Nos. 23-235 & 23-236

In the Supreme Court of the United States

U.S. FOOD & DRUG ADMINISTRATION, ET AL.,
Petitioners,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

DANCO LABORATORIES, L.L.C.,
Petitioner,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Respondents.

On Writs of Certiorari to the United States Court of Appeals for the Fifth Circuit

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*[1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies. PhRMA advocates in support of public policies that encourage the discovery of life-saving and life-enhancing new medicines. PhRMA's members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. Since 2000, PhRMA's member companies have invested more than $1.2 trillion into discovering and developing new medicines, including $100.8 billion in 2022 alone. *See* PhRMA, *Annual Membership Survey* at 3 tbl. 1 (2023).[2] 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 the drug approval process facilitated by the United States Food and Drug Administration ("FDA") makes that risk tolerable.

PhRMA's members share a significant interest in protecting against disruptions to the stable and predictable statutory framework Congress created to govern FDA's drug approvals. The framework Congress established in the Federal Food, Drug, and

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[1] Pursuant to Rule 37.6, no party's counsel authored this brief in whole or in part. No party, counsel for a party, or person other than *amicus curiae,* its members, and its counsel made any monetary contribution intended to fund the preparation or submission of this brief.

[2] https://perma.cc/XD8B-8B8X (archived Oct. 11, 2023).

Cosmetic Act ("FDCA"), 21 U.S.C. § 355, *et seq.*, 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. This Court should reverse the Fifth Circuit's judgment because it sets a precedent that—if left undisturbed—could significantly disrupt the biopharmaceutical industry, harm patients, and stifle innovation in drug development.

INTRODUCTION AND SUMMARY OF ARGUMENT

Congress vested FDA with the authority to evaluate the safety and efficacy of the nation's drugs. And for decades, biopharmaceutical companies, healthcare providers, patients, and other stakeholders have relied on FDA's expert scientific judgment 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.

The Fifth Circuit's ruling upends this settled regulatory scheme and the investments that hinge upon it. Although the Fifth Circuit purported to limit the damage by reversing the district court's order as to the drug at issue's initial approval, the Fifth Circuit ruling nevertheless poses a serious threat to the health and stability of the nation's biopharmaceutical industry.

Amicus addresses three core issues with the decision below:

First, the Fifth Circuit's flawed standing analysis threatens limitless litigation by inviting virtually *any* healthcare provider to bring suit to challenge *any* drug approval or subsequent change. Biopharmaceutical research and development is expensive, time consuming, and risky. Nevertheless, drug developers invest in new medicines because, if their investments succeed, FDA's rigorous drug approvals and subsequent regulatory actions are sturdy enough to facilitate reliable returns. If endorsed by this Court, the Fifth Circuit's attenuated standing analysis

threatens to subject every drug approval and later action to a substantial risk of litigation, reducing revenues that drive investment and thereby diminishing the incentives to innovate in the first place.

Second, the Fifth Circuit's ruling undermines Congress's scheme for drug regulation by overriding FDA's considered scientific judgments concerning clinical studies and adverse event reporting practices. Congress vested FDA with the power to make science-based safety and effectiveness determinations. Such determinations are the bedrock of the nation's drug approval process. This process involves not only thorough scientific review of New Drug Applications, but also of Supplemental New Drug Applications—including proposed Risk Evaluation and Mitigation Strategies ("REMS") modifications—that seek to facilitate patient access to safe and effective medicines. Notwithstanding that congressional mandate, the Fifth Circuit effectively supplanted the FDA's science-backed determinations with its own judge-made requirements. For example, the Fifth Circuit imposed its own judgment regarding the clinical study requirements for determining the appropriate conditions of use for a drug. And the Fifth Circuit fundamentally misunderstood FDA's robust adverse event reporting system. If left uncorrected, the Fifth Circuit's ruling could give license to courts to act contrary to the system Congress charged FDA with implementing.

Third, the lower courts' approach to remedy further exacerbates the potential for harm to the biopharmaceutical industry and patients. Congress mandated by statute a process for the withdrawal or

suspension of an FDA approval decision. But the district court circumvented that process by staying the effective date of all of FDA's challenged actions, and the Fifth Circuit blessed that approach in part by affirming. If *every* FDA drug approval decision—and every subsequent decision approving a supplemental application—can be invalidated by a court through what is effectively a preliminary injunction, it could discourage biopharmaceutical companies from making the necessary investments to advance new and approved medicines that benefit patients. The extraordinary nature of this remedy is all the more striking where, as here, the lower courts failed to provide FDA an opportunity to supplement its reasoning before effectively vacating the agency's actions.

