Nos. 22A902

IN THE

Supreme Court of the United States

U.S. FOOD & 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, et al.,

Applicants,

v.

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.,

Respondents.

To the Honorable Samuel Anthony Alito, Jr.,
Associate Justice of the United States Supreme Court and
Circuit Justice for the Fifth Circuit

BRIEF OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS AMICUS CURIAE IN SUPPORT OF APPLICANTS

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INTERESTS OF AMICUS CURIAE

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, non-profit association representing the Nation's leading pharmaceutical and biotechnology companies.[1] 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 nearly $1.1 trillion since 2000 in the search for new treatments and cures, including $102.3 billion in 2021 alone. *See* PhRMA, *Research and Development*, https://phrma.org/policy-issues/Research-and-Development-Policy-Framework (last visited Apr. 13, 2023). A return on these substantial investments is never guaranteed because of the risks inherent in scientific innovation and discovery, but a critical premise is the reliability and rigor of the drug approval process in this country.

The United States' biopharmaceutical industry is the world leader in the development of new medications, due in no small part to the stability that Congress cultivated through the framework it created in the Federal Food, Drug, and Cosmetic Act ("FDCA"). The rigorous statutory scheme assures patients, healthcare providers, and drug developers that the drugs approved by the Food and Drug Administration ("FDA") are safe and effective, and therefore worthy of substantial financial

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[1] Pursuant to Rule 37.6, *amicus curiae* affirms that no party's counsel authored this brief in whole or in part, and that no person other than *amicus curiae*, its members, or its counsel made any monetary contribution intended to fund the preparation or submission of this brief. A complete list of PhRMA members is available at http://www.phrma.org/about/members (last visited Apr. 13, 2023).

investment. FDA brings extensive scientific expertise to bear in approving prescription medicines with labeling and other conditions to ensure their safe use.

PhRMA members have a significant interest in maintenance of the status quo during the resolution of the pending appeal, in order to protect against disruptions to the significant investments in drug development. The district court's analysis threatens to derail the development and approval of new drugs because it departs from the statutory framework created by Congress for FDA's drug approval process, and is an unprecedented assault on FDA's approval decisions.

INTRODUCTION AND SUMMARY OF ARGUMENT

Congress made clear that FDA is the expert when it comes to evaluating the safety and efficacy of drugs. For decades, biopharmaceutical companies, healthcare providers, patients, and other stakeholders have relied on FDA's expert judgments on drug approval, labeling, and post-approval marketing requirements. Indeed, biopharmaceutical companies invest tens of billions of dollars every year against the regulatory backdrop that Congress established. They reasonably expect that when a drug becomes one of the tiny few that receives FDA's stamp of approval—at the tail end of a process that typically stretches over a decade or more and involves multiple stages of preclinical and clinical trials—absent exigent circumstances, the drug will be marketable for a period that justifies the sizeable investment. Of course, companies and the public fully expect that the risk-benefit analysis of the product will continue to be evaluated, monitored, and assessed by the company and FDA throughout its lifecycle.

The rulings below strike a severe blow to this settled regulatory framework, and the investments that hinge upon it. Indeed, the district court's ruling one week ago marked the first time in the agency's nearly century-long history that any court had nullified an FDA approval by second-guessing a safety-and-effectiveness determination. The fact that the district court did so in the context of a preliminary injunction, without the benefit of an administrative record, and without even affording FDA an opportunity to address in a remand the purported deficiencies in its approval decision, all serve to underline the truly unprecedented character of the court's decision.

No doubt, the Fifth Circuit was correct in ordering a stay of the district court's ruling as to FDA's 2000 approval decision.

But the Fifth Circuit did not go far enough because it refused to stay the whole of the district court's ruling, which also invalidated FDA's modifications of the Risk Evaluation and Mitigation Strategies ("REMS"), *see* 21 U.S.C. § 355-1, that FDA approved for the drug at issue. The court of appeals also committed several errors of its own. Various of those errors could bring consequences for the biopharmaceutical industry that are adverse and potentially severe. PhRMA submits this *amicus* brief to address three of the most significant errors.

