No. 23-10362

UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS AND GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL AND DENTAL ASSOCIATIONS; SHAUN JESTER, D.O.; REGINA FROST-CLARK, M.D.; TYLER JOHNSON, D.O.; GEORGE DELGADO, M.D.,
Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION; ROBERT M. CALIFF, M.D., in his official capacity as Commissioner of Food and Drugs; JANET WOODCOCK, M.D., in her official capacity as Principal Deputy Commissioner; PATRIZIA CAVAZONNI, M.D., in her official capacity as Director, Center for Drug Evaluation and Research; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; and XAVIER BECERRA, in his official capacity as Secretary, U.S. Department of Health and Human Services,
Defendants-Appellants,

DANCO LABORATORIES, LLC,
Intervenor-Appellant.

On Appeal from the United States District Court
for the Northern District of Texas
Case No. 2:22-cv-00223-Z

BRIEF OF FORMER COMMISSIONERS OF THE U.S. FOOD AND DRUG ADMINISTRATION AS *AMICI CURIAE* IN SUPPORT OF DEFENDANTS-APPELLANTS

William B. Schultz
Margaret M. Dotzel
Alyssa M. Howard
Zuckerman Spaeder LLP
1800 M Street NW, Suite 1000
Washington, D.C.
(202) 778-1800
wschultz@zuckerman.com

Counsel for Amici Curiae

CERTIFICATE OF INTERESTED PERSONS

In addition to the persons and entities listed in the Defendants-Appellants' Certificate of Interested Persons, undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Rule 28.2.1 have an interest in the outcome of this case. These representations are made in order that the judges of this court may evaluate possible disqualification or recusal.

Amici Curiae

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.

Norman E. "Ned" Sharpless, M.D.

Attorneys for *Amici Curiae*

William B. Schultz
Margaret M. Dotzel
Alyssa M. Howard
Zuckerman Spaeder LLP
1800 M Street NW, Suite 1000
Washington, D.C. 20036

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes

Regulations

Other Authorities

INTEREST OF *AMICI CURIAE*[1]

Amici served as commissioners and acting commissioners of the U.S. Food and Drug Administration (FDA), and place a high value on the regulatory framework that provides patients access to critical drugs and vaccines. The district court's order threatens to destroy the complex, evidence-based drug approval process that *Amici* oversaw during their time leading the Agency. As experts in the drug approval process, *Amici* are qualified to explain how the district court fundamentally misunderstood the science of FDA's approval and subsequent actions with respect to mifepristone. *Amici* will also describe how the district court's opinion, if allowed to stand, would harm patients nationwide. *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)

[1] Pursuant to Federal Rule of Appellate Procedure 29, undersigned 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. All parties have consented to the filing of this *amicus* brief in this litigation. This brief represents the views of the individual *Amici* and not necessarily of their organizations.

SUMMARY OF ARGUMENT

For more than 60 years, Congress has entrusted FDA to ensure that manufacturers have conducted studies that demonstrate that their new drugs are safe and effective. Every drug approved by the Agency is the product of hundreds of scientific judgments by a team of experts, which includes physicians, chemists, 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 a period of years and always involving many scientific judgments by experts at the forefront of public health.

In reviewing an administrative agency's action based on the agency's evaluation of scientific evidence, such as FDA drug approval decisions, courts have emphasized that they will uphold the action as long as it is within a zone of reasonableness and meets the standard of rationality required by the Administrative Procedure Act. In this case, instead of reviewing FDA's approval of mifepristone and subsequent modifications to its conditions of use under this firmly established standard, the district court substituted its own opinions about FDA's evaluation of the scientific data for the expert judgments of FDA clinicians and scientists, and on

that basis overturned FDA's approval of mifepristone. This unprecedented order turns Congress's desired regulatory scheme on its head and opens the door to constant legal challenges of drug approvals. If allowed to stand, the district court's order would threaten the incentives for drug companies to undertake the time-consuming and costly investment required to develop new drugs and provide patients access to critical remedies that prevent suffering and save lives.