In short, the Fifth Circuit's deeply flawed ruling would jeopardize the settled regulatory framework that facilitates the development of life-saving medicines. This Court should reverse.

ARGUMENT

I. THE FIFTH CIRCUIT'S OVERBROAD STANDING THEORY THREATENS TO STIFLE BIOPHARMACEUTICAL INNOVATION.

The Fifth Circuit held that Plaintiff-Physicians had individual standing to challenge the 2016 Amendments and 2021 Non-Enforcement Decision and that Plaintiff-Associations had derivative associational

standing. FDA Pet. App. 41a.[3] If left undisturbed, these holdings could encourage prolific litigation based on the routine implementation of statutory provisions, such as the assessment and potential modification of REMS, which focus on preventing and managing risks associated with a particular drug's use. This could lead to decreased biopharmaceutical investments, to the detriment of patients.

A. The Biopharmaceutical Industry Invests Heavily in Research and Development in Reliance on the FDA-Administered Regulatory Scheme that Congress Created.

Biopharmaceutical research and development is expensive, time-consuming, and risky. Compliance with FDA's review process requires enormous expenditures, and the low likelihood of successfully developing an approved product means that pharmaceutical firms make these expenditures without knowing whether their efforts will bear fruit. Nevertheless, pharmaceutical firms continue to invest in new medicines because Congress has established a reliable regulatory scheme that allows for the prospect of a reasonable return, discussed further in section II.A, *infra*. That stable FDA-administered scheme encourages the research and development expenditures

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[3] The Fifth Circuit's opinion is reported at 78 F.4th 210 (5th Cir. 2023). For consistency, this brief cites to FDA's Appendix to the Petition for a Writ of Certiorari filed in No. 23-235. FDA Pet. App. 1a–110a.

necessary to produce safe and effective, life-saving and life-improving drugs.

Biopharmaceutical companies invest enormous sums in order to develop new medicines. From drug discovery through FDA approval, developing a new medicine costs $2.6 billion on average. PhRMA, *Research & Development: Clinical Trials*.[4] Since 2000, PhRMA members have invested over $1.2 trillion to develop novel treatments and cures, including $100.8 billion in 2022. PhRMA, *Annual Membership Survey* at 3 tbl. 1. Over the last decade, PhRMA members have spent approximately 22.8% of their domestic sales revenue on research and development. *Id.* at 3 tbl. 1, 5 tbl. 4. By contrast, "average R&D intensity across all industries typically ranges between 2 percent and 3 percent." Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* at 3 (Apr. 2021) ("CBO Report").[5] Even other investment-dependent enterprises—like software and semiconductor companies—spend significantly less than pharmaceutical firms as a proportion of sales. *See id.* at 5. The biopharmaceutical sector is thus among the nation's most research and development–intensive industries. *See id.*

This research and development process consumes significant time, with PhRMA members taking an average of ten years to bring a new drug from discovery to FDA approval. PhRMA, *Research & Development:*

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[4] https://perma.cc/EMP4-RQLY (archived Apr. 29, 2023).

[5] https://perma.cc/2NTL-PHJ2 (archived Apr. 29, 2023).

Clinical Trials. Even after FDA approves new medicines, PhRMA members often engage in additional research and development to improve patient care. This can include, for example, the identification and development of new uses, new formulations, new dose regimens, and better manufacturing processes for quality control of already-approved medicines. For instance, nearly 60% of oncology medicines approved over a decade ago received additional approvals in later years, leading to new indications and treatments and improved patient care. PhRMA, *Cancer Post Approval Infographic* at 1 (Aug. 2022).[6] In 2022, 11.5% of PhRMA members' $100.8 billion research and development expenditures supported post-approval research and development. PhRMA, *Annual Membership Survey* at 4 tbl. 3.

