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 and Appellees

v.

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

DANCO LABORATORIES, LLC,
Defendant-Intervenor and Appellant

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

Motion for Leave to File Brief As *Amici Curiae* in Support of Appellants

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CERTIFICATE OF INTERESTED PARTIES

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Fifth Circuit Rule 28.2.1 have an interest in the outcome of this case. These representations are made so that the judges of this Court may evaluate possible disqualification or recusal.

Plaintiffs-Appellees

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2. American Association of Pro-Life Obstetricians and Gynecologists
3. American College of Pediatricians
4. Christian Medical and Dental Associations
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DATED: May 1, 2023

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MOTION FOR LEAVE TO FILE BRIEF AS *AMICI CURIAE*

1. Pursuant to Rule 29(b) of the Federal Rules of Appellate Procedure, former Food and Drug Administration ("FDA") officials hereby move for leave to file a brief as *amici curiae* in support of Defendants-Appellants. The proposed brief is attached. All parties have consented to the filing of this brief.

2. Proposed *amici* are former FDA officials who served in both Republican and Democratic administrations in a wide variety of roles, including principal deputy commissioner, medical officer, legal counsel, policy advisor, and historian. Based on their collective decades of experience at all levels of FDA, *amici* are deeply familiar with how FDA approves drugs and the agency's history and have a strong interest in ensuring that the drug-approval process Congress created and FDA implemented continues to work as intended and that FDA can continue to ensure the safety, efficacy, and security of drugs and medical treatments through reasoned expert judgment. *Amici* are:

- **Julie Bullock, PharmD**, who served at FDA from 2004 to 2014 as a Senior Clinical Pharmacology Reviewer and then as a Clinical Pharmacology Team Leader.
- **Scott Danzis**, who served as Special Assistant to the FDA Chief Counsel from 2006 to 2008.

- **Daniel Davis, M.D., M.P.H.**, who served as a Medical Officer at FDA's Center for Drug Evaluation and Research from 1997 to 2016, where he was one of three primary medical reviewers for Mifeprex from 2000 to 2016.

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- **Jeremy Sharp**, who served as FDA Deputy Commissioner for Policy, Planning, Legislation, and Analysis from 2015 to 2017.

- **Krithika Shetty, Ph.D.**, who served at FDA from 2019 to 2021 as a Clinical Pharmacology Reviewer.

- **Rachel Sherman, M.D., M.P.H., F.A.C.P.**, who served at FDA in five administrations across 30 years from 1989 to 2014 and 2015 to 2019, including as Principal Deputy Commissioner of Food and Drugs (2017-19), Director of the Office of Medical Policy and the Associated Director of Medical Policy at the Center for Drug Evaluation and Research (2009-14), and a Medical Officer and Expert Medical Reviewer (1989-93).

3. As required by Fifth Circuit Rule 29.2, the proposed brief "avoid[s] the repetition of facts or legal arguments contained in" the United States' brief and the briefs of other amici and "focus[es] on points . . . not adequately discussed" in those briefs. In the order below, the trial court vacated over two decades of FDA's regulatory actions regarding mifepristone, a drug first approved by FDA in 2000 for use in medication abortions. As former FDA officials, proposed amici are well qualified to explain how FDA's drug approval process works and how it developed over time, as well as the importance of FDA's role in safeguarding the public health. Proposed amici also submit this brief to explain how and why Congress entrusted drug approvals to FDA's scientific judgment and expertise and to stress that judicial second-guessing of FDA's safety determinations has serious negative consequences for the public health.

DATED: May 1, 2023

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that on May 1, 2023, the foregoing document was served on all parties or their counsel of record through the CM/ECF system.

DATED: May 1, 2023

/s/ Jordan D. Segall
Jordan Segall

No. 23-10362

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Brief of *Amici Curiae* Former FDA Officials in Support of Appellants

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

CASES

STATUTES

FEDERAL REGULATIONS

OTHER AUTHORITIES

INTERESTS OF THE *AMICI CURIAE*[1]

This case challenges FDA regulatory actions regarding mifepristone, a drug first approved by FDA in 2000 for use in medication abortions. *Amici curiae* are former FDA officials who served in both Republican and Democratic administrations in a wide variety of roles, including principal deputy commissioner, medical officer, legal counsel, policy advisor, and historian. Based on their collective decades of experience at all levels of FDA, *amici* are deeply familiar with how FDA approves drugs and the agency's history and have a strong interest in ensuring that the drug-approval process Congress created and FDA implemented continues to work as intended and that FDA can continue to ensure the safety, efficacy, and security of drugs and medical treatments through reasoned expert judgment.

