No. 23-10362

In the United States Court of Appeals for the Fifth Circuit

ALLIANCE FOR HIPPOCRATIC MEDICINE; AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIANS & GYNECOLOGISTS; AMERICAN COLLEGE OF PEDIATRICIANS; CHRISTIAN MEDICAL & 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, COMMISSIONER OF FOOD AND DRUGS; JANET WOODCOCK, M.D., IN HER OFFICIAL CAPACITY AS PRINCIPAL DEPUTY COMMISSIONER, U.S. FOOD AND DRUG ADMINISTRATION; PATRIZIA CAVAZZONI, M.D., IN HER OFFICIAL CAPACITY AS DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION; UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES; XAVIER BECERRA, SECRETARY, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,

Defendants - Appellants,

v.

DANCO LABORATORIES, L.L.C.,

Intervenor - Appellant.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS

BRIEF OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, ADVANCED MEDICAL TECHNOLOGY ASSOCIATION, CONSUMER HEALTHCARE PRODUCTS ASSOCIATION & NATIONAL ASSOCIATION OF MANUFACTURERS AS *AMICI CURIAE* IN SUPPORT OF DEFENDANTS-APPELLANTS AND INTERVENOR-APPELLANT

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SUPPLEMENTAL CERTIFICATE OF INTERESTED PERSONS

No. 23-10362, *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*.

Under Fifth Circuit Rule 29.2, the undersigned counsel of record for *amici curiae* certifies that the following listed persons and entities, in addition to those listed in the Defendants-Appellants' and Intervenor-Appellant's Certificate of Interested Persons, have an interest in this brief. These representations are made in order that judges of this Court may evaluate possible disqualification or recusal:

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Advanced Medical Technology Association
Consumer Healthcare Products Association
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INTEREST OF *AMICI CURIAE*[1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA"), Advanced Medical Technology Association ("AdvaMed"), Consumer Healthcare Products Association ("CHPA"), and National Association of Manufacturers ("NAM") submit this brief as *amici curiae* in support of Defendants-Appellants and Intervenor-Appellant. *Amici* share a significant interest in protecting against disruptions to the stable and predictable statutory framework Congress created to govern drug approvals by the Food and Drug Administration ("FDA"). The framework Congress established in the Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717 ("FDCA") is thorough and rigorous, thereby assuring patients, healthcare providers, drug and device developers, and drug and device manufacturers that the drugs approved for market by FDA are safe and effective for their intended uses. *Amici* demonstrate how the district court's overriding of Congress's statutory framework would severely disrupt industry and stifle innovation in drug development.

[1] No party's counsel authored any portion of this brief. No person other than *amici curiae*, its members, and its counsel contributed any money to fund the preparation or submission of this brief. Plaintiffs-Appellees, Defendants-Appellants, and Intervenor-Appellant have consented to the filing of this brief.

PhRMA is a voluntary, non-profit association representing the Nation's leading pharmaceutical and biotechnology companies.[2] Every day, PhRMA members strive to produce cutting-edge medicines, medical treatments, and vaccines that save, extend, and improve the lives of countless Americans. PhRMA members have invested more than $1.1 trillion since 2000 in the search for new treatments and cures, including $102.3 billion in 2021 alone. PhRMA, *Research and Development*.[3] Although a return on these substantial investments is never guaranteed because of the risks inherent in scientific innovation and discovery, the reliability and rigor of FDA's drug approval process makes that risk tolerable. PhRMA members have a significant interest in protecting against disruptions to their members' considerable investments in drug development, such as the district court's unprecedented assault on FDA's science-based judgments here.

AdvaMed is the world's largest medical technology association, with more than 400 member companies that develop medical devices, diagnostic tools, and health information systems. Its members span every field of medical science and range from cutting-edge startups to multinational manufacturers, all dedicated to advancing clinician and patient access to safe, effective medical technologies in accordance with the highest ethical standards. The innovations created by

[2] PhRMA's members are listed at https://phrma.org/About (last visited Apr. 29, 2023).

[3] https://perma.cc/QFF7-3U7Z (last visited Apr. 29, 2023).

AdvaMed's members advance efficiency in health care through earlier disease detection and more effective treatments which, in turn, reduce the economic burden of disease and allow people to live longer, healthier, and more productive lives. Respecting the FDA decision making process is paramount to medtech's ability to innovate and develop the best tools to diagnose and treat patients. AdvaMed and its member companies join this brief primarily to highlight their support for the arguments set forth in Section I, *infra*. All medical devices used in the United States are regulated by FDA in a two-part process. First, a medical device is grouped into one of three classes depending on its risk profile. Second, the device's risk profile is used to determine what review process and controls are needed to provide a reasonable assurance of safety and effectiveness. Both determinations require FDA to make fact-intensive and technical inquiries. To do this, FDA relies heavily on its experts to provide professional advice on the various complex scientific, technical, and policy issues that arise in this process. Undermining FDA's decision making process would create uncertainty for medical device manufacturers and ultimately stifle innovation to the detriment of patients.