First, the court of appeals faulted FDA for failing to rely on a controlled study when it modified the REMS requirements in 2016. But when Congress enacted the FDCA, it included no controlled study requirement for REMS modifications. Instead, Congress provided that FDA may require a REMS modification based on any number

of factors—for example, to "minimize the burden on the health care delivery system." 21 U.S.C. § 355-1(g)(4)(B)(i). The court of appeals' ruling contravened the REMS framework in the statute, and the court of appeals' rationale would ultimately undermine the public interest by impeding access to medication for patients.

Second, the court of appeals criticized FDA for making a safety-related determination in 2021 based on the absence of non-fatal adverse event reports. The court of appeals took issue with this determination because the FDA had in 2016 removed the requirement that healthcare providers make those reports to the holder of the drug application. But the court of appeals ignored the fact that FDA maintains an adverse event reporting database that contains adverse event reports from *multiple* different sources—including mandatory non-fatal and fatal adverse event reports from holders of drug applications, as well as such reports submitted regularly and voluntarily by healthcare professionals and patients to further the safety of patient care. It was therefore quite reasonable for FDA to make a safety determination based on data in the adverse event reporting database.

Third, the court of appeals endorsed a sweeping theory of standing that would potentially invite limitless court challenges to FDA-approved drugs based on the mere possibility of future purported harms that are commonplace in the medical field. In particular, plaintiff-physicians assert standing based on the speculative assumption that they will at some point in the future treat a patient for complications related to the drug at issue. To say the least, that theory fails to meet Article III because it is highly "attenuated," *Clapper v. Amnesty Int'l USA*, 568 U.S. 398, 401

(2013), and reliant on "choices made by independent actors not before the courts," *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 562 (1992). And it is also problematic because it would disrupt the stability of the Nation's market for medical treatment—threatening to allow limitless litigation aimed at overturning FDA's expert drug approval decisions. That prospect of expansive litigation would undermine incentives for the biopharmaceutical industry's investments in drug discovery and development.

In light of these errors, Applicants are likely to succeed on the merits of their case. This Court should grant the application and maintain the status quo in order to preserve the settled regulatory framework that Congress established for determining the safety and effectiveness of medicines, pre- and post-approval.

ARGUMENT

I. Congress Vested FDA with Authority to Make Safety and Effectiveness Determinations that Rely on the Expertise of the Agency, Extensive Input from Other Stakeholders, and a Thorough and Rigorous Process.

Congress granted FDA the authority 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). "Viewing the FDCA as a whole, it is evident that one of the Act's core objectives is to ensure that any product regulated by the FDA is 'safe' and 'effective' for its intended use." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2020). Indeed, that "essential purpose pervades the FDCA." *Id.* 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 FDCA requires premarket approval demonstrating that any new drug is safe and effective for its intended uses before it may be "introduce[d] or deliver[ed] for introduction into interstate commerce." 21 U.S.C. § 355(a), (d). That approval process—which is necessary to bring a new medicine to market—is lengthy, rigorous, and expensive. Before studying a new medicine in humans, a pharmaceutical company must generally conduct a series of nonclinical studies to begin to test how the medicine works and assess its safety. *See* 21 C.F.R. § 312.23(a)(8). If the results are promising, the company submits an investigational new drug application ("IND") to FDA that outlines the preclinical study 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). Under one or more INDs, the company then typically conducts three phases of clinical trials, each of which must be completed successfully before the potential new medicine may undergo FDA review and approval. *See* 21 C.F.R. § 312.21. If clinical trial results show that the medicine's benefits outweigh its risks, the sponsoring company can seek FDA's approval to market the medicine by submitting a new drug application ("NDA"). The NDA 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 may approve a new drug application only after finding that "none" of seven specified "grounds for denying approval"

applies. *See id.* § 355(c)(1)(A), (d). FDA must conclude both that a drug is safe and that it 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 an NDA . . . if 'substantial evidence' that the drug is effective for its intended use is lacking").