Amici submit this brief to explain why Congress entrusted drug approvals to FDA's scientific judgment and expertise, how FDA's drug approval process works, and why judicial second-guessing of FDA's safety

[1] This brief is submitted under Federal Rule of Appellate Procedure 29(a). Undersigned counsel for amici curiae certify that this brief was not authored in whole or part by counsel for any of the parties; no party or party's counsel contributed money for this brief; and no one other than amici and their counsel have contributed money for this brief. All parties have consented to the filing of this brief.

determinations would have serious negative consequences for the public health. *Amici* are:

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INTRODUCTION

For over a century, Congress has entrusted to FDA the responsibility to protect the public health by applying scientific and medical expertise to evaluate the safety and efficacy of drugs. In 2000, FDA exercised its congressionally delegated authority to approve mifepristone for use in medication abortions, after a lengthy and thorough approval process that was consistent with congressional legislation and agency regulations. The district court's decision, which vacated every FDA decision regarding mifepristone since 2000, is the first time a court has ever second-guessed FDA's scientific judgment by vacating a drug's approval on the ground that FDA got the science wrong.

The decision below sets the country on a dangerous path back to the piecemeal regulatory scheme that Congress rejected in 1938, when Congress decided that the best way to protect the public health and promote access to safe and effective medication was to rely on an expert agency to regulate and approve drugs. Courts lack the expertise to step into FDA's shoes by second-guessing FDA's experts on the safety and efficacy of drugs. Assuming that role requires inexpert judges to learn how to do what FDA's expert pharmacologists, toxicologists, chemists,

epidemiologists, physicians, and data scientists have spent lifetimes training to do. Getting it wrong can lead to catastrophic consequences—measured not in dollars, but in human lives—and deprive patients of life-saving medication they depend upon. This Court should reverse the judgment below and permit FDA to continue to protect the public health and ensure that patients have access to needed medications, as Congress intended.

ARGUMENT

I. Congress Gave FDA Broad Authority Over Drug Approvals to Safeguard the Public Health

FDA's modern authority over drug approvals evolved in response to a series of public health crises that occurred over the last century. In response to these crises, Congress steadily expanded and centralized FDA's authority over drug approvals to give FDA more discretion to protect public health. The result is an agency that exercises robust control over what drugs can be marketed and how they are labeled in the United States.

A. Sulfanilamide and the Food, Drug, and Cosmetic Act of 1938

Congress's first attempt to regulate drug safety in the United States was a near-total failure. In 1906, Congress passed the Pure Food

and Drugs Act, Pub. L. No. 59-834, empowering the predecessor to the modern FDA to regulate labeling of food and drug products. But the 1906 Act permitted any "medication" to remain on the market so long as its label accurately listed the ingredients in it and its maker did not intentionally deceive the public when describing the product's purported health benefits. *Part I: The 1906 Food and Drugs Act and Its Enforcement*, U.S. Food & Drug Admin. (Apr. 24, 2019).[2] As a result, many demonstrably harmful products remained on the market, including "Banbar," a mixture of alcohol, water, and plant extracts marketed by an ex-shirt salesman as a cure for diabetes that killed patients who took it instead of insulin. *Banbar: Another Nostrum for Diabetes*, 100 J. Am. Med. Ass'n 1882, 1882 (June 10, 1933);[3] Suzanne White Junod, *FDA and Clinical Drug Trials: A Short History*, U.S. Food & Drug Admin., at 4-5 (2008) ("Junod, *Clinical Drug Trials*").[4]

The flaws of the 1906 Act became impossible to ignore. In the early 1930s, scientists discovered sulfanilamide, an antibacterial drug that

[2] https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-i-1906-food-and-drugs-act-and-its-enforcement.
[3] https://jamanetwork.com/journals/jama/article-abstract/243476.
[4] https://www.fda.gov/media/110437/download.