BACKGROUND

A. Congress Granted FDA Broad Authority to Review and Approve Drugs.

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.

1. The Drug Approval Process

In the Federal Food, Drug, and Cosmetic Act (FDCA) enacted in 1938, Congress tasked FDA with determining that a new drug is safe before it can be marketed. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301–399i). In 1962, Congress further required that FDA ascertain a drug's

effectiveness before it is marketed. Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781–82 (codified as amended at various sections of 21 U.S.C.). Thus, for more than 80 years, FDA has been responsible for reviewing applications for new drugs before they may be sold. 21 U.S.C. §§ 321(p), 355, 393(b)(2)(B). In order for a new drug to be approved, the 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 that describe 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.

FDA 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 averaging 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.

FDA imposes complex, rigorous standards in its review of NDAs. To pass muster, an NDA must demonstrate that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the proposed labeling. *Id.* §§ 355(b), (d)(1), (2), (4), (5); 21 C.F.R. § 314.50(a)(1). Because of the high statutory standard, many NDAs are never approved.

Congress requires that FDA conduct a careful risk-benefit analysis in considering each NDA. 21 U.S.C. § 355(d)(7) ("The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs."); *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.'"). The expertise of FDA's teams of reviewers is crucial to this rigorous review because all drugs have some potential for adverse effects that could harm patients, and those risks must be balanced against the benefits of promoting access to critical remedies. Accordingly, the FDCA does not require a sponsor to demonstrate a complete absence of risk, but rather that the drug's benefits outweigh any risks it poses to patients. *See Benefit-Risk Assessment for New Drug and Biological Products, Guidance for Industry, Draft Guidance*, FDA, 3 (Sept. 2021), https://www.fda.gov/media/152544/download (last

visited Apr. 30, 2023) ("Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks.").

Even after a drug is approved, the NDA sponsor is required to monitor its safety and report adverse events to FDA. *See* 21 C.F.R. § 314.80. FDA regularly evaluates these safety reports. After a product is approved and used by larger numbers of people, its safety profile may change. Sometimes additional safety concerns are uncovered, and FDA requires that a drug be withdrawn from the market. Sometimes (as with mifepristone) the safety profile of the drug is improved.[2]

Under the FDCA, there is no "study-match" requirement—that is, 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. Congress directed FDA to evaluate drug safety based on "the information submitted . . . as part of the application" and "any other information" before the Agency. 21 U.S.C. § 355(d)(4). No FDCA provision or FDA regulation requires that conditions on a drug's approved label match the precise protocols used in clinical trials or existing studies, and FDA has never adopted such a limitation. Indeed, "[m]any clinical trial designs are

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

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." Letter from Dr. Janet Woodcock to Dr. Donna J. Harrison et al. (Mar. 29, 2016) ("2016 Petition Denial"), ROA.662. 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 ensure patient safety, FDA approved those drugs without mandated biopsies. *Id.*

Each drug approval decision by the Agency entails hundreds of scientific judgments by FDA reviewers. Of course, not every agency scientist will agree on all issues, and in fact FDA has long facilitated robust scientific debate among its experts. *See Scientific Integrity at FDA*, FDA (Oct. 18, 2021), https://www.fda.gov/science-research/about-science-research-fda/scientific-integrity-fda (last visited Apr. 30, 2023). Accordingly, FDA also maintains processes to resolve scientific disputes when they arise.[3]

Industry members and consumers around the world regard FDA's rigorous review of NDAs as the "gold standard" in ensuring drug safety and efficacy. For this reason, FDA's approval of a new drug promotes its uptake and acceptance. Drug

[3] *See FDA Staff Manual Guides Vol. IV – Agency Program Directives – Scientific Dispute Resolution at FDA, SMG 9010.1*, FDA (May 21, 2021), https://www.fda.gov/media/79659/download (last visited Apr. 30, 2023).

