(c).

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[4] 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/.

Thus, the law places considerable responsibility on manufacturers to assure the continued safety of their drugs. For example, when new information about the safety of a drug becomes available, FDA's regulations permit the manufacturer to add information to the drug's label without the Agency's approval. See 21 C.F.R. § 314.70(c)(6)(iii)(A); *Wyeth v. Levine*, 555 U.S. 555 (2009). 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 safety profile of the drug improves.[5]

B. After a drug's approval, FDA continues to monitor safety data and retains the authority to restrict its distribution through REMS.

In 1992, FDA promulgated regulations for drugs intended to treat "serious or life-threatening illnesses" that "provide[d] meaningful therapeutic benefit to patients over existing treatments." 21 C.F.R. § 314.500, Subpart H. The Subpart H regulations authorized FDA

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[5] 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).

to impose conditions needed "to assure safe use," including distribution restrictions.[6]

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 "risk evaluation and mitigation strategy" (REMS) when it finds that restrictions on use are necessary to meet FDA's safety and efficacy standards, which apply to every drug. *Id.*

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, FDA may modify a drug's approved REMS. *Id.* §§ 355-1(g), (h).

II. 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

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[6] Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942, 58,958 (Dec. 11, 1992) (codified at 21 C.F.R. §§ 314.500, 314.520).

terminate pregnancy through the first seven weeks of gestation. J.A. 224–232. 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. *Ibid.*

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 outweighed its risks. In reaching this conclusion, FDA experts performed an exhaustive review of large volumes of clinical trial data across three rounds of review over the course of more than four years.[7] Mifepristone's approval was carried out using the process Congress created and FDA has been implementing since its enactment 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.[8] In 2008,

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[7] *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").

[8] 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. See J.A. 201–223. 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

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.[9]

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.[10] These trials included more than 4,000 patients across the different studies.[11]

FDA also convened an advisory committee of reproductive health drug experts to evaluate the data on mifepristone.[12] That committee voted six to zero, with two abstentions, that the benefits of mifepristone

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U.S. Government Accountability Office issued its comprehensive review of the 2000 approval and oversight of mifepristone, concluding that there were no irregularities. See GAO-08-751.

[9] GAO-08-751 at 6.

[10] *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 94 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.

[11] *Id.*

[12] *Id.* at 16–17.

outweigh its risks and seven to zero, with one abstention, that mifepristone is safe.[13]

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.

III. Consistent with the FDCA and FDA regulations and mifepristone's improved safety profile, FDA amended the drug's postmarketing restrictions in 2016 and 2021.

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 was 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-

[13] *Id.*

reviewed medical literature since the drug's approval. J.A. 284–291.

Relying on safety and efficacy data from more than 20 studies, FDA increased the gestational age limit from seven to ten weeks. J.A. 283–291, 298–300, 450–456. Relying on an additional dozen studies, FDA also reduced the number of required in-person clinical visits from three to one, allowing patients to self-administer misoprostol at home. J.A. 300–302, 456–457. Based on five studies including more than 3,000 patients, FDA 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. J.A. 309–310, 461–462.

Finally, FDA modified a prior requirement that prescribers of mifepristone report certain non-fatal adverse events such as hospitalizations and blood transfusions to Danco. J.A. 319. After considering 15 years of adverse event reporting since mifepristone's approval in 2000, which 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. *Ibid.* This change did not impact reporting requirements for Danco, which remain unchanged, *supra* Part I.A; instead it eliminated some, but not all, of the reporting requirements for prescribers, which typically are not required for prescription drugs.

In 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. J.A. 377. 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]

IV. Under the proper standard of review, which requires significant deference to FDA's scientific experts, the challenges to FDA's decisions must be rejected.