could treat strep throat. Paul M. Wax, *Elixirs, Diluents, and the Passage of the 1938 Federal Food, Drug, and Cosmetic Act*, 122 Annals Internal Med. 456, 456 (1995).[5] One company "developed" Elixir Sulfanilamide, a mixture of sulfanilamide dissolved in diethylene glycol, water, and raspberry flavoring. *Id.* While the company tested the mixture's flavor, it did not test its toxicity. *Id.* Tragically, over 100 people, nearly one-third of whom were children, died of kidney failure after taking Elixir Sulfanilamide. *Id.* at 458. Later testing revealed that diethylene glycol is highly toxic to humans; the chemical is now commonly used in antifreeze, brake fluid, and other industrial applications. Alicia Minns, *Diethylene Glycol Poisoning*, Cal. Poison Control System (Dec. 21, 2012).[6]

In response to the sulfanilamide disaster, Congress passed the Food, Drug, and Cosmetic Act of 1938. Rather than relegate FDA to merely respond to dangerous drugs on the market, the 1938 Act empowered FDA to prevent dangerous drugs from reaching the market in the first place. The Act achieved this by creating a premarket approval system for drugs, under which drugs could not be marketed or sold unless

[5] https://pubmed.ncbi.nlm.nih.gov/7856995/.
[6] https://calpoison.org/news/diethylene-glycol-poisoning.

manufacturers could prove to FDA that their drugs were safe. The act also defined "drug" broadly, including both "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man." 21 U.S.C. § 321(g)(1)(B)-(C); *see also FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 126 (2000). Congress's unmistakable intent was to give FDA robust authority to keep a wide range of unsafe treatments and medications off the market.

B. Thalidomide and the Kefauver-Harris Amendments of 1962

But even the 1938 Act was not enough. Early safety submissions were often light on substance and badly lacking in scientific rigor. Junod, *Clinical Drug Trials*, *supra*, at 12. FDA's drug approval division was also woefully understaffed: In 1958, FDA had just seven physicians on staff tasked with evaluating thousands of applications each year. *Id.* at 9; Suzanne White Junod & Lara Marks, *Women's Trials: The Approval of the First Oral Contraceptive Pill in the United States and Great Britain*, 57 J. Hist. Med. 117, 130 (Apr. 2002).[7]

[7] https://academic.oup.com/jhmas/article/57/2/117/740421.

About one month after joining FDA in 1960, Dr. Frances Oldham Kelsey was assigned to review a new drug application for thalidomide, a drug approved and widely sold in Europe as a sleeping and morning sickness medication. Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, FDA Consumer (2001).[8] Unconvinced by the application's safety data, Dr. Kelsey refused to approve the application despite significant pressure from the drug's manufacturer. *Id.* Soon after, physicians in Europe started reporting babies born with debilitating deformities seemingly caused by their mothers taking thalidomide while pregnant. All told, an estimated 10,000 children were born with thalidomide-caused deformities, many in countries that did not have pre-market approval systems for drugs. Katie Thomas, *The Unseen Survivors of Thalidomide Want to Be Heard*, N.Y. Times (Mar. 23, 2020).[9] But because FDA had exercised its congressionally granted authority and refused to approve thalidomide, the drug had a much smaller toll in the United States than it did elsewhere. *Id.*

[8] https://web.archive.org/web/20061020043712/https://www.fda.gov/fdac/features/2001/201_kelsey.html.

[9] https://www.nytimes.com/2020/03/23/health/thalidomide-survivors-usa.html.

Some patients in the United States, however, obtained thalidomide through loosely regulated clinical trials. *Id.* In the ensuing uproar, Congress passed the Kefauver-Harris Amendments, expanding FDA's premarket authority by requiring drug manufacturers to prove, through rigorous studies and reliable data, that their products were both safe and effective. FDA then exercised its delegated authority and worked with professional medical and scientific organizations to develop standards for clinical trials and investigative protocols. *See* 21 U.S.C. § 371(a). FDA issued regulations clarifying what it expected of studies and clinical data before it would approve new drugs, and held workshops for drug companies and other industry stakeholders to explain FDA's new standards and how to satisfy them. Junod, *Clinical Drug Trials*, *supra*, at 12-13. FDA's efforts to work with industry, rather than against it, simultaneously ensured that FDA got the data it needed to evaluate drugs and reduced the likelihood that drug manufacturers would waste time and resources by making noncompliant submissions.