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. *See* Br. of Pharmaceutical Companies, Executives, and Investors as *Amici Curiae* in Support of Appellants' Motion for Stay Pending Appeal ("Pharm. Amicus Br.") at 9, ECF No. 118.

2. The Authority to Restrict the Distribution of Drugs

In 1992, FDA promulgated regulations under Subpart H 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. Part 314.500, Subpart H. The Subpart H regulations did not allow new drugs to circumvent the requisite standards for drug approval, including demonstrated safety and efficacy. *See generally* Final Rule: New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval, 57 Fed. Reg. 58,942 (Dec. 11, 1992). Rather, for drugs that met the legal requirements of the FDCA and other FDA regulations, Subpart H facilitated accelerated approval under certain circumstances and authorized FDA to impose conditions "needed to assure safe use," including distribution restrictions. *Id.* at 58,958 (codified at 21 C.F.R. §§ 314.500, 314.520).

In 2007, Congress ratified and expanded on Subpart H through the passage of the 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. 823. The FDAAA

authorized the Agency to require a "risk evaluation and mitigation strategy" (REMS) when it finds that restrictions on use are necessary to ensure that the benefits of a drug outweigh the potential for adverse events—the standard that FDA applies to every drug. *Id.* Under this provision, 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). Under the REMS framework, FDA's approval of any drug may include "elements to assure safe use," including regarding who can prescribe a particular drug and the clinical setting in which a drug may be dispensed. 21 U.S.C. § 355-1(f)(3). 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).

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

More than twenty years ago—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 in 2000 (under the brand name Mifeprex®) as safe and effective to terminate pregnancy through the first seven weeks of gestation.[4] Letter from Center for Drug Evaluation and Research (CDER) to Population Council (Sept. 28, 2000) ("2000 Approval"), ROA.591–98.

[4] Mifepristone is used with the drug misoprostol to terminate early pregnancy.

Pursuant to its authority under Subpart H, FDA placed certain restrictions on the drug's distribution, including a requirement that mifepristone be dispensed in person by or under the supervision of a doctor with specified qualifications. 2000 Approval, ROA.592.[5]

Mifepristone's approval was based on the statutory evidentiary standard and was not accelerated. 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. *Id.* In reaching this conclusion, FDA performed an exhaustive review of large 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 same process Congress created and FDA has been implementing since its inception. If anything, the external pressure and sensitivity surrounding the approval of mifepristone resulted in FDA taking particular care because the Agency knew that approval of mifepristone would

[5] The district court erred in finding that the 2000 Approval violated Subpart H. Contrary to the court's conclusions, FDA properly invoked Subpart H to implement restrictions on mifepristone's distribution, not to facilitate an accelerated approval process, which was not used for mifepristone. FDA's authority to *approve* mifepristone came from 21 U.S.C. § 355, not Subpart H. In any event, for the reasons set forth in Defendants-Appellants' Brief ("Def-App. Br.") at 45, ECF No. 222, even if FDA had erred in relying on Subpart H, that error has been cured because the FDAAA has since superseded Subpart H.

[6] *See generally Food and Drug Administration: Approval and Oversight of the Drug Mifeprex*, GAO-08-751, Gov't Accountability Office (Aug. 2008) ("GAO 2008 Report").

face scrutiny.[7] In 2008, the 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. GAO 2008 Report at 6.

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.[8] *Id.* at 15–16. These studies included over 4,000 patients across the different experiments. *Id.* In its decision approving mifepristone, FDA relied on historically controlled clinical trials because (1) pregnancy is well-studied and therefore "adequately documented," and (2) the effect of mifepristone—termination of an early-stage pregnancy—is "self-evident." *Id.* at 16 & n.31 (*citing* 21 C.F.R. § 314.126(b)(2)(v)). Moreover, it would

[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. *See, e.g.*, 2002 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to FDA (Aug. 20, 2002), ROA.635. In 2006, there was a Congressional hearing on the approval. *See The FDA and RU-486: Lowering the 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. 4 (2006), ROA.313. In 2008, GAO issued the results of its comprehensive review of the 2000 Approval and oversight of mifepristone concluding that there were no irregularities. *See* GAO 2008 Report.