In reviewing FDA's approval of mifepristone, the courts below did not review FDA's interpretation of a law. Instead, they reviewed FDA's scientific evaluation of the studies and other data supporting the Agency's modifications of mifepristone's conditions of use in 2016 and 2021. In finding that Respondents were likely to prevail on the merits of their APA claims, the Fifth Circuit misapplied the well-established arbitrary and capricious standard and failed to give FDA the requisite deference. *See*, e.g., *Prometheus*, 592 U.S. at 423. Under this standard, the courts' role is to

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[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.

ascertain whether agency decisions were "reasonable and reasonably explained." *Id.* As long as "the agency has acted within a zone of reasonableness," the administrative action must be upheld. *Id.*

The scope of judicial review in assessing an agency's evaluation of data is even narrower when an agency action is based on its analysis of scientific evidence. Where a court reviews an agency's decision based on "scientific data within its technical expertise," the arbitrary and capricious standard of review is "extreme[ly] deferential." *Nuclear Energy Inst., Inc. v. EPA*, 373 F.3d 1251, 1289 (D.C. Cir. 2004) (citation omitted); see also *Shrimpers & Fishermen of the RGV v. U.S. Army Corps of Eng'rs*, 56 F.4th 992, 1001 (5th Cir. 2023)

The reason for this deference is clear: Courts ensure agencies' compliance with the law, but they are ill-equipped to second-guess the technical judgments of an agency within the scope of its subject-matter expertise. *Troy Corp. v. Browner*, 120 F.3d 277, 283 (D.C. Cir. 1997) (citation omitted) (explaining that courts "review scientific judgments of the agency not as the chemist, biologist, or statistician that we are qualified neither by training nor experience to be, but as a reviewing court exercising our narrowly defined duty of holding agencies to certain minimal standards of rationality") (internal citation and quotation marks omitted). In other words, judges are not "scientists independently capable of assessing the validity of the agency's determination." *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1327 (D.C. Cir. 1998); see also *Balt. Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983); *NRDC v. U.S. Nuclear Regul. Comm'n*, 823 F.3d 641, 649 (D.C. Cir.

2016); *Zero Zone, Inc. v. U.S. Dep't of Energy*, 832 F.3d 654, 668 (7th Cir. 2016).

Here, "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference" from reviewing courts. See *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995); see also *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 579 (2021) (Roberts, C.J., concurring) ("[C]ourts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health.'"); *Pharm. Mfg. Rsch. Servs., Inc. v. FDA*, 957 F.3d 254, 262 (D.C. Cir. 2020).

Serono is instructive. 158 F.3d at 1327. In that case, the D.C. Circuit rejected the district court's reversal of FDA's drug approval, explaining that, in evaluating a technical decision of an agency based on scientific data, the court's role was limited to "holding [FDA] to the standards of rationality required by the Administrative Procedure Act." *Id*. Indeed, insofar as can be determined, no court has ever restricted access of an FDA-approved drug by invalidating FDA's modification of a drug approval, as the Fifth Circuit did here. See, e.g., *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 5, 28–29 (D.D.C. 2012) (citing Serono, 158 F.3d at 1327) ("To the best of the parties' and the Court's knowledge, the extraordinary relief that [plaintiff] seeks is unprecedented in this jurisdiction."). Further, the only two district courts to overturn FDA drug approvals were each reversed by the D.C. Circuit and Fifth Circuit, respectively. See *Serono*, 158 F.3d at 1327; Pet. App. 1a–110a.

Here, in finding that Respondents would likely prevail in their challenges to the 2016 and 2021 changes to mifepristone's REMS, the Fifth Circuit ignored important parts of the administrative record and the correct standard of review. When the proper standard of review is applied, the challenges to FDA's decisions must be dismissed.

V. FDA's 2016 changes to mifepristone's REMS were not arbitrary and capricious.

The Fifth Circuit erred in finding that FDA's modifications of the mifepristone's REMS in 2016—increasing the gestational age limit, reducing the number of required clinic visits, expanding the types of providers who could prescribe, and removing the requirement that prescribers report non-fatal adverse events to FDA—were likely arbitrary and capricious. Before approving the changes to mifepristone's conditions of use and relabeling the drug, Agency experts reviewed more than 20 years of data from around the world demonstrating mifepristone's safety and efficacy.[15] These studies, which included more than 45,000 patients, demonstrated the efficacy and safety of the proposed changes to mifepristone's labeling.[16] For example, a literature review of 87 studies concluded that home use of misoprostol did not lead to increased rates of treatment failure or serious

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[15] U.S. Gov't Accountability Off., *Food and Drug Administration: Information on Mifeprex Labeling Changes and Ongoing Monitoring Efforts* at 16, GAO-18-292 (Mar. 2018) ("GAO-18-292").