C. The HIV/AIDS Epidemic, Subpart H, and the Food and Drug Administration Amendments Act of 2007

Requiring rigorous scientific proof of safety and efficacy, however, could potentially delay access to important medications and leave some

clinical needs unfilled. In the late 1980s and early 1990s, the HIV/AIDS epidemic was raging in the United States but no drugs were approved to treat HIV/AIDS. Pursuant to FDA's authority under 21 U.S.C. § 355, FDA promulgated Subpart H to fill this gap, balance the need for treatments with the need for safety, and ensure that patients could access potentially lifesaving medication. *See* 57 Fed. Reg. 13234, 13234-13235 (1992).

Subpart H created two distinct approval mechanisms for drugs "that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses." 21 C.F.R. § 314.500. First, FDA could accelerate approval of drugs that offer significantly greater therapeutic benefits over existing treatments. 21 C.F.R. § 314.510. Second, Subpart H included restricted distribution provisions that permitted FDA to condition (accelerated or ordinary) approval upon additional safety measures if FDA determines that a drug "can be safely used only if distribution or use is restricted." 21 C.F.R. § 314.520(a). In its final rule, FDA made clear that the term "illnesses" was meant broadly and included "illnesses," "diseases," and other "conditions." 57 Fed. Reg. 58942, 58946 (1992). For instance, FDA explained that drugs

that treat epilepsy and similar "conditions or diseases that can be serious" would be eligible for approval under Subpart H. *Id.*

FDA has used both Subpart H mechanisms to approve a wide array of drugs. *See Accelerated and Restricted Approvals Under Subpart H (Drugs) and Subpart E (Biologics)*, Food & Drug Admin. (Aug. 26, 2014).[10] Many of the drugs approved under Subpart H treated serious diseases, including HIV/AIDS and cancer. *Id.* But FDA, consistent with what it said when promulgating the rule, also used Subpart H to approve or restrict distribution of drugs that treat serious conditions that many would not consider "illnesses" in a conventional sense, including acute acne (Accutane), infertility (Luveris), and inflammation (Thalomid). *Id.* FDA also used Subpart H's restricted distribution provisions to approve mifepristone after three review cycles that spanned four years from 1996 to 2000. Gov. Accountability Office, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex* (No. GAO-08-751) at 15 (Aug. 7, 2008) ("GAO Report").[11]

[10] https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/accelerated-and-restricted-approvals-under-subpart-h-drugs-and-subpart-e-biologics.

[11] https://www.gao.gov/products/gao-08-751.

Congress codified Subpart H in two steps, recognizing each time that Subpart H had been, and could continue to be, used to approve drugs that treat serious "conditions." First, it codified FDA's authority to impose distribution restrictions by passing the Food and Drug Administration Amendments Act of 2007. *See* Pub. L. No. 110-85, § 901. The 2007 Act permitted FDA to instate additional safety restrictions based on the "seriousness of the disease or condition" and the "expected benefit of the drug with respect to such disease or condition." 21 U.S.C. § 355-1(a)(1)(B)-(C). The Act also grandfathered restrictions on drugs imposed under Subpart H into the new statutory framework. Pub. L. No. 110-85, § 909(b).

Second, Congress codified FDA's accelerated approval authority in 2012, when it passed the Food and Drug Administration Safety and Innovation Act. *See* Pub. L. No. 112-114, § 901. The Act permitted FDA to grant accelerated approval for drugs that treat "a serious or life-threatening disease or condition." 21 U.S.C. § 356(c)(1)(A).

II. FDA Exercises its Congressionally Granted Authority to Safeguard the Public Health and Facilitate Access to Safe and Effective Drugs through Expert Scientific Judgment

Over more than a century, informed by scientific advances, the growing complexity of pharmaceutical research and development, and a series of public health crises demanding a public response, Congress developed FDA into a comprehensive and highly expert agency for the approval of drugs according to the best available scientific principles. Today, FDA employs thousands of drug reviewers and personnel who evaluate new drug applications, work with private drug sponsors to design studies and collect needed data, and monitor drugs after approval to ensure that they are both safe and effective. These employees bring their specialized knowledge to bear at all stages of the drug approval process, beginning long before a final new drug application is submitted and continuing well after a drug is approved.