[8] By the time FDA approved mifepristone in 2000, the drug had already been approved 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 Mifepristone Approved*, Gynuity Health Projects, https://gynuity.org/assets/resources/mapmifelist_en.pdf (last visited Apr. 30, 2023).

have been unethical to give some patients seeking to terminate a pregnancy a placebo.

FDA also convened an advisory committee of reproductive health drug experts to evaluate the data on mifepristone. *Id.* at 16-17. That committee voted six to zero, with two abstentions, that the benefits of mifepristone outweigh its risks and seven to zero, with one abstention, that mifepristone is safe. *Id.*

As is often the case, FDA did not approve mifepristone after the sponsor's initial submission. Instead, FDA denied approval twice to solicit 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. *See* 2000 Approval, ROA.591–98.

Following mifepristone's approval, several groups petitioned FDA to reverse its regulatory decisions and to withdraw mifepristone. *See* 2002 Citizen Petition of Am. Ass'n of Pro-Life Obstetricians & Gynecologists to FDA (Aug. 20, 2002) ("2002 Citizen Petition"), ROA.403. Once again, FDA experts reviewed adverse event reports and relevant data and concluded that there was no basis to find that mifepristone's potential safety concerns outweighed the benefits of keeping it on the market. *See* 2016 Petition Denial, ROA.635–67.

C. FDA's Subsequent Amendments to Mifepristone's REMS Were Based on Its Comprehensive Consideration of Peer-Reviewed Data.

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 March 2016, following a comprehensive scientific review by multiple FDA scientific experts who examined 20 years of experience with mifepristone, guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature, FDA modified its approval of mifepristone in several ways. *Center for Drug Evaluation and Research, Summary Review of Application Number: 020687Orig1s020*, FDA (March 29, 2016) ("2016 Summary Review"), ROA.698–725.

In reliance on safety and efficacy data from more than 20 studies, FDA increased the gestational age limit from seven to ten weeks. 2016 Summary Review, ROA.713–15. Relying on an additional dozen studies, FDA also reduced the number of required in-person clinical visits from three to one. *Id.* And 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. *Id.* at ROA.722–24. Finally, FDA modified a prior requirement pursuant to which prescribers of mifepristone had to agree to report certain adverse events such as hospitalizations and blood transfusions to the drug's sponsor. *Id.* at ROA.724. FDA concluded, based on "15 years of reporting," that

the requirement was no longer warranted and that, as with most other drugs, information on non-fatal adverse events could instead be "collected in the periodic safety update reports and annual reports" submitted by the drug's sponsor to FDA. *Id.* at ROA.724.[9]

Three years later, in 2019, FDA approved the application of GenBioPro, Inc. to market a generic version of mifepristone upon FDA's finding that the generic was therapeutically equivalent to Mifeprex®. Letter from CDER to Danco Laboratories, LLC (Apr. 11, 2019) ("2019 Approval"), ROA.775; *see* 21 U.S.C. § 355(j). The same REMS applies to both versions of mifepristone. 2019 Approval, ROA.768–69.