The FDCA contains detailed processes for withdrawing or suspending FDA approval. *See* 21 U.S.C. § 355(e). For example, "if the Secretary finds" that "experience," "tests," or "scientific data," or other "new evidence" shows that an approved drug "is unsafe for use under the conditions" upon which it was approved, the Secretary "shall" withdraw approval after providing the holder of the drug application "due notice and opportunity for hearing." *Id.* The Secretary "shall" also withdraw approval after notice and opportunity for a hearing if there is a "lack of substantial evidence that the drug will have the effect" it claims it will have. *Id.* If the Secretary "finds that there is an imminent hazard to the public health," the Secretary "may suspend the approval of such application immediately." *Id.*

The statute makes clear that FDA is the scientific *expert* when it comes to evaluating the safety and efficacy of drugs. That does not mean that Congress recognized any particular agency expertise on issues of law or statutory interpretation, or that PhRMA and its members necessarily agree with FDA on all such issues. But 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), and the Health and Human Services Secretary must "implement programs and policies that will foster collaboration between the [FDA], the National Institutes of Health, and *other science-based* Federal agencies," *id.* § 393(c) (emphasis added). The statute further authorizes FDA 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 ensures "technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards." *Id.* § 355(b)(5)(A).

Congress vested FDA with authority to impose a REMS on a drug in certain circumstances as part of its approval, and to modify a REMS as well. *See* 21 U.S.C. § 355-1. A REMS is a safety program that FDA is authorized to define and require for a particular medication. *Id.* A REMS is included so that the risks of the medication can be further mitigated by the required strategies, and thus outweighed by the benefits. *Id.* Dozens of FDA-approved medications have a REMS.

II. Applicants are Likely to Succeed on the Merits Against Plaintiffs' Challenge to FDA's REMS Modifications.

Two errors are especially problematic in the court of appeals' refusal to stay the district court's invalidation of FDA's REMS modifications in 2016.[2] They demonstrate how the reasoning of the lower courts is critically flawed. Both errors are premised on an incorrect understanding of the REMS process created by Congress and FDA's adverse event reporting system. These errors, as well as the many other errors identified by the parties and other amici, demonstrate that Applicants are likely to succeed on the merits, and the district court was wrong in determining that FDA's modification of the REMs was arbitrary and capricious. Accordingly, the district court ruling on this issue should be stayed pending appeal.

First, the court of appeals concluded that FDA "failed to 'examine the relevant data' when it made the 2016 Major REMS changes." U.S. Stay Appl. App. 34a. According to the court, FDA had "eliminated REMS safeguards based on studies that *included those very safeguards*."[3] *Id.* The court also opined that FDA "relied on zero studies that evaluated the safety and effectiveness consequences of the 2016 REMS Changes *as a whole*." *Id.* at 34a-35a. But Congress did not require a controlled study

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[2] The court of appeals described these as follows: "FDA changed four of the 2000 Approval's REMS: (1) increased maximum gestational age to 70 days; (2) reduced required in-person office visits to one; (3) allowed non-doctors to prescribe and administer mifepristone; and (4) eliminated reporting of non-fatal adverse events." U.S. Stay Appl. App. 7a.

[3] FDA indicated that, in modifying the REMS, it relied on REMS Assessment Reports, safety data gathered since the approval, and current clinical practice at that time. FDA, Risk Evaluation and Mitigation Review(s) for Mifeprex (mifepristone) Oral Tablets, NDA 020687 (Mar. 29, 2016).

before a REMS can be modified, as discussed further below. For example, the statute expressly provides that FDA can require modification of a REMS to minimize the health care delivery system's compliance burden.

Second, the court of appeals concluded that, after the FDA modified the REMS in 2016 to make it non-mandatory for healthcare providers to report non-fatal adverse events, "FDA turned around in 2021 and declared the absence of non-fatal adverse event reports means mifepristone is 'safe.'" *Id.* at 35a. That characterization inaccurately implies that the REMS modification in reporting deprived FDA of data necessary to make an informed evaluation of the product's safety. To the contrary, such data is received by FDA from other sources, as explained below.

A. FDA's Use of Data that Involved the REMS Does Not Mean It Had Inadequate Data to Support a Change in the REMS.

Congress did not require that modification of an approved REMS be premised on a study comparing safety and effectiveness of a drug with an approved REMS and a drug with a modified REMS, *i.e.*, a controlled study.

The FDCA specifically addresses the modification of a REMS. Congress provided that FDA may require a REMS modification based, for instance, on:

- a determination that one or more goals or elements should be modified from the approved REMS to assure the drug's benefits outweigh its risks; or
- to minimize the health care delivery system's compliance burden; or

- to accommodate different, comparable aspects of an abbreviated new drug application's elements to assure safe use, or elements to assure safe use.