[16] *Id.* at 12–16.

complications.[17] Additional studies confirmed that the risk associated with taking mifepristone was very low.[18] FDA also reviewed 15 years of adverse event reporting from the drug's approval in 2000 through November 17, 2015. During that time period, there were 17 reported deaths associated with mifepristone, eight of which were associated with sepsis.[19] Further, this data showed that "the rates of hospitalizations, severe infections, blood loss requiring transfusion, and complications related to ectopic pregnancy remained stable and acceptably low."[20]

Although the Fifth Circuit correctly recognized that FDA was not required to rely on studies with matching conditions of use to those set forth in the 2016 REMS, *supra* Part I.A, the court effectively imposed such a requirement when it found that the 2016 changes likely violated the Administrative Procedure Act because FDA failed to consider the effect of all the changes "as a whole." Pet. App. 53a. The Fifth Circuit's analysis misapprehends the applicable legal standard and ignores the administrative record. First, the Fifth Circuit adopted the erroneous reasoning of the district court opinion, which cited *Michigan v. EPA*, a case

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[17] *Id.* at 14 (citing Elizabeth G. Raymond and David A. Grimes, *The Comparative Safety of Legal Induced Abortion and Childbirth in the United States*, 119 Obstetrics & Gynecology 215 (2012)).

[18] See *id.* (citing Daniel Grossman et al., *Effectiveness and Acceptability of Medical Abortion Provided through Telemedicine*, 118 Obstetrics & Gynecology 296 (2011)).

[19] GAO-18-292 at 17 (explaining that "[s]even of the 8 sepsis cases were associated with vaginal use of misoprostol, which was, but no longer is, a common practice, according to FDA").

[20] *Id.*

reviewing an agency's interpretation of its enabling statute—not the agency's evaluation of scientific evidence before it. 576 U.S. 743 (2015). The scope of judicial review that this Court articulated in *Michigan v. EPA* is distinct from the extremely deferential standard that applies to an agency's evaluation of scientific data. See, e.g., *Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. at 579 (2021) (Roberts, C.J., concurring) ("[C]ourts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health.'").

Further, the Fifth Circuit ignored the portions of the record which showed that FDA did consider the cumulative effect of the changes through at least three studies that implemented multiple changes at once.[21] This demonstrates that FDA did consider the cumulative safety of the amendments to mifepristone's REMS.

The Fifth Circuit likewise erred in finding that FDA's 2016 removal of the non-fatal adverse event reporting requirement for prescribers was likely arbitrary and capricious. A review of the administrative record confirms that this change was also supported by ample evidence. As GAO recognized in a review of mifepristone's labeling changes and FDA's continuous safety monitoring in 2018, the

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[21] See, e.g., J.A. 299 n.1, 3, 4 (citing studies applying at least three of the challenged 2016 changes). One cited study implemented all changes except the removal of the FAERS reporting requirement. See J.A. 299 n.4 (citing Claudia Diaz Olavarrieta et al., *Nurse versus physician-provision of early medical abortion in Mexico: a randomized controlled non-inferiority trial*, 93 Bull World Health Organ 249 (2015)).

Agency relied on 15 years of periodic adverse event reports as well as studies demonstrating that the proposed changes did not significantly change mifepristone's risk profile.[22]

VI. FDA's decision not to enforce the in-person dispensing requirement in 2021 was not arbitrary and capricious.

FDA also acted reasonably in 2021 when it relied on available data to remove mifepristone's in-person dispensing requirement. Just as it had before re-labeling mifepristone in 2016, the Agency undertook a rigorous analysis of the evidence before changing the drug's REMS. FDA required data from mifepristone's sponsors to support its decision and also relied on "an extensive review of the published literature," which was summarized in the administrative record. See J.A. 399–408. Further, FDA concluded from its review of the available data that there was no evidence of "a difference in adverse events when in-person dispensing was and was not enforced." J.A. 399; see J.A. 398–408.