A. FDA's Approval Process is Thorough and Science-Grounded at Every Stage

Pre-Application Analysis. Before drug sponsors submit new drug applications, they often work closely with FDA to design clinical trials and other experiments to minimize the risk that sponsors' research and development efforts go to waste. Many drug sponsors file investigational

new drug ("IND") applications to obtain FDA's approval to begin testing in humans in the United States based upon an adequate showing of preclinical non-human safety, compliance with ethical and professional standards, and experimental rigor. *See* 21 C.F.R. §§ 312.20, 312.22. The IND process "assure[s] the safety and rights of subjects" and "assure[s] that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." 21 C.F.R. § 312.22(a). Through the IND process, FDA protects potentially vulnerable patients, front-loads some of the approval process by ensuring that experiments are sufficiently rigorous before the sponsors perform them, and minimizes the risk that sponsors waste limited resources on flawed tests. FDA also regularly issues regulations, guidance documents, and other informational materials to help sponsors design scientifically rigorous tests that can help their drugs get approved.

Evaluating New Drug Applications. After a sponsor submits a new drug application, FDA refers it to a wide array of expert reviewers, including doctors, pharmacologists, chemists, biologists, and statisticians, who review every aspect of the application. All drugs—including those that were approved under Subpart H—must meet the

same standard for safety and effectiveness before FDA can approve them. 21 U.S.C. § 355(d). By statute, the Secretary of Health and Human Services shall reject a new drug application if he finds that the safety testing was inadequate or that, "on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports . . . under the conditions of use prescribed." *Id.* "[S]ubstantial evidence means evidence consisting of adequate and well-controlled investigations . . . by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." *Id.* The statute then leaves it to FDA to promulgate regulations explaining what constitutes an "adequate and well-controlled investigation" and whether an investigation is sufficiently probative of a drug's effect in the real world. *See* 21 C.F.R. § 314.126; *see also* 21 U.S.C. § 371(a). The statute does not require that the conditions of the trial match the conditions of use prescribed.

FDA regulations specify a number of controls that it can rely on when assessing drug safety and efficacy. 21 C.F.R. § 314.126(b)(2). Ordinarily, FDA approves a drug based on a clinical trial that uses an

"internal control"—that is, a study that divides subjects into control and experimental groups and treats both groups concurrently. *See* 21 C.F.R. § 314.126(b)(2)(i). In certain circumstances, FDA relies on "external controls" and compares results from a study to results or data from a group of patients external to the study. External controls are far from unusual and are especially common in oncology: One study found that between 2000 and 2019, FDA approved 45 non-oncological products using studies that included external controls. Mahta Jahanshahi et al., *The Use of External Controls in FDA Regulatory Decision Making*, 55 Therapeutic Innovation & Reg. Sci. 1019, 1022-23 (May 20, 2021).[12] One common external control, and the one used in mifepristone's approval, is a "historical control," in which the treatment group is compared against preexisting patient data, either from another experiment or from real-world observations of untreated patients. Under FDA regulations, FDA may consider clinical studies with historical controls when approving drugs that treat "adequately documented . . . disease[s] or condition[s]" in "special circumstances," such as in "studies of diseases with high and predictable mortality" and "studies in which the effect of the drug is self-

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/.

evident." 21 C.F.R. § 314.126(b)(2)(v). FDA routinely relies on historical controls to approve drugs. For instance, FDA relied on historically controlled studies to approve Defitelio (defibrotide sodium), a drug used to treat a rare and lethal liver condition. *See FDA Approves First Treatment for Rare Disease in Patients Who Receive Stem Cell Transplant From Blood or Bone Marrow*, U.S. Food & Drug Admin. (Mar. 30, 2016).[13] Because of the condition's extremely high mortality rate, FDA, in consultation with outside experts, concluded that it would be unethical to perform an internally controlled clinical trial where some of the patients would receive placebos. *See* Ctr. for Drug Evaluation & Rsch., *Medical Review(s), Application Number: 208114Orig1s000*, U.S. Food & Drug Admin. at 44 (Mar. 18, 2016).[14] Instead, FDA and the drug sponsor developed a selection protocol for constructing a historical control group of patients who did not receive Defitelio. *Id.* at 47-48, 58-63. After the study was completed, FDA reviewed every step of the selection process, including the reasons for excluding or including specific patients, and

[13] https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-rare-disease-patients-who-receive-stem-cell-transplant-blood-or-bone.
[14] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208114Orig1s000MedR.pdf.

ultimately approved the drug. *Id.* at 62-63. Defitelio's approval exemplifies how FDA employees use their expertise to design studies, evaluate whether studies were conducted in accordance with best scientific practices, and determine whether the data provide sufficient evidence of both safety and efficacy. This is precisely the kind of detailed analysis and exhaustive scrutiny that FDA applies to all drug safety and efficacy submissions—including for mifepristone.