21 U.S.C. § 355-1(g)(4)(B).

A REMS also can be modified at the initiative of the holder of the drug application, if the holder submits an "adequate rationale" along with the proposed change. *Id.* § 355-1(g)(4)(A). That "rationale may include, but is not limited to, the reason(s) why the proposed modification is necessary; the potential effect of the proposed modification on how the REMS addresses the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change." FDA, Guidance for Industry, *Risk Evaluation and Mitigation Strategies: Modifications and Revisions* at 12 (June 2020 Rev. 2), https://perma.cc/R42Y-7WUT. The rationale supplied via a REMS assessment as part of an efficacy supplement for a new indication for use should include, in every case, "an evaluation of how the benefit-risk profile will or will not change with the new indication and the implications of any changes on the currently approved REMS." *Id.*

A controlled study is not required before a REMS can be modified. The absence of such a study is not a failing on the part of FDA to "examine the relevant data," as the court of appeals found. A REMS can be modified, in accord with the statute and FDA guidance, based on support that is different than a controlled study comparing safety and effectiveness of the drug under an approved REMS and modified REMS.

FDA can assess the potential effect of the proposed modification, for example, based on how the REMS addresses the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system.

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 ongoing review and that a variety of metrics, data sources, and methodologies are appropriate to inform potential modifications to the REMS. Congress requires the holder of the drug application to submit periodic assessments of the REMS on the drug to FDA on a timetable specified in the statute. 21 U.S.C. § 355-1(c), (d). That is in addition to submitting a REMS assessment to FDA when they submit a supplemental application for a new indication; when required by the REMS themselves; and when FDA determines that an assessment of 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. 21 U.S.C. § 355-1(g)(2).

FDA expressly recognizes that "[c]onsidering their limitations, no single metric, data source, or methodology should be relied upon to assess the effectiveness of REMS." FDA, Guidance for Industry, *REMS Assessment: Planning and Reporting* at 5 (Jan. 2019), https://perma.cc/9JS7-L8AN. FDA describes examples of a wide range of data sources that may be appropriate, including REMS data from the drug applicant, surveys, postmarketing adverse event data, observational/epidemiology data, data from root cause analysis, and data from stakeholder outreach. *Id.* at 7–12.

When a holder of a drug application submits a REMS Assessment Report, FDA suggests that it include a section about proposed modifications to the REMS or revisions to the REMS Assessment Plan. *Id.* at 18.

The court of appeals' misinterpretation of the statute to require a controlled study as relevant data before FDA modifies a REMS would undermine the public interest in lowering barriers that patients face in accessing medication. Between 2008 and 2023, FDA approved over 300 REMS and made nearly 800 modifications to REMS. *See* FDA REMS Public Dashboard (as of Apr. 13, 2023). The approach proposed by the court of appeals and district court could, however, mean that FDA could no longer make these important modifications without requiring drug application holders to conduct expensive, resource-intensive controlled studies. If controlled studies were required, there would be a serious decline in the number of REMS modifications, as the high cost of pursuing such modifications would discourage drug application holders from doing so. This outcome would be bad for healthcare providers and patients because various medications would be subject to unnecessary and prohibitive REMS restrictions, despite the existence of a good reason, consistent with the statute, for removing those restrictions. 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.

B. FDA's Elimination of Mandatory Reporting by Healthcare Providers of Non-Fatal Adverse Events to Drug Application Holders Does Not Deprive FDA of Data Necessary to its Safety Evaluation.

The court of appeals relied on the fact that the initial REMS at the time of approval required provision of the drug under physician supervision, and required that physicians report any hospitalization, transfusion or other serious events to the holder of the drug application or its designee. *See* 21 C.F.R. § 314.520. The court of appeals disapproved of FDA's 2016 modification of the REMS reporting requirement on prescribers, but it relied on a misconception of the impact of that change. The change did not deprive FDA of the data necessary to make an informed evaluation of the product's safety in 2021.