CHPA is a nonprofit association representing manufacturers of over-the-counter medicines, dietary supplements, and consumer medical devices. CHPA works to empower self-care by preserving and expanding choice and availability of consumer healthcare products. One of the processes for over-the-counter medicines

to come to market is the same rigorous process that applies to new prescription drugs: The new drug approval process created by Congress in the FDCA. Over-the-counter medicines with new ingredients or indications made available to Americans over the past 30-plus years have been introduced through this process. As such, CHPA members have a significant interest in protecting against disruptions in development and approval of over-the-counter medicines under the New Drug Approval framework.

NAM is the largest manufacturing association in the United States, representing small and large manufacturers in all 50 states and in every industrial sector, including in the biopharmaceutical industry. Manufacturing employs nearly 13 million men and women, contributes $2.9 trillion to the United States economy annually, has the largest economic impact of any major sector, and accounts for over half of all private-sector research and development in the nation. NAM is the voice of the manufacturing community and the leading advocate for a policy agenda that helps manufacturers compete in the global economy and create jobs across the United States. NAM has a strong interest in the predictability and integrity of the regulatory process to ensure that all its members, including its biopharmaceutical members, can rely on regulatory approvals of their products when they have been properly undertaken.

INTRODUCTION & SUMMARY OF ARGUMENT

Congress vested FDA with the authority to evaluate a drug's safety and effectiveness using science-based evidence to determine whether it can be marketed in this country for its intended use. For decades, biopharmaceutical companies, healthcare providers, patients, and other stakeholders have relied on FDA's scientific judgments to develop and utilize innovative new drugs. The district court's order strikes a severe blow to Congress's regulatory framework and the investments that hinge upon it, for two significant reasons:

First, the district court's order cannot be reconciled with FDA's mandate from Congress. The district court erred by replacing FDA's scientific judgments with its own views on what information should be considered and how it should be assessed. The district court compounded those errors by imposing its own extra-statutory requirements—including that approved-use conditions align with clinical trial conditions; that modifications to Risk Evaluation and Mitigation Strategies ("REMS") be based on a controlled study; and that extra adverse event reporting be mandated before a REMS can be modified. But Congress clearly opted not to impose these requirements, and for good reason: They are contrary to well-understood scientific methods and FDA's correct exercise of its expertise.

Second, the extraordinary action and invalid reasoning by the court below risks stifling pharmaceutical innovation by disrupting industry's reasonable

investment-backed expectations. FDA's approval process is rigorous and thorough, and pharmaceutical companies invest billions of dollars in research and development to meet scientific standards. But if every FDA drug approval decision is subject to an appreciable risk of being invalidated by a court based on judicially created requirements that are contrary to the statutory framework, biopharmaceutical companies will invest less in the advancement of new medicines and will be less likely to take risks that could benefit patients. The district court's standing ruling makes that all the more probable. Under the court's reasoning, any healthcare provider could bring suit to challenge any drug approval at any time. The court's remedy also denies the holder of a drug application the notice and hearing that Congress required as part of any suspension or withdrawal of an FDA drug approval. In short, the district court's ruling is deeply flawed and would jeopardize biopharmaceutical innovation.

ARGUMENT

I. The District Court Order Cannot Be Reconciled with the Authority Congress Vested in FDA to Approve and Regulate Drugs Marketed in This Country.

Congress charged FDA with the responsibility of serving as the Nation's expert for evaluating the safety and efficacy of drugs that are allowed to be marketed in this country. Congress specified a complex and thorough framework within which the agency must operate. That statutory framework requires that FDA

exercise expertise in evaluating and regulating drugs by, among other things: analyzing the significant amounts of information nongovernmental stakeholders are required to submit about a drug's safety and effectiveness; consulting with science experts both outside the government, as well as within other parts of the government; and considering submissions from the public. The district court's order cannot be reconciled with this statutory framework because the court displaced FDA's expertise rather than reviewing it under the appropriate arbitrary and capricious standard. Worse yet, the district court supplanted FDA's science-backed conclusions based on inaccurate descriptions of relevant information and misapplications of pertinent scientific studies.

A. Congress Directed FDA to Exercise Its Expertise and Make Science-Based Safety and Effectiveness Decisions.

Congress directed FDA to regulate "drug[s]," broadly defined to include "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals . . . [or] intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. § 321(g)(1); *see also* FDCA, 52 Stat. at 1041. FDA's "[m]ission" is to "protect the public health by ensuring that . . . drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B).