FDA also regularly approves labeling and indications for drugs that do not exactly match the conditions and requirements of the underlying clinical trials used to evaluate the drug's efficacy. Neither statute nor regulation requires a one-to-one correspondence between the conditions of the trial and the conditions of use approved by FDA. Indeed, best scientific practices often require that clinical trials be conducted with additional safety measures in place because many trial participants are taking drugs that have not yet been fully evaluated by FDA for safety and efficacy. *See*, *e.g.*, App. Pl.'s Mot. Prelim. Inj. 589 (denying the 2002 citizen petition). Once the drug is fully tested and approved, many of these additional safety measures are no longer necessary. "For example, in menopausal hormonal therapy trials, specialists performed periodic

endometrial biopsies to establish the safety of long-term hormone use. Once the safety of the product has been established, these biopsies are not recommended in the approved product labeling, nor are they routinely performed in actual use with the approved product." *Id.*

As part of the approval process, FDA also balances safety concerns against the need for patient access to potentially life-saving medication, cognizant that undue delay may carry a heavy human cost. For example, under the FDA Amendments Act of 2007, FDA may "expedite the development and review of [a] drug if the drug is intended . . . to treat a serious or life-threatening disease or condition." 21 U.S.C. § 356(a)(1). FDA may also approve abbreviated new drug applications for generic drugs that are "bioequivalent" to their name-brand counterparts. 21 U.S.C. § 355(j). While these review processes may be faster than FDA's process for an ordinary new drug application, they are rigorous: FDA reviews detailed chemical, safety, and medical data before approving drugs submitted under either pathway. Once approved, these drugs help ensure that patients have access to medications that they need and depend on.

Post-Market Monitoring. After FDA approves a drug, it monitors the drug to ensure that its real-world performance and safety characteristics are consistent with the experimental data submitted during the approval process. *See* 21 U.S.C. § 360*l*. In many cases, FDA requires sponsors to perform post-market studies and works with sponsors to design those studies. Failure to perform the required studies can lead FDA to rescind a drug's approval and pull it from the market.

FDA may also withdraw a drug's approval if post-market studies demonstrate that the drug is not sufficiently effective or safe or if new evidence undermines the data included in the new drug application. 21 U.S.C. § 355(e)(1)-(3); 21 C.F.R. § 314.150(a)(2). For example, one drug company recently pulled Makena, a drug aimed at treating preterm labor, from the market after FDA commenced withdrawal proceedings and an independent committee concluded that post-market testing demonstrated that Makena has no significant clinical benefit. Christina Jewett, *Preterm Birth Drug Withdrawn After 12 Years*, N.Y. Times (Mar. 7, 2023).[15] FDA's process that led to the withdrawal of Makena was comprehensive and rigorous. FDA first engaged in informal dialogue with

[15] https://www.nytimes.com/2023/03/07/health/preterm-birth-drug-makena-fda.html.

the drug's sponsor to wind down distribution of the drug. *Id.*; *see also* 21 C.F.R. § 314.150(d). After FDA and the sponsor failed to agree on a plan, FDA convened public hearings before a panel of 16 experts that included ten practicing obstetricians, one biostatistician, one epidemiologist, one consumer representative, one patient representative, and one industry representative. Celia M. Witten, *Presiding Officer Witten's Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdraw Approval of MAKENA*, U.S. Food & Drug Admin. at 4 (Jan. 19, 2023);[16] *see also* 21 U.S.C. § 355(e); 21 C.F.R. § 314.150(a). The committee evaluated clinical trial data involving hundreds of patients; solicited written comments from the public; and heard presentations from the FDA branch responsible for evaluating drugs, the drug sponsor, and 20 public commentors representing groups, individual practitioners, and patients. Witten, *supra*, at 4-5. Based on these open hearings, the committee's expert decisionmakers and physicians ultimately concluded that the data did not demonstrate that

[16] https://int.nyt.com/data/documenttools/fda-2020-n-2029-0379-attachment-1/0fa41638a81362bb/full.pdf.

the drug had any significant clinical benefits and that the drug should be withdrawn. *Id.* at 5-14.