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. *See* Letter from Dr. Patrizia A. Cavazzoni to Drs. Donna J. Harrison & Quentin L. Van Meter (Dec. 16, 2021), ROA.807. Then, following another thorough review by multiple scientists, Mifepristone's REMS

[9] FDA also changed the approved dosing regimen—reducing the amount of mifepristone from 600 mg to 200 mg per dose, increasing the amount of misoprostol per dose, and directing the misoprostol to the dissolved in the cheek pouch rather than taken orally. *See Medical Review – Mifepristone*, FDA (Mar. 29, 2016) ("2016 Medical Review"), ROA.2148. Appellees have not challenged the dosing regimen changes in this litigation, and the lower court did not suggest that they were unlawful.

were further amended on January 3, 2023 to remove the in-person dispensing requirement. *See REMS Single Shared System for Mifepristone 200 mg*, FDA (Jan. 2023), https://www.accessdata.fda.gov/drugsatfda_docs/rems/Mifepristone_2023_01_03_REMS_Full.pdf (last visited Apr. 30, 2023).[10]

ARGUMENT

The district court's order is fundamentally flawed. Because it misunderstood its role, the district court erred as a matter of law. Instead of reviewing FDA's approval of mifepristone for reasonableness—as legally required—the district court substituted its own opinion regarding the correctness of FDA's scientific analysis for the expert scientific judgments of FDA. Further, even if it were appropriate for a district court to review FDA's scientific decisions, the district court erred in its evaluation of the science. The lower court's analysis mischaracterized the record and otherwise largely relied on studies or other information cited by Plaintiffs-Appellees in their complaint and motion for preliminary injunction that were outside the record and that on their face were scientifically unsound. The court did not engage with the enormous record of evidence relied upon by FDA to approve and further regulate mifepristone.

The lower court's order should be reversed. To endorse its erroneous holding would upend decades of effective drug regulation—replacing Congress's desired

[10] FDA's 2023 action is not challenged in this litigation.

system directing FDA to weigh the risks and benefits of new drugs with a scheme that would threaten patient access to safe and effective medications. The court's approach would also impede pharmaceutical innovation and undermine the development of new drugs by allowing litigants to challenge any FDA drug or vaccine approval at any time. This Court should reject Plaintiffs-Appellees' invitation to destabilize the reasoned, scientific judgments of FDA.[11]

A. Under the Proper Standard of Review, Which Requires Deference to the Decisions of FDA's Scientific Experts, FDA's Decision Stands.

The question before the district court should have been whether FDA's actions were arbitrary, capricious, or an abuse of discretion. *See, e.g.*, *Dep't of Commerce v. New York*, 139 S. Ct. 2551, 2569 (2019); *Butte Cnty. v. Hogen*, 613 F.3d 190, 194 (D.C. Cir. 2010). Under this standard, courts are limited to ascertaining whether agency decisions were "reasonable and reasonably explained." *F.C.C. v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). Accordingly, as long as "the agency has acted within a zone of reasonableness," the administrative action will be upheld. *Id.*

This standard of review reflects the well-established "narrow" role of the courts in evaluating agency actions under the Administrative Procedure Act. *Motor*

[11] Plaintiffs-Appellees' claims also fail for all the other reasons set forth in Defendants-Appellants' Brief. *See generally* Def-App. Br.

Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). Under this standard, "a court is not to substitute its judgment for that of the agency." *Id.* Rather, the court must "consider whether the decision was based on a consideration of the relevant factors and whether there has been a clear error of judgment." *Id.* In making this determination, courts consider the record that was before the agency at the time of its decision, not the record created for the purpose of judicial review. *See Camp v. Pitts*, 411 U.S. 138, 142–43 (1973).

A court "must be 'most deferential' to the agency where, as here, its decision is based upon its evaluation of complex scientific data within its technical expertise." *Shrimpers & Fishermen of the RGV v. U.S. Army Corps of Engineers*, 56 F.4th 992, 1001 (5th Cir. 2023) (quoting *Sierra Club v. EPA*, 939 F.3d 649, 680 (5th Cir. 2019)). 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. In other words, judges are not "scientists independently capable of assessing the validity of the agency's determination." *Serono Labs., Inc. v. Shalala* (*Serono II*), 158 F.3d 1313, 1320 (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. Research Servs., Inc. v. FDA*, 957 F.3d 254, 262 (D.C. Cir. 2020).