The Supreme Court has repeatedly recognized the significant authority, and indeed responsibility, that FDA bears at the instruction of Congress. The Court has emphasized that it is FDA's "objective" to "ensure that any product regulated" is

"'safe' and 'effective' for its intended use." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). Indeed, that "essential purpose" pervades Congress's commands to FDA in the Food, Drug, and Cosmetic Act, 21 U.S.C. § 355, *et. seq.* *Id.*

Congress required that FDA approve a drug before it can be "introduce[d] or deliver[ed] for introduction into interstate commerce." 21 U.S.C. § 355(a), (d). FDA's approval must be based on a demonstration that the new drug is safe and effective for its approved uses. And FDA's process for that approval determination is lengthy and rigorous.

A pharmaceutical company must generally conduct a series of laboratory studies not involving human testing to begin to test how a proposed medicine works, assess its safety, and demonstrate that "it is reasonably safe to conduct the proposed clinical investigations." *See* 21 C.F.R. § 312.23(a)(8). If the results of such studies are promising, the company submits an investigational New Drug Application to FDA that outlines those results and offers a plan for multiple phases of clinical trials in humans. *See* 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). The company then typically conducts three phases of clinical trials and, upon their completion, seeks FDA drug approval by submitting a New Drug Application and thus becomes the holder of that drug application. *See* 21 C.F.R. § 312.21. The New Drug Application often exceeds 100,000 pages in length and must include (among other

things) "full reports of investigations which have been made to show whether such drug is safe for use and whether such drug is effective in use," and "a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug." 21 U.S.C. § 355(b)(1)(A).

At the end of this extensive process, FDA is allowed by Congress to approve a New Drug Application only if FDA finds that "none" of seven specified "grounds for denying approval" applies. *See id.* § 355(c)(1)(A), (d). FDA must conclude that a drug is safe, and that the drug is effective based on "substantial evidence"—*i.e.*, "evidence consisting of adequate and well-controlled investigations, including clinical investigations." *Id.* § 355(d); *see also Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613 (1973) (FDA must "refuse approval" of a New Drug Application "if 'substantial evidence' that the drug is effective for its intended use is lacking").

Congress made clear that FDA is the scientific expert when it comes to evaluating the safety and efficacy of drugs that are marketed in this country. With regard to scientific expertise on drug approval decisions, the agency is tasked with "promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products." 21 U.S.C. § 393(b)(1). FDA must grow and develop its expertise through "consultation with experts in science, medicine, and public health." *Id.* § 393(b)(4). Congress further specified that FDA is to

"establish such technical and scientific review groups as are needed to carry out the functions of the Administration." *Id.* § 393(e). FDA's scientific expertise carries over to the specific context of new drug approvals. For instance, FDA officials review applications in accordance with mandatory guidance that is required by statute to ensure "technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards." *Id.* § 355(b)(5)(A).

Many courts and jurists have recognized over the years that "[a] court is ill-equipped to second-guess" FDA's "scientific judgment" under the guise of the Administrative Procedure Act's arbitrary and capricious standard. *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 927 (D.C. Cir. 2013) (Kavanaugh, J.). Indeed, "courts owe significant deference to the politically accountable entities with the 'background, competence, and expertise to assess public health.'" *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578, 578–79 (2021) (Roberts, C.J., concurring in grant of application for stay).

B. The District Court Improperly Replaced FDA's Expert Scientific Judgment with Inaccurate Assessments of Studies and Anecdotes.

The district court failed to adhere to the statutory structure Congress established. Congress provided that one expert agency—FDA—is charged with making safety and effectiveness determinations about drugs that can be marketed by applying its specialized knowledge in the fields of medicine, pharmacology, epidemiology, statistics, pharmacy, and toxicology, among others. But the district

court assumed that role for itself, rather than applying the appropriate arbitrary-and-capricious standard. At nearly every turn, the district court stepped into FDA's shoes and displaced the agency's expert scientific judgments, in excess of the court's role. And the court did so without the scientific expertise of the agency, without the administrative record that was before the agency, and without FDA's review of additional materials that post-dated FDA's approval decisions and were submitted to the court during this litigation.

First, the district court supplanted FDA's comprehensive safety analysis with an inaccurate, over-simplified view of data regarding the drug at issue. FDA had made its approval determination based on eleven different studies, containing data "on well over 30,000 patients." ROA.2192, 2201 (CDER, *Clinical Review* (Mar. 29, 2016)). The district court, by contrast, addressed only a handful of studies and articles, including some that were not submitted to FDA. *See* ROA.4351–52. The district court wholly disregarded studies that support FDA's safety determination. *See, e.g.*, ROA.2192–2201 (CDER, *Clinical Review* (Mar. 29, 2016)).