Pharmaceutical firms make these heavy investments of money and time without a guaranteed return: Just one out of every 5,000 to 10,000 compounds under development, and less than 12% of candidate medicines that make it to Phase 1 clinical trials, are approved by FDA as meeting its safety and effectiveness standards. PhRMA, *Research & Development: Clinical Trials*. Although thousands of compounds are investigated as potential drugs, and hundreds proceed to clinical trials each year, FDA approved an average of only 46 novel drugs (*i.e.*, those containing active ingredients not previously approved) annually over the last decade. FDA, *New*

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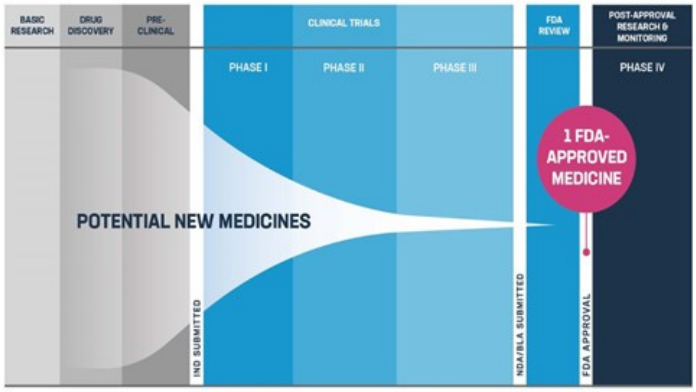
[6] https://perma.cc/3QXZ-7U44 (archived Oct. 3, 2023).

Drug Therapy Approvals 2023 at 6 (Jan. 2024).[7] The graphic below illustrates this winnowing process:



PhRMA, *Research & Development: Clinical Trials*.

This thorough, rigorous, and reliable system—established by Congress and administered by FDA—assures patients, healthcare providers, and drug developers that FDA-approved drugs are safe and effective for their intended purposes. Without this predictable regime, pharmaceutical firms could not expect returns on investment adequate to justify the significant research and development expenses that make life-saving medicines available in the United States.

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[7] https://perma.cc/U4NJ-HG5C (archived Jan. 29, 2024).

B. The Fifth Circuit's Standing Theory Could Enable Speculative Challenges to Initial or Supplemental Approvals, Including REMS Modifications, Jeopardizing Incentives to Innovate and Invest.

The Fifth Circuit's ruling deals a major blow to this regulatory scheme and the investments it supports. By endorsing a sweeping theory of standing, the decision could permit plaintiffs with speculative asserted injuries to challenge FDA's drug approvals and post-approval decisions. The threat of such litigation undermines the reliability and stability of the regime that Congress established, thus jeopardizing pharmaceutical investments and diminishing incentives to pursue further research and development.

To establish Article III standing, "a plaintiff must show (i) that he suffered an injury in fact that is concrete, particularized, and actual or imminent; (ii) that the injury was likely caused by the defendant; and (iii) that the injury would likely be redressed by judicial relief." *TransUnion LLC v. Ramirez*, 594 U.S. 413, 423 (2021). Plaintiff-Physicians fail to satisfy these basic requirements as they are normally applied: They rely on a generalized, multistep theory that heaps speculation upon speculation. In holding that this theory complies with Article III, the Fifth Circuit impermissibly expanded the class of claims for which this Court has recognized standing.

If affirmed, the decision below could invite virtually any healthcare provider to challenge any FDA approval or post-approval action for any drug. The upshot will be a proliferation of court challenges to

medicines that FDA has, in its expert scientific opinion, approved as safe and effective through the comprehensive and rigorous process that Congress prescribed.

1. Plaintiff-Physicians' Amorphous Injuries Could Easily Be Alleged by Virtually Any Healthcare Provider.

Injury in fact must be both "imminent" and "concrete." *Spokeo, Inc. v. Robins*, 578 U.S. 330, 339 (2016) (citation omitted). Plaintiff-Physicians' alleged injuries are neither.

To satisfy Article III, alleged future 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, Plaintiff-Physicians impermissibly rely on an "attenuated chain of possibilities," *Clapper*, 568 U.S. at 401, all of which "depend[] on the unfettered choices made by independent actors not before the courts," *Lujan v. Defs. of Wildlife*, 504 U.S. 555, 562 (1992).

Their theory is as follows: 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 would have to seek the assistance of a different healthcare provider—perhaps one of the Plaintiff-Physicians—rather than contacting the prescribing provider. Fourth, Plaintiff-Physician's provision of that medical care—or even just a related issue, such as an increased workload—

would become a cognizable harm to Plaintiff-Physician. Such harm cannot qualify as "certainly impending" without engaging in the "attenuated chain of possibilities" this Court has rejected. *Clapper*, 568 U.S. at 401.