As the Makena withdrawal demonstrates, Congress gave FDA the appropriate tools to revisit prior drug approvals and determine whether an approved drug is safe and effective enough to remain on the market. FDA then exercises that authority in a science-based process that affords drug sponsors adequate notice and an opportunity to be heard and gives due consideration to the views of the public and other stakeholders. The decision below, by contrast, represents a form of judicial intervention that arrogates to an inexpert court the error-correction function that properly belongs to FDA.

B. FDA Approved Mifepristone Pursuant to this Expert Process

Mifepristone's approval was the function of the orderly operation of the agency process described above. FDA performed an exhaustive review of large volumes of clinical trial data across three rounds of review that spanned four years. *See generally* GAO Report, *supra*. In its first round of 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. *Id.*

at 15-16. These studies included over 4,000 patients across the different clinical trials—which by FDA standards significantly exceeds the typical number of patients in most clinical trials. *See id.*

FDA decided to use historically controlled clinical trials when approving mifepristone because, as required by FDA regulations, (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 have been unethical to give some patients seeking to terminate a pregnancy a placebo to see if the pregnancy would spontaneously abort. FDA also concluded that pregnancy is a serious condition within the meaning of Subpart H because pregnancy, especially unwanted or unplanned pregnancy, entails a number of potential risks, including miscarriage, preeclampsia, high blood pressure, maternal mortality, and more. FDA also convened an advisory committee of reproductive health drug experts to evaluate the data as well. *Id.* at 16-17. That committee voted 6-0, with two abstentions, that the data showed that the benefits of mifepristone outweighed its risks. *Id.* After soliciting and evaluating additional data and information from the drug sponsor in

the next two rounds of review, FDA concluded, based on its own 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.

After approving mifepristone, FDA spent 23 years monitoring mifepristone by reviewing adverse event reports, analyzing trends and data, and studying the medical literature. Any decisions or findings made on the basis of these reviews were subject to stringent internal checks that often entailed multiple levels of review by senior career FDA officials across multiple departments and offices. And after groups petitioned FDA to withdraw mifepristone or reverse its regulatory decisions, FDA experts reviewed adverse event reports and relevant data and concluded that there was no reason to think that mifepristone's potential safety concerns outweighed the benefits of keeping it on the market. *See, e.g.*, Ltr. from Patrizia A. Cavazzoni to Donna J. Harrison & Quentin L. Van Meter (Dec. 16, 2021).[17]

In short, mifepristone's approval entailed a straightforward and thorough application of the expert scientific review process that Congress

[17] https://downloads.regulations.gov/FDA-2019-P-1534-0016/attachment_1.pdf.

delegated to FDA when it passed the Food, Drug, and Cosmetic Act of 1938 and has subsequently amended at relevant intervals.

III. Courts Should Not Second-Guess FDA's Determinations of Drug Safety and Efficacy That Are Supported by Scientific Evidence

1. The district court's order is the first time that any court has second-guessed FDA's determination that a drug is safe and effective. During the preliminary injunction hearing, Respondents cited *Serono Labs., Inc. v. Shalala*, 974 F. Supp. 29 (D.D.C. 1997), as the only case supporting their position that courts can and have reevaluated FDA's determinations of a drug's safety and efficacy. Tr. of Mar. 15, 2023 Hr'g Pl.'s Mot. Prelim. Inj. at 34:22-35:3. But a unanimous panel of the D.C. Circuit reversed that decision. *Serono Labs., Inc. v. Shalala* (*Serono II*), 158 F.3d 1313, 1327 (D.C. Cir. 1998). As the court of appeals explained, "[n]either we, nor the district judge, are scientists independently capable of assessing the validity of the [FDA's] determination—beyond holding it to the standards of rationality required by the Administrative Procedure Act." *Id.* And in a later case brought by a drug company seeking to force FDA to withdraw a competitor's drug from the market on the grounds that FDA lacked adequate safety and efficacy data, the D.C. district court

observed that "[t]o the best of the parties' and the Court's knowledge, the extraordinary relief that [plaintiff] seeks is unprecedented in this jurisdiction." *ViroPharma, Inc. v. Hamburg*, 898 F. Supp. 2d 1, 5, 28-29 (D.D.C. 2012) (citing *Serono II*, 158 F.3d at 1327); *see also id.* at 29 n.35.