Second, the district court erroneously evaluated the reliability of clinical studies that informed FDA's approval decision. For example, the district court ignored two studies on the basis that another trial "was larger" than the other two combined "and is therefore the more reliable study." ROA.4355 n.47. But it is well-established in the scientific community that a larger study is not necessarily more

reliable by virtue of its size. *See, e.g.*, Aaron Cypess, M.D., Ph.D., M.M.Sc., National Institutes of Health, *Understanding Study Size* (July 2, 2019) ("It is a common misconception that the larger a clinical trial, the better the study is and the more important the results.").[4] Moreover, the existence of a larger study does not justify disregarding smaller studies. *See* 21 C.F.R. § 314.50 (requiring *all* clinical studies to be submitted as part of a New Drug Application).

Third, the district court drew sweeping conclusions about medical science based on pure anecdote. For example, in one instance, the district court opined on "error in FDA's judgments" by pointing to a handful of "stories." ROA.4358. But it is well-established that anecdotes are at the bottom of the hierarchy of reliable information for scientific consideration and are not sufficient to establish a drug's safety or effectiveness. *See, e.g.*, 21 C.F.R. § 314.126(e) ("[i]solated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered" as bases for the approval of effectiveness claims). FDA has the scientific expertise necessary to assess these anecdotes appropriately in their proper context.

These fundamental missteps highlight the need for FDA's expertise to navigate the complexities associated with a drug product's safety and efficacy

[4] https://perma.cc/U7P9-6HXY.

evaluation. The district court's displacement of FDA's conclusions based on its own assessment undermines the statutory structure established by Congress.

C. The District Court Incorrectly Invalidated FDA's Drug Approval and FDA-Approved REMS Based on Mischaracterizations of Statutory Requirements.

The district court's invalidation of FDA actions is based on multiple misunderstandings of the governing statutory framework. Its judgment cannot be reconciled with Congress's directives to FDA.

1. Congress Did Not Require the Exact Alignment Between Clinical Trial Conditions and Approved-Use Conditions That the District Court Effectively Imposed.

Congress did not require exact alignment between the conditions that are in place for a clinical trial that *tests* the safety and effectiveness of a drug and the ultimate conditions of *use* that are included in the labeling FDA approves for marketing.

Congress provided that the application required to be submitted to FDA to seek approval of a new drug must include "adequate tests . . . to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 312.21(c) (clinical trials must "provide an adequate basis for physician labeling"). The district court, however, specifically faulted FDA for failing to include on the labeling several conditions that were in effect during the clinical trials, such as

geographic proximity to emergency facilities. In other words, contrary to the correct statutory standard, the district court effectively required an exact alignment between testing conditions and approved-use conditions. *See, e.g.*, ROA.4355 (faulting FDA for failing to include various clinical trial conditions in its 2000 drug approval).

The district court's incorrect legal analysis also does not make sense as a scientific or regulatory matter. For multiple reasons, clinical trial conditions are nearly always more restrictive than the conditions applicable to the approved use.

To start with the most obvious, when a drug is administered in the context of a pre-approval clinical trial, the drug has not yet been determined to be safe and effective. The whole point of late-stage clinical trials is to generate "information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling." *See, e.g.*, 21 C.F.R § 312.21(c). That means that additional safeguards may be appropriate in certain instances during clinical development but are no longer appropriate after the drug's safety and effectiveness have been established. As a result, maintaining such unnecessary conditions on the approved use would be unduly restrictive and unnecessarily burdensome. FDA has explained that, "[w]hen there are limited data on the safety of the investigational drug (i.e., early in development), it is especially important that an extensive array of clinical and laboratory assessments be performed frequently," *but* "[a]s safety data accumulate,

the nature and extent of safety monitoring should be adjusted accordingly." FDA, *Good Review Practice: Clinical Review of Investigational New Drug Applications* at 84 (Dec. 2013).[5]

In addition, testing conditions and approved-use conditions differ because clinical trials are designed to answer specific scientific questions, and so typically include conditions that are intended to control for variability or otherwise improve the quality of the data produced. For example, clinical trials may include procedures to ensure adherence by the patients to the dosing regimen. *See id.* at 35. This can include directly observing administration of the drug to patients, pill counts at each visit, blood testing for levels of the drug, or other measures to verify that the patient receives the intended dose of the drug being tested. *See id.* The use of such conditions in a clinical trial does not imply that the same procedures are appropriate in practice after drug approval. Such requirements may be overly restrictive in the post-approval context, where the treatment of patients is the primary aim, and approved labeling addresses information for safe and effective use. Once a drug has been FDA-approved, continuing to apply a full panoply of clinical trial restrictions could unduly burden the healthcare system and improperly intrude on decisions that are appropriately left to a healthcare provider's clinical judgment in the context of the provider-patient relationship.