FDA maintains an adverse event reporting system (FAERS). The database contains adverse event reports, medication error reports, and product quality complaints resulting in adverse events that are submitted to the agency by a number of different sources. For example, drug application holders are *required* by FDA to report to FDA non-fatal, as well as fatal, adverse events. 21 C.F.R. §§ 314.98, 314.80, 314.81. The agency also receives voluntary adverse event reports directly from healthcare professionals and consumers, and drug application holders also receive them from providers and consumers and report them to FDA. *See, e.g.*, Gerald J. Dal Pan et al., *Postmarketing Spontaneous Pharmacovigilance Reporting Systems*, *in Textbook of Pharmacoepidemiology* 115, 118 (3d ed. 2021). FDA *may* impose additional reporting requirements as part of a REMS, 21 U.S.C. § 355-1(a), including requiring healthcare providers to report adverse events that otherwise would be subject to voluntary reporting. Regardless of whether such a REMS requirement is

imposed, however, drug product application holders are required to submit adverse event reports to FDA, and patients, physicians, nurses, pharmacists and anyone else is encouraged and incentivized in the interest of safe patient care to report suspected associations between a medicine and an adverse event to FDA. Those reports are reflected in the FAERS. *See*, *e.g.*, FDA, MedWatch: Safety Information and Adverse Event Reporting Program, https://perma.cc/4WQX-ZJ4B (last visited Apr. 13, 2023) ("MedWatch receives reports from the public and when appropriate, publishes safety alerts for FDA-regulated products.").

Thus, FDA may modify a REMS reporting requirement (as FDA did here), 21 U.S.C. § 355-1(d)(4)(C), (g), and that does not deprive FDA of adverse event data about the product. FDA still receives mandatory adverse event reports, both non-fatal and fatal, from the holder of the drug application and voluntary reports from healthcare providers and others in the healthcare system in the interests of ongoing patient safety. And that is the same system of adverse event reporting that exists for all other FDA-approved drugs that are not subject to special adverse event reporting requirements under a REMS.

FDA's modification of the REMS and its determination that the change did not raise new safety concerns does not constitute an "ostrich's-head-in-the-sand approach," as the court of appeals suggested. U.S. Stay Appl. App. 35a. And FDA's removal of the REMS requirement did not render the FAERS a "database designed to produce a nullset," as the district court indicated, *id.* at 81a, nor one that is "likely incomplete because FDA now only requires reporting on deaths," *id.* at 95a. To the

contrary, the FAERS database still included adverse event reports (fatal and non-fatal) that are mandatorily reported to FDA by holders of drug applications; fatal adverse event reports submitted by prescribers, as required by the REMS; and adverse event reports (fatal and non-fatal) submitted voluntarily from many sources across the healthcare system.

In sum, the implications of the court's erroneous reasoning are significant. FDA mandates adverse event reporting by holders of drug applications for both fatal and non-fatal adverse events. Other participants in the healthcare system have incentives to voluntarily report in the interest of their patients. And, of course, patients themselves have every incentive to report adverse events. Suggestions that the system cannot be relied on is contrary to FDA's 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.

III. Applicants are Likely to Succeed on their Challenge to Standing Because Plaintiffs Are Multiple Steps Removed from Any Alleged Actual Injury.

Plaintiff-physicians assert standing based on a generalized, multi-step theory that heaps speculation upon speculation. That approach, endorsed by the lower courts, is contrary to Article III and risks limitless court challenges to drugs that have been approved as safe and effective through the comprehensive and rigorous process Congress requires of FDA. The lower courts' rulings suggest that standing could be predicated on purported "harms" that are, in fact, merely particularly challenging aspects inherent in the practice of medicine. Such an attenuated theory of standing,

if endorsed to challenge FDA drug approvals and REMS modifications, would be highly disruptive to the stability of the Nation's market for medical treatments. Permitting suits by plaintiffs alleging highly tenuous causation and wholly speculative injury would undermine the value of an FDA-approved drug, and adversely impact the United States biopharmaceutical industry innovation that is fueled by private investments in research and development made against the backdrop of robust FDA evaluations.

To establish standing based on the threat of future injuries under Article III as plaintiffs claim here, the alleged injuries must be "certainly impending," *Clapper*, 568 U.S. at 401, 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*, 504 U.S. at 562.