Serono II 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 other than the district court here and the district court in *Serono* (which was reversed) has ever overruled FDA's approval of a drug. *See, e.g., ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 5, 28–29 (D.D.C. 2012) (citing *Serono II*, 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.").

Here, in granting the unprecedented relief sought by Plaintiffs-Appellees, the lower court blatantly ignored the applicable standard of review. Instead of reviewing

the reasonableness of FDA's decisions in light of the record as it existed at the time of FDA's 2000 Approval and subsequent modifications to the prior conditions of use, *see Camp*, 411 U.S. at 142–43, the district court substituted its own evaluation of various scientific issues for FDA's scientific judgments largely based on studies cited by Plaintiffs-Appellees that were not in the administrative record.[12] This is not the correct inquiry under the law of the Supreme Court or any Circuit. *See, e.g.*, *Prometheus*, 141 S. Ct. at 1158.

When the proper standard of review is applied, FDA's decision stands. As explained above, in evaluating a new drug application, FDA was not charged by Congress with determining whether the drug it is evaluating has *no* risks. Rather the FDCA requires FDA to perform a risk-benefit analysis to weigh the drug's risks against its benefits to patients. *See United States v. Rutherford*, 442 U.S. 544, 555 (1979); 21 U.S.C. § 355(d). Based on numerous peer-reviewed, clinical studies and more than 20 years of experience with mifepristone, FDA has found that serious adverse events associated with the drug are "exceedingly rare." *Medical Review – Mifepristone*, FDA (Mar. 29, 2016) ("2016 Medical Review"), ROA.2189. For example, mifepristone's label indicates that the drug entails no greater than a 0.2% risk

[12] Many of the studies cited by Plaintiffs-Appellees and the district court did not even exist at the time of FDA's challenged actions. *See, e.g.*, ROA.4353 n.44, 4359 n.55. And many of the studies that did exist at the time of FDA's challenged actions were not cited in either of the citizen petitions.

of hemorrhage and sepsis and a 0.7% risk of transfusions and hospitalization. *See Mifeprex® (mifepristone) tablets, for oral use*, FDA, 8 (Jan. 2023) https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020687Orig1s026lbl.pdf (last visited Apr. 30, 2023); *see also* 2016 Summary Review, ROA.708–709.

To support its conclusion that mifepristone is unsafe, the district court cherry-picked misleading quotations from the record. Upon examination, these assertions all fall apart. For example, the district court stated that FDA issued its September 28, 2000 approval letter despite finding in February 2000 that the drug was unsafe and that the Agency harbored "serious reservations" about the drug's safety. ROA.4360. There is no support for either of these statements in the record. Rather, as the context of the February 2000 letter makes clear, FDA explained that, based on the available data at that time, FDA would require the sponsor to amend the restrictions on mifepristone's distribution before its approval, and seven months later FDA concluded that "adequate information has been presented to approve" mifepristone *with* those restrictions. 2000 Approval, ROA.600.

Further, the district court's quotation about FDA's purported "serious reservations" actually came from the minutes of a July 1996 FDA advisory committee meeting and reflected the opinion of a single individual who was not even an FDA employee. *See* 2002 Citizen Petition, ROA.403 (citing FDA Advisory Committee, *Minutes of July 19, 1996 Meeting* (approved July 23, 1996): at 7 [FDA FOIA Release:

MIF 000539-451]). That opinion expressed during an open debate that occurred four years before the actual approval and offered before the distribution restrictions were considered is hardly evidence of "serious reservations" of even the individual who offered the opinion, and certainly not of FDA, about the eventual course of action.

B. The District Court's Erroneous Analysis Does Not Present Any Bases for Overturning the Sound Scientific Judgments of FDA.