[5] https://perma.cc/N43W-T73K.

2. Congress Did Not Require REMS Modifications to Be Premised on Controlled Studies as the District Court Did.

In 2008, Congress gave FDA statutory authority over drug safety programs known as REMS as a means of providing that the benefits of the drug outweigh its risks. *See* 21 U.S.C. § 355-1. REMS focus on preventing and managing risks associated with a drug, including by providing information to providers and patients, and by reinforcing particular practices among providers and patients. *See* FDA, *Risk Evaluation and Mitigation Strategies* (Dec. 17, 2021).[6] FDA has approved more than 300 REMS since 2008 and has made more than 800 modifications to REMS. FDA, *REMS Public Data* ("Total REMS" and "Modifications" tabs).[7]

Congress specified the circumstances under which FDA can modify REMS. Specifically, the statute provides that REMS may be modified "[o]n initiative" of either the holder of the drug application or FDA. 21 U.S.C. § 355-1(g)(4). The drug application holder may propose a REMS modification based on an "adequate rationale" that supports the proposed modification. *Id.* And FDA may modify a REMS based on a determination that the modification is appropriate, including to "ensure the benefits of the drug outweigh the risks of the drug," or to "minimize the burden on the health care delivery system of complying with the [REMS]." *Id.*

[6] https://perma.cc/CQK5-ZAJM.

[7] https://fis.fda.gov/sense/app/ca606d81-3f9b-4480-9e47-8a8649da6470/sheet/ef8079fb-65dd-4fe7-b469-6653cfbc1646/state/analysis (last visited Apr. 29, 2023).

§ 355-1(g)(4)(B)(i), (ii). FDA can evaluate a proposed modification based on a number of factors, including how the modification would impact relevant risks, patient access to the drug, and the burdens on the health care delivery system. *See* FDA, *Guidance for Industry, Risk Evaluation and Mitigation Strategies: Modifications and Revisions* at 12 (June 2020 Rev. 2).[8]

Indeed, the statutory requirements for assessments of REMS, and FDA's implementation of those requirements, demonstrate that a REMS is intended to be subject to modification. A variety of metrics, data sources, and methodologies are appropriate to inform potential modifications to a REMS. The holder of the drug application is required to submit periodic assessments of the REMS for its drug to FDA on a timetable specified in the statute. 21 U.S.C. § 355-1(c), (d). That is in addition to requirements that the drug application holder submit a REMS assessment to FDA in certain other circumstances, including: when it submits a supplemental application for a new indication; when required by the REMS itself; and when FDA determines that an assessment of the REMS is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the strategy. *Id.* § 355-1(g)(2).

[8] https://perma.cc/R42Y-7WUT.

Congress did not require FDA to cite a controlled study that incorporates all of the proposed REMS changes in order to justify a modification of a REMS. But the district court invalidated the 2016 REMS for failure to meet that non-existent requirement. The district court ruled the 2016 REMS modifications were invalid because "[n]one of the studies" on which FDA relied "compared the safety of the changes against the then-current regimen." ROA.4365; *see also* Order Granting in Part Mot. for Stay at 35 (ECF No. 183-2) (panel reviewing stay application on emergency basis recognized "FDA studied the safety consequences" of the elements of the 2016 REMS modifications, but faulted FDA for citing "zero studies that evaluated the safety-and-effectiveness consequences of the 2016 Major REMS Changes *as a whole*").

Requiring a controlled study before FDA modifies a REMS would have significant negative ramifications. As noted above, FDA has made more than 800 modifications to REMS since Congress established REMS authority in 2008. *See* n.7, *supra*. But under the district court's approach, FDA could no longer make these important modifications without requiring drug application holders to conduct expensive, lengthy, resource-intensive and time-intensive controlled studies. If controlled studies were required, there would likely be a serious decline in the number of REMS modifications because such studies can be expensive to design and can face difficulties recruiting patients to participate. These realities would

discourage drug application holders from pursuing such modifications. This outcome would be bad for healthcare providers and patients because various medications would be subject to unnecessary REMS restrictions, despite removal of the restriction being consistent with the statute and with FDA's expert judgment. Furthermore, requiring controlled studies would impose a significant and unnecessary financial burden on pharmaceutical and biotechnology companies, and undermine incentives to pursue approval of products that would require REMS in the first place.

3. Congress Did Not Require the Additional Adverse Event Data Required by the District Court to Make a Safety Evaluation for the 2021 REMS Modification.