This is plaintiffs' theory: First, some unspecified, non-plaintiff healthcare provider writes a prescription for a patient. Second, the patient happens to experience a rare side effect after taking the drug. Third, the patient does not go back to their treating healthcare provider but, instead, chooses to go to a different healthcare provider who is a plaintiff-physician for treatment related to that complication. Fourth, the 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 a different healthcare provider that happened to result in an unusual complication 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.

PhRMA submits this *amicus* brief in part to emphasize that this same piling of speculation on speculation risks being misapplied in the context of other FDA-approved drugs as well. That would be to the great detriment of the Nation's healthcare system—including biopharmaceutical innovation—and the patients who rely on it.

Plaintiffs couple their speculative theory of causation with an extraordinarily broad view of relevant *harms*. For example, plaintiffs allege a handful of prior instances where they treated patients experiencing complications from medication. The lower courts improperly credited these *past* alleged experiences as the basis for establishing the certainty of *future* harm. Past harm "does not suffice" to establish standing partly "because it relates to past injury rather than imminent future injury that is sought to be enjoined." *Summers v. Earth Island Inst.*, 555 U.S. 488, 495 (2009).

The lower courts characterized plaintiffs' alleged harms in terms that could easily describe work that *every* physician is required to undertake in the course of his or her daily treatment of patients. For example, the district court relied on plaintiffs'

claim that they were required to provide "medical intervention and attention" to patients experiencing complications. U.S. Stay Appl. App. 55a. And the court of appeals relied on plaintiffs' claim that they faced "enormous stress and pressure" in the course of treating medical complications. *Id.* at 14a.

The lower courts' rulings on standing raise the specter of endless litigation challenges to FDA-approved drugs. That much is clear from the face of the lower courts' opinions. For example, the court of appeals concluded that plaintiffs had established standing because, as "doctors," they "have had to devote significant time and resources to caring for women experiencing mifepristone's harmful effects." U.S. Stay Appl. App. 14a. And the district court rejected the notion that plaintiffs' standing theory was speculative by pointing to the "existence of adverse events," combined with isolated instances where plaintiffs had previously treated patients for complications. *Id.* at 55a-56a. These sentences could easily apply to other FDA-approved medications.

The court of appeals suggested that its ruling on standing was "narrow[]," since, in its view, the regulation of the drug at issue here was "exceedingly unusual" because it can be prescribed by non-physicians and carries a boxed warning on its label. *Id.* at 19a-21a. But hundreds of FDA-approved drugs have boxed warnings, *see* Christine M. Cheng et al., *Coverage of FDA Medication Boxed Warnings in Commonly Used Drug Information Resources*, 170 Arch. Intern. Med. 831 (2010), and many drugs can be prescribed by non-physicians, such as physician assistants and nurse practitioners, provided that state law permits it.

Congress did not require the impossible from FDA. Congress understood that the "safe and effective" standard it requires of FDA does not rely on a finding that the drug is risk-free, but rather that the benefits of the drug outweigh its risks. *See* 21 U.S.C. § 355(d) (discussing "risk-benefit assessment framework" for drug approval process); FDA, *Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry* at 3 (Sept. 2021), https://perma.cc/GUU7-R99N ("Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks[.]").

If plaintiffs' theory of standing were accepted, it would threaten to create instability that could chill investment in development of medicines in the United States and slow innovation. Biopharmaceutical companies make enormous investments in drug development based on the reasonable expectation that once a drug product is approved finally by FDA under the statutory standards, barring emerging scientific data, it will be lawful and profitable to sell that product for an extended period in the United States. And the size of investment is critical because only a tiny fraction of potential drug compounds are able to survive the rigorous FDA scrutiny to be approved. As mentioned above, PhRMA member companies have invested more than $1.1 trillion in the development of new treatments and cures since 2000, including $102.3 billion in 2021 alone. *See* PhRMA, Annual Membership Survey at 3, tbl. 1 (2022), https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Refresh/Report-PDFs/P-R/PhRMA_membership-survey_2022_final.pdf. The standing rulings by the courts below would undermine the durability of FDA

drug approvals, and in turn, diminish the incentives for biopharmaceutical companies to invest in new medications. This Court should reject plaintiffs' standing theory—and its attendant threats to biopharmaceutical innovation.

CONCLUSION

The Court should grant the Application.

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Respectfully submitted,

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