Even if it were appropriate for the district court to review the specific scientific decisions made by FDA in connection with approving mifepristone rather than reviewing the decision in its entirety to determine whether it satisfied judicial standards of rationality in light of the court's narrow role, the district court's decision must be reversed.

FDA's 2000 Approval of mifepristone, the 2016 modifications to its conditions for use, the 2019 approval of the generic version, and the 2021 suspension of the requirement for in-person dispensing were all the product of extensive reviews by FDA experts of rigorous scientific studies. By contrast, the district court's review of FDA's actions relied on a host of unsubstantiated studies outside the record considered by FDA that would not have met FDA's standards for valid scientific evidence, mischaracterizations of FDA's statements, and misguided lay analysis of scientific data. These errors illustrate why Congress tasked FDA—not the courts—with evaluating the safety and efficacy of drugs and highlight the risks of allowing judges to second-guess FDA.

Adverse Reactions. The district court questioned FDA's assessment of the safety data before the Agency in 2000. ROA.4359. But the court offered no *data* to contradict FDA's findings on the infrequency of serious adverse events. Rather, the district court relied largely on anecdotes from "myriad stories and studies brought to the Court's attention" that have never been presented to FDA and are contrary to FDA's findings. ROA.4358. The cited evidence does not rebut the rarity of serious adverse effects demonstrated by the studies upon which FDA relied.

Further, the district court repeatedly stated that the true rate of serious adverse effects cannot be known because FDA removed the reporting requirement for prescribers. *See, e.g.*, ROA.4364. This is incorrect. As explained above, although *prescribers* are no longer mandated to report non-fatal adverse events, the drug's sponsor is. This approach is consistent with FDA's requirements for most drugs, and, in any event, adverse events are still reported through periodic safety and annual reports, pursuant to FDA regulations. Indeed, the district court cited data accumulated from these reports. *See* ROA.4359 (citing *Mifepristone U.S. Post-Marketing Adverse Events Summary through 06/30/2022*, FDA, https://www.fda.gov/media/164331/download).

Psychological Considerations. The district court cited an unsubstantiated study based on review of anonymous blog posts submitted to a website called *Abortion Changes You* to support a finding that the use of mifepristone negatively impacts

patients' mental health. *See* ROA.4314, 4352. Even the study's authors acknowledged that "the population of women who write an anonymous post about their abortion experience may be different from those who do not." *See* Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 Health Comm. 1485, 1492 (2021), ROA.517. This is not the type of rigorous, controlled study that FDA considers or should consider when evaluating the safety and efficacy of a drug.

Dating Pregnancy and Diagnosing Ectopic Pregnancy. The district court also found that FDA's deferral to medical providers on the appropriate method for dating pregnancies and diagnosing ectopic pregnancies was arbitrary and capricious. ROA.4357–65. But the court offered no substantiated data for this claim and instead relied largely on anecdotal evidence based on the purported experiences of a few pregnant patients among the more than five million patients who have taken mifepristone in the United States since its approval. These stories do not call into question FDA's well-established, evidence-based finding that health care providers are best positioned to make clinical decisions for their patients. The district court also did not rebut FDA's determination based on peer-reviewed studies that *clinicians* rarely underestimate gestational age. *See* ROA.4358 ("Studies reflect that *women* recurrently miscalculate their unborn child's gestational age.") (emphasis added).

Nothing about FDA's reliance on the professional judgment of healthcare providers was unreasonable.

Trial Conditions. The lower court found that FDA's approval decisions were flawed because the clinical trials cited by FDA in its 2000 Approval and 2016 changes were performed under conditions that did not match those ultimately approved in mifepristone's conditions for use. ROA.4355. There is no legal or scientific basis for such a requirement, and, as far as can be determined, FDA has never adopted—or even considered adopting—such a requirement. As the court acknowledges, the FDCA includes no provision imposing this "study-match" requirement. ROA.4356 n.48. To the contrary, Congress granted FDA broad authority to "exercise [its] discretion or subjective judgment in determining whether a study is adequate and well controlled." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 621 n.17 (1973).