The final step in that chain illustrates another defect in Plaintiff-Physicians' standing theory: The alleged harms are not sufficiently "concrete" and "particularized." *TransUnion*, 594 U.S. at 423. The Fifth Circuit held that Plaintiff-Physicians would "sustain a concrete injury" if they were "forced to divert time and resources away from their regular patients" by rendering emergent care, or if rendering such care "expose[d] them to greater liability and increased insurance costs." FDA Pet. App. 31a. But these alleged harms describe the work that *all* physicians routinely perform during their daily treatment of patients.

By endorsing a standing theory that fails to satisfy Article III's injury-in-fact requirements, the Fifth Circuit's ruling risks enabling suits from virtually any medical practitioner opposed to any drug. *Cf. Pub. Citizen, Inc. v. NHTSA*, 489 F.3d 1279, 1295 (D.C. Cir. 2007) (Kavanaugh, J.) ("Under [Plaintiff's] theory of probabilistic injury, after an agency takes virtually any action, virtually any citizen—because of a fractional chance of benefit from alternative action—would have standing to obtain judicial review of the agency's choice."). That threatens limitless litigation that would undermine the regulatory scheme and, consequently, the reliability of biopharmaceutical investments.

2. Plaintiff-Physicians' Sweeping Theory of Traceability Would Confer Standing on Those Harmed by Independent, Third-Party Choices.

Plaintiff-Physicians' standing theory also fails for lack of causation. In assessing whether a defendant likely caused an injury in a way that is "fairly traceable" to the defendant's conduct, this Court has emphasized its "reluctance to endorse standing theories that rest on speculation about the decisions of independent actors." *Clapper*, 568 U.S. at 414. In such situations, "it is ordinarily substantially more difficult" for a plaintiff to establish traceability. *Lujan*, 504 U.S. at 562 (cleaned up). Such is the case here.

The Fifth Circuit concluded that Plaintiff-Physicians had shown causation by speculating that the 2016 Amendments and 2021 Non-Enforcement Decision would increase the number of patients who suffer complications from the drug at issue. FDA Pet. App. 36a. But such a hypothetical harm is far removed from Plaintiff-Physicians. It turns on the unpredictable "decisions of . . . independent third parties"—such as patients, prescribers, and other medical practitioners—and cannot satisfy the "substantially more difficult" traceability standard that applies under such circumstances. *California v. Texas*, 141 S. Ct. 2104, 2117 (2021) (cleaned up).

Plaintiffs-Appellees are not the first to try to challenge FDA's ability to approve medical products for use by *other* people. Faced with similar challenges, courts routinely refuse to find standing, correctly rejecting the tenuous theories of imminent injury and

traceability underlying such suits. *See, e.g.*, *Coal. for Mercury-Free Drugs v. Sebelius*, 671 F.3d 1275, 1277 (D.C. Cir. 2012) (Kavanaugh, J.) ("[Plaintiffs] do not have standing to challenge FDA's decision to allow *other people* to receive . . . vaccines.").[8]

The Fifth Circuit accepted the unsubstantiated assertion that increasing access to a drug will necessarily result in an increased risk of adverse events. In doing so, it ignored that FDA must conduct a benefit-risk assessment whenever it evaluates a proposed change—including a REMS modification—to an approved New Drug Application. *See* 21 U.S.C. § 355(d) (requiring FDA to "implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks"); *id.* § 355-1(g)(4)(B)(i) (discussing benefit-risk assessment in the context of REMS modifications); FDA, *Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry* at 3 (Oct. 2023) ("Because all drugs can have adverse effects, the demonstration of safety requires a showing that the benefits of the drug outweigh its risks.").[9]

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[8] *See also Int'l Acad. of Oral Med. & Toxicology v. FDA*, 195 F. Supp. 3d 243, 264–66 (D.D.C. 2016) (concluding that dental association lacked standing to compel harsher FDA mercury-filling regulations because it could not identify any members who would be exposed to mercury); *Guillot v. Aventis Pasteur, Inc.*, 2013 WL 4508003, at *8 (E.D. La. Aug. 22, 2013) (holding that parents who oppose vaccinations lacked standing to enjoin distribution of thimerosal-containing vaccine because their child would likely not receive such a vaccine).

[9] https://perma.cc/EV8A-86YV (archived Jan. 25, 2024).