2. This Court should adopt the D.C. Circuit's approach and refrain from interfering with FDA's determinations of drug safety and efficacy rationally supported by scientific evidence for at least two reasons: congressional intent and agency expertise.

First, Congress entrusted drug safety to FDA, not the courts. Drug safety and effectiveness are complex determinations requiring the balancing of risk and benefit based on detailed analysis of evidence from laboratory, animal, and human testing. The "traditional rule" in these circumstances is that Congress has "wide discretion to pass legislation in areas where there is medical and scientific uncertainty." *Gonzales v. Carhart*, 550 U.S. 124, 163 (2007). Congress exercised that discretion when it chose to vest an expert agency with plenary authority over new drug approvals. It did so for a simple reason: The alternatives had failed to keep the public safe. After public health crises revealed the weaknesses of earlier drug regulatory schemes, Congress enacted a

regulatory scheme that empowered an expert agency to prevent unsafe drugs from reaching the market and issue regulations complementing Congress's chosen scheme. The result of Congress's legislation and FDA's gap-filling is a comprehensive drug approval process that relies on medical, scientific, and statistical expertise at every step to make as accurate of a determination as possible of whether a drug is safe and effective before it is marketed and sold to patients. Congress's repeated ratification of that system through new legislation only affirms the success of that system in safeguarding the public health.

Second, courts lack the expertise to make the scientific and clinical determinations needed to evaluate the safety and efficacy of new drugs. While judges are experts on what the law means, and have a duty to ensure that an agency acts consistently with its congressionally defined remit, they lack the expertise to second-guess the results of agency processes that are consistent with the law, endorsed by outside expert advisers, and supported by major professional medical associates. So long as FDA's drug approval decisions are reasonably based on scientific evidence of efficacy and safety, courts should not substitute their judgment for the agency's by second-guessing what FDA's scientific and

medical experts have determined. *Cf. Dep't of Commerce v. New York*, 136 S. Ct. 2551, 2571 (2019) ("By second-guessing the Secretary's weighing of risks and benefits . . . Justice Breyer—like the District Court—substitutes his judgment for that of the agency."). Any other holding would undermine Congress's chosen regulatory scheme, dangerously weaken FDA's role in drug approvals, and set the country on a backsliding path toward the piecemeal regulatory system that Congress rejected in 1938.

The district court's order undermines Congress's chosen scheme by opening the door to endless re-litigation of FDA's decisions with potentially disastrous consequences. Patients who suffered from side effects could seek to pull drugs from the market notwithstanding the proven benefits of the drug to vast numbers of other patients. Drug companies could try to pull their competitors' drugs from the market based on a supposed mismatch between clinical trial conditions and the recommendations listed on the label. And companies that invested millions of dollars into a drug that FDA rejected could seek a second opinion from the courts. These cases would require generalist federal judges to sift through clinical trial data, examine experimental protocols,

interpret adverse event reports, and review statistical regressions and cost-benefit analyses. In other words, these cases would require inexpert judges to be proficient in exactly what FDA's experts have spent their lives training to do. And as history shows, getting it wrong could lead to catastrophic consequences, whether it were to result in allowing an unsafe or ineffective drug to be sold to the public or depriving patients of access to a potentially life-saving therapy.

Congress decided long ago that the best way to protect the public health was to entrust drug regulation to an expert agency. This Court should respect that decision and reverse the district court's order granting Respondents a preliminary injunction.

CONCLUSION

The district court's order granting Respondents a preliminary injunction should be reversed.

DATED: May 1, 2023

Respectfully submitted,

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CERTIFICATE OF SERVICE

I certify that on May 1, 2023, the foregoing document was served on all parties or their counsel of record through the CM/ECF system.

DATED: May 1, 2023

/s/ Jordan D. Segall
Jordan Segall

CERTIFICATE OF COMPLIANCE

1. This document, excluding the parts of the document exempted by Fed. R. App. P. 32(f), contains 5,601 words.

2. This document complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type-style requirements of Fed. R. App. P. 32(a)(6) because this document has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point New Century Schoolbook.

DATED: May 1, 2023

/s/ Jordan D. Segall
Jordan Segall