Nor does the district court's requirement have a scientific basis. FDA addressed this issue at length in its response to the 2002 Citizen Petition, explaining that "safeguards employed in clinical trials are often not reflected in approved drug product labeling nor are they necessarily needed for the safe and effective use of the drug product after approval." 2016 Petition Denial, ROA.662. Instead, "this additional level of caution is exercised until the safety and efficacy of the product is demonstrated." *Id.* Indeed, the conditions of use for many drugs differ from those used in the clinical trials on which FDA relied in its approvals. For example, routine biopsies were performed

in trials for menopause hormonal therapy drugs to establish their safety, but FDA did not require biopsies in those drugs' approved conditions of use. 2016 Petition Denial, ROA.662.

The court is also incorrect that the 2016 modifications were not studied before they were implemented. Rather, as explained above, FDA relied on clinical trials implementing each of the challenged modifications as well as 20 years of data demonstrating the safety of mifepristone. 2016 Medical Review, ROA.2159, 2143–2242. Again, the lower court does not offer any support for its conclusion that FDA could only rely on a clinical trial that simultaneously implemented *all* of the conditions of use that were ultimately approved.

C. Allowing the District Court's Decision to Stand Would Upend FDA's Drug Approval System and Harm Patients.

The district court's order flips Congress's chosen scheme on its head—subjecting scientific decisions by FDA's expert doctors, pharmacologists, chemists, biologists, and statisticians to being second-guessed by federal judges. Each drug approval decision made by FDA 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.

Adopting the district court's approach to drug regulation 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 on the basis of their disagreement with 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 seek 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 unnecessary restrictions to be applied. 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 also adversely impacts healthcare providers who rely on FDA approval when making critical treatment decisions. At the same time, drug companies unhappy that FDA has denied their new drug applications could seek court rulings that would allow 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. *See generally* Pharm. Amicus Br., ECF No. 118. 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.[13] As a result of the lower court's approach, even the relatively few drugs that attain FDA approval would be perpetually susceptible to legal challenges—discouraging companies from investing in new life-saving remedies.

If this Court upholds the order of the district court and upends the regulatory framework designed by Congress that has produced essential drugs for more than 80 years, patients in need will ultimately bear the catastrophic consequences of the resulting instability.

[13] *See Research and Development in the Pharmaceutical Industry*, Cong. Budget Office, 2 (Apr. 2021), https://www.cbo.gov/publication/57126 (last visited Apr. 30, 2023).

CONCLUSION

For the foregoing reasons and those set forth in Defendants-Appellants' Brief, the district court's order should be reversed.

Date: May 1, 2023

Respectfully submitted,

/s/ William B. Schultz
William B. Schultz
Margaret M. Dotzel
Alyssa M. Howard
Zuckerman Spaeder LLP
1800 M Street NW, Suite 1000
Washington, D.C.
(202) 778-1800
wschultz@zuckerman.com

Counsel for Amici Curiae

CERTIFICATE OF SERVICE

I certify that on May 1, 2023, the foregoing Brief of Former Commissioners of the U.S. Food and Drug Administration as *Amici Curiae* in Support of Defendants-Appellants was filed electronically and has been served via the Court's ECF filing system in compliance with Rule 25(b) and (c) of the Federal Rules of Appellate Procedure on all registered counsel of record.

/s/ William B. Schultz
Counsel for Amici Curiae

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 6,462 words, as counted by Microsoft Word, excluding the parts of the brief excluded by Federal Rule of Appellate Procedure 32(f). This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because it has been prepared using Microsoft Word in 14-point Times New Roman font.

I further certify that (1) any required privacy redactions have been made, 5th Cir. R. 25.2.13; and (2) the electronic submission is an exact copy of the paper document, 5th Cir. R. 25.2.1.

/s/ William B. Schultz
Counsel for Amici Curiae