FDA's 2021 REMS modification of the drug at issue removed the requirement that the drug be dispensed in person by the healthcare provider who prescribed the medication, and allowed the prescription to be dispensed by pharmacies as medications generally are. FDA did so in part based on low rates of adverse events. *See* ROA.2100–01 (FDA Br. in Opp'n to Mot. for Prelim. Inj.); ROA.1784–85 (FDA Ltr. to Am. Coll. of Obstetricians et al. re Mifepristone REMS (Apr. 12, 2021)).

The district court held that the 2021 REMS modification was arbitrary and capricious, however, because FDA's earlier 2016 REMS modification had removed the requirement that healthcare providers report to the drug application holder any non-fatal "hospitalization, transfusion or other serious event" related to the drug.

Compare ROA.1680 (2011 REMS) *with* New Drug Application 020687 REMS (modified Mar. 2016) (2016 REMS).[9] In the district court's view, FDA's 2021 modification was "predetermined" because it relied on "a database designed to produce a null set" of adverse events. ROA.4344–45; *see also* Order Granting in Part Mot. for Stay at 35 (panel reviewing stay application on emergency basis criticizing FDA for eliminating non-fatal adverse event reporting requirement and making safety finding based on "the absence of non-fatal adverse-event reports").

That reasoning is deeply flawed.

The 2016 REMS modification applied to adverse-event reporting *only* by healthcare providers and *only* for non-fatal events. But wholly apart from the REMS, FDA receives adverse event reports from multiple sources, the same as it does for every FDA-approved drug that is not subject to a REMS.

Adverse event reporting responsibilities start with the holder of the drug application, which is often the drug manufacturer. Federal law *mandates* that the holder of the drug application report all adverse events to FDA. *See* 21 C.F.R. §§ 314.98, 314.80, 314.81. The holder of the drug application obtains adverse event reports directly and indirectly from many sources, including healthcare providers, patients, postmarketing clinical investigations, epidemiological/surveillance studies, scientific literature, and unpublished scientific papers. *See id.* § 314.80(b). Once an

[9] https://perma.cc/7EAW-HHWJ.

application holder has received an adverse event report, federal law *requires* it to "promptly review all adverse drug experience information obtained or otherwise received" and "develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA." *Id*.

If a drug application holder fails to make the mandated reports of adverse events to FDA, or even fails to maintain the appropriate records, FDA can withdraw approval of the drug application. *See id.* § 314.80(k). That would prohibit continued marketing of the drug product that is the subject of the application. In addition, the drug application holder has commercial incentives to report adverse event data to FDA to keep labeling up-to-date in case new side effects emerge or become more frequent.

And of course, stakeholders have a strong incentive to report adverse events to the application holder to improve patient healthcare. *See, e.g.*, Gerald J. Dal Pan et al., *Postmarketing Spontaneous Pharmacovigilance Reporting Systems, in Textbook of Pharmacoepidemiology* 115, 118 (3d ed. 2021). Indeed, to facilitate adverse event reporting, federal law generally requires that prescription drug product labeling include the following verbatim statement: "To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at (insert current FDA phone number and

Web address for voluntary reporting of adverse reactions)." 21 C.F.R. § 201.57(a)(11)(ii)

FDA maintains a database of adverse event reports ("FAERS"). *See, e.g.*, FDA, *Adverse Event Reporting System*, https://open.fda.gov/data/faers/ (last visited Apr. 29, 2023) (FAERS "is a database that contains information on adverse event and medication error reports submitted to FDA."). This hardly is the "null set" suggested by the district court.

In light of the above, it was not arbitrary or capricious for FDA to rely on low rates of adverse events when making a safety determination to modify the REMS in 2021. This Court should reject the district court's contrary conclusion, which could have significant implications for FDA and the industry as a whole. FDA has longstanding experience using the database for identifying new safety concerns that might be related to a marketed product and, where appropriate, taking regulatory action to improve product safety and protect the public health. There is no basis for the district court's contrary suggestions.

II. The District Court's Order Threatens to Stifle Pharmaceutical Innovation by Disrupting Industry's Investment-Backed Expectations and Reliance on the Stability of FDA's Scientific Judgments.

The biopharmaceutical industry relies on the stable drug evaluation and approval process that Congress imposed on FDA. Companies make decisions to invest in research and development of new medicines with the expectation that their

enormous financial investments will ultimately generate a return because the few drugs that receive FDA approval will have predictable access to a dependable market.

But if the district court's order is allowed to stand, FDA's approval decisions risk becoming mere precursors to litigation, not durable judgments that mark the culmination of a company's enormous investment in the product's lengthy scientific approval process. The district court's invalidation of an FDA drug approval for the first time based on the court supplanting the role of FDA threatens to disrupt the cycle of drug development and upend the investment-backed expectations of industry.