The Fifth Circuit compounds its error by deeming FDA's analysis of adverse event data insufficient to support the 2021 change due to the "uncontested limitations" of the FDA Adverse Event Reporting System (FAERS) database. See Pet App. 59a. The court incorrectly suggested that there was no mandatory adverse event reporting system for mifepristone after 2016. Pet. App. 59a–63a. To the contrary, the 2016 changes implemented for mifepristone the same reporting system required for all other approved drugs.

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[22] See GAO-18-292 at 17.

Accordingly, since 2016, FDA has continually received and monitored data about serious adverse events through the FAERS database for mifepristone. This is confirmed by the fact that, as the Fifth Circuit pointed out, "Danco's data was exactly the same as the data FDA obtained from FAERS." Pet. App. 61a. Further, as previously explained, *supra* Part III, the 2016 REMS only removed prescribers' requirement to report non-fatal adverse events to FDA. The Fifth Circuit's questions about the reliability of FAERS data are far beyond the scope of judicial review of an agency's evaluation of scientific data and amount to an inappropriate attempt to "substitute its own policy judgment for that of the agency." See *Prometheus*, 592 U.S. at 423.

VII. Allowing the Fifth Circuit's decision to stand would upend FDA's drug approval system and harm patients.

The Fifth Circuit's opinion flips Congress's chosen scheme on its head—subjecting scientific decisions by FDA's expert doctors, pharmacologists, chemists, biologists, and statisticians to unscientific second-guessing by courts. Every time FDA modifies the postmarketing restrictions for an approved drug, it is the product of hundreds of scientific judgments, including analysis of clinical trial data, examination of experimental controls, and interpretation of adverse event reports. Opening each of these judgments up to fresh review by courts would supplant this rational, evidence-based drug regulatory scheme with a chaotic patchwork susceptible to endless legal challenges and inconsistent outcomes.

Further, adopting the Fifth Circuit's approach—which expands the scope of judicial review to allow courts to upend the scientific judgments of Agency experts—would open the door to the re-litigation of drug approvals by many interested parties. Drug companies seeking to protect their investments and potential future profits could challenge the approval of a competitor's drug by challenging one of the many scientific judgments that go into each drug approval. After the denial of an NDA, companies could also use the courts to obtain reversal of FDA's scientific judgments. Interest groups that question the use of drugs for certain conditions could sue to have their approval revoked or to require application of unnecessary restrictions. Organizations representing patients who experience rare adverse events could challenge FDA's risk-benefit analyses and attempt to bar access to safe and effective remedies for others who need them.

This new paradigm would take a significant toll on public health. Successful litigation challenging drug approvals could threaten patient access to necessary drugs and vaccines. It would also adversely impact the effectiveness of healthcare providers who rely on FDA approval when making critical treatment decisions. At the same time, drug companies unhappy with FDA's denial of their new drug applications could seek court rulings that would risk allowing the introduction of unsafe drugs into the market.

Further, this new patchwork system for evaluating drug safety and efficacy would chill crucial investment in pharmaceutical research and the development of new medications. As it is, drug development is a risky,

cost-intensive proposition: Research and development costs for each new drug can reach upwards of $2 billion, and only about 12% of drugs that undergo clinical trials are ultimately approved.[23] As a result of the Fifth Circuit's approach, even the relatively few drugs that attain FDA approval would be perpetually susceptible to legal challenges to applicable conditions of use—discouraging companies from investing in new life-saving remedies. The Fifth Circuit's approach upends the regulatory framework designed by Congress that has produced essential drugs for more than 60 years. Patients in need will ultimately bear the catastrophic consequences of the resulting instability.

CONCLUSION

The Court should reverse the Fifth Circuit's judgment.

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[23] See Cong. Budget Off., *Research and Development in the Pharmaceutical Industry* at 2 (Apr. 2021), https://www.cbo.gov/publication/57126.

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February 1, 2024