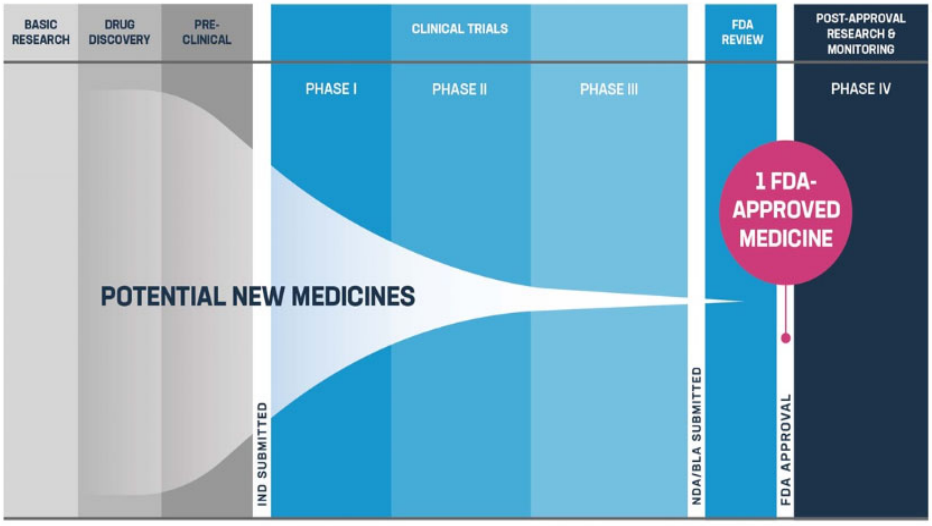
The district court's order also rests on legal errors related to standing and remedy that will further unsettle FDA approvals and the investments that hinge upon them.

A. The District Court's Unprecedented Invalidation of an FDA Drug Approval Jeopardizes Industry's Robust Investment in Research and Development.

The process of researching and developing new medicines is expensive and risky for pharmaceutical companies. From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion. *See* PhRMA, *Research & Development: Clinical Trials*.[10]

[10] https://perma.cc/EMP4-RQLY (last visited Apr. 29, 2023).

Moreover, pharmaceutical companies must invest heavily on developing drugs without knowing whether they will be ultimately approved by FDA. Just one out of every 5,000 to 10,000 compounds under development, and less than 12% of the candidate medicines that make it into Phase 1 clinical trials, are approved by FDA as meeting its safety and effectiveness standards. *See id.* Although hundreds of thousands of compounds are initially investigated as potential drugs, and hundreds proceed to clinical trials, FDA has approved an average of only 38 drugs annually between 2010 and 2019 (which was an increase over the previous decade). *See* Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* at 1 (Apr. 2021) ("CBO Report").[11] This winnowing process is illustrated by the graphic below:



Given the protracted nature of the FDA evaluation and approval process, pharmaceutical companies make extraordinary investments in research and

[11] https://perma.cc/2NTL-PHJ2.

development. For example, since 2000, PhRMA member companies have invested more than $1.1 trillion in the development of new treatments and cures, including $102.3 billion in 2021 alone. *See* PhRMA, *Annual Membership Survey* at 3 tbl. 1 (2022).[12]

Indeed, the biopharmaceutical sector is the most R&D-intensive industry in the Nation's economy. Over the past ten years, PhRMA's member companies have spent an average of approximately 21% to 25% of their domestic sales revenue on research and development. *See id.* at 4, tbl. 2. By contrast, that same figure across all other industries "typically ranges between 2 percent and 3 percent." CBO Report at 3. Even other investment-dependent enterprises—like software and semiconductor companies—spend significantly less than biopharmaceutical companies as a proportion of sales. *See id.*

Biopharmaceutical companies make these investments in scientific research and development against the backdrop of FDA's scientifically based and predictable regulatory process. Biopharmaceutical companies make investment decisions based on the reasonable expectation—grounded in the exclusive regulatory authority Congress has conferred on FDA—that once a drug product is finally approved by FDA, absent exigent circumstances, it will be lawful and potentially profitable to market that product for an extended period anywhere in the United States. Without

[12] https://perma.cc/R4S2-KE79.

that assurance, the incentive to innovate diminishes. The reason is simple. If every FDA drug approval decision is subject to an appreciable risk of being upended by a court based on flawed assessments of studies, reliance on anecdotes, and judicially added requirements, biopharmaceutical companies could have dramatically lower anticipated revenues from an approved drug and thus decide to invest less in the advancement of new medicines. *See* CBO Report at 1 (explaining that investment amounts are a function of anticipated revenues).

In such an uncertain legal landscape that runs counter to the authority Congress gave FDA, there would be even "fewer new drugs, because there would be less incentive for companies to spend on [research and development]." *Id.* at 12. That would be to the detriment of both patients and industry.

B. The District Court's Legal Errors on Standing and Remedy Risk Further Unsettling Industry's Investment-Backed Expectations.

The district court unsettled the statutory scheme by invalidating an FDA drug approval and REMS modifications based on a flawed understanding of FDA's scientific processes and the approval framework created by Congress. Additionally, the district court made key legal errors that invite further unwarranted court challenges to FDA's approval process. If left uncorrected, these errors would undermine the stability of FDA's approval determinations going forward.

1. The Standing Theory of Plaintiff-Physicians in This Case Would Risk a Proliferation of Unwarranted Challenges to FDA Drug Approvals and FDA-Approved REMS.

The plaintiff-physicians in this case assert an overly broad, generalized, multi-step theory of future harm that heaps speculation upon speculation, contrary to the requirements of Article III. The district court's acceptance of that as one of its bases for finding standing of plaintiff-associations is particularly problematic. Judicial recognition of such a boundless basis for standing risks limitless and meritless court challenges to drugs that have been approved as safe and effective through the comprehensive and rigorous process Congress requires of FDA.

The Supreme Court has made clear that to establish standing based on the threat of future injuries under Article III, the alleged injuries must be "certainly impending," *Clapper v. Amnesty Int'l USA*, 568 U.S. 398, 401 (2013), such that there is "a real and immediate threat" of future harm, *City of Los Angeles v. Lyons*, 461 U.S. 95, 105 (1983). But here, plaintiffs impermissibly relied on an "attenuated chain of possibilities," *Clapper*, 568 U.S. at 401, all of which are "depend[ent] on the unfettered choices made by independent actors not before the courts," *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 562 (1992).

The plaintiff-physicians' theory falls far short of the Article III requirement: First, some unspecified, non-plaintiff healthcare provider might write a prescription for a patient. Second, the patient experiences a rare side effect after taking the drug

as prescribed. Third, the patient does not go back to the treating healthcare provider for treatment related to the side effect, but instead goes to a different healthcare provider. Fourth, the new plaintiff-physician's provision of that medical care—or even just a related issue, such as an increased workload—somehow becomes cognizable harm to the physician.

The view that the plaintiff-physician in this scenario has standing to challenge FDA approval of the drug that was prescribed by the other healthcare provider that resulted in an unusual side effect for a patient that the plaintiff-physician happened to treat is beyond the pale. This sequence of events is wholly speculative and any alleged added burden involving the plaintiff-physician is much too removed from FDA's approval of the drug. It does not satisfy Article III. *See Clapper*, 568 U.S. at 401. If carried to its logical conclusion, any treating physician could have standing to challenge any FDA-approved drug based on any treatment by a physician of a patient with a drug side effect notwithstanding that such treatment is inherent in the practice of medicine. That would be to the great detriment of the Nation's healthcare system—including biopharmaceutical innovation—and the patients who rely on it.

2. The District Court's Creation of a Remedy That Retroactively Stayed the FDA's 2000 Drug Approval Circumvents the Process Created by Congress for FDA Withdrawal or Suspension of an Approved Drug.

The district court's substantive scientific and legal errors were compounded by its remedy. The court took the extraordinary step of retroactively staying a 23-

year-old drug approval. That order is contrary to Congress's detailed process for withdrawal or suspension of an FDA drug approval.

Congress vested FDA with the exclusive authority to withdraw FDA approval of a drug if it finds that "experience," "tests," or "scientific data," or other "new evidence" shows that the drug "is unsafe for use under the conditions" for which it was approved. 21 U.S.C. § 355(e). FDA must provide the holder of the drug application "due notice and opportunity for hearing." *Id.* FDA has authority to suspend a drug approval "immediately" if it makes a series of findings that show "there is an imminent hazard to the public health." *Id.* But FDA must still provide the drug application holder in such circumstances with the opportunity for an expedited hearing, albeit post-suspension. *Id.* The district court's retroactive stay of the 23-year-old drug approval under 5 U.S.C. § 705, a provision directed at "postpon[ing]" an effective date of agency action pending judicial review, violated the statutory rights of the drug application holder to such process. Such retroactive stays deprive drug application holders of their property interests without proper notice or a hearing.

CONCLUSION

For the reasons set forth above and in the Defendants-Appellants' and Intervenor-Appellant's briefing, the Court should reverse.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I, Beth S. Brinkmann, hereby certify that this brief complies with the type-volume limitations of Fed. R. App. P. 29(a)(5) and Fed. R. App. P. 32(a)(7)(B)(i) because this brief contains 6,397 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(f); and this brief 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 brief has been prepared in a proportionally spaced typeface using Microsoft Office Word 2016 in 14-point, Times New Roman font.

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