By artificially inflating the "risks" of greater access and failing to account adequately for the benefits, Plaintiff-Physicians' theory seeks to skew a drug's benefit-risk profile against REMS modifications that are otherwise warranted, such as to improve patient access to a drug or reduce burdens on the healthcare delivery system. Such an outcome would be contrary to FDA's statutory requirement to weigh these factors, among others, for the type of REMS at issue in this case. *See* 21 U.S.C. § 355-1(f)(2). This fear is not hypothetical. The FDCA requires manufacturers of drugs that are subject to REMS to conduct and submit periodic REMS assessments; it also empowers FDA to determine whether the findings in such assessments warrant REMS modifications or, more generally, whether the statutory standard for modifications has been met. *Id.* § 355-1(g). Manufacturers also may propose a REMS modification "at any time." *Id.* Plaintiff-Physicians' theory of traceability would threaten to transform this routine implementation of the statute into sources of litigation.

In sum, the Fifth Circuit's ruling depends on a flawed standing analysis that threatens to invite attenuated challenges to countless drug approvals and post-approval changes, such as new uses and REMS modifications. Under such a regime, drug approvals and REMS modifications could become litigation triggers.

II. BY OVERRIDING FDA'S CONSIDERED SCIENTIFIC JUDGMENTS, THE FIFTH CIRCUIT'S RULING UNDERMINES CONGRESS'S SCHEME FOR DRUG REGULATION.

Congress charged FDA with the responsibility of serving as the nation's expert for evaluating the safety and effectiveness of drugs in this country. These evaluations occur both before FDA approves a drug for the first time and after the drug has entered the market, including when FDA reviews proposed changes to an approved New Drug Application (such as new uses). Congress specified a complex and thorough framework within which the agency must operate. That statutory framework requires FDA to exercise expertise in evaluating and regulating drugs by, among other things: analyzing the significant amounts of information received from various sources such as the manufacturer or third parties about a drug's safety or effectiveness (which applies equally to original and supplemental applications); consulting with scientific experts outside the government, as well as within other parts of the government when needed; and considering submissions from the public. The Fifth Circuit's decision upends this framework by overriding FDA's expert judgments, imposing new judicially created requirements, and fundamentally misconstruing the operative statute.

A. Congress Directed FDA to Apply Its Expertise by Making Science-Based Safety and Effectiveness Decisions.

FDA's congressionally mandated "[m]ission" is to "protect the public health by ensuring that . . . drugs

are safe and effective." 21 U.S.C. § 393(b)(2)(B). This Court has emphasized that FDA's "objective" is 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). That "essential purpose pervades the FDCA." *Id.*

As part of FDA's congressionally mandated mission, Congress designated the agency as the scientific expert when it comes to evaluating the safety and effectiveness of drugs approved in this country. 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). When considering drug applications, FDA must "promptly and efficiently review[] clinical research and tak[e] appropriate action on the marketing of regulated products." *Id.* § 393(b)(1). It must also grow and develop its expertise by "consult[ing] with experts in science, medicine, and public health." *Id.* § 393(b)(4).

To start the approval process for a new drug, a pharmaceutical company must generally conduct a series of laboratory studies to test how a proposed medicine works and assess its safety. *See* 21 C.F.R. § 312.23(a)(8). If such studies produce promising results, the company submits an Investigational New Drug Application to FDA outlining those results and offers a plan for clinical trials. *See* 21 U.S.C. § 355(i)(2); 21 C.F.R. § 312.20(a)–(b). After completing multiple rounds of clinical trials, the company can submit a New Drug Application to seek FDA drug approval. *See* 21 C.F.R. § 312.21. A 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." 21 U.S.C. § 355(b)(1)(A).

Once a company files a New Drug Application, an FDA review team of multidisciplinary experts diligently evaluates whether the studies submitted show that the drug is safe and effective for its proposed use. "Safe" in this context means that the benefits of the drug outweigh the known risks. A safety assessment is based on information in the New Drug Application, which includes the reports of investigations by the applicant and information about the drug pertinent to the application's evaluation from any source. *See* 21 C.F.R. § 314.50. Effectiveness must be based on "substantial evidence"—*i.e.*, "evidence consisting of adequate and well-controlled investigations." *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613, 617 (1973) (noting that FDA must "refuse approval" of a New Drug Application "if 'substantial evidence' that the drug is effective for its intended use is lacking") (cleaned up). If FDA concludes that a drug is safe and effective for its proposed use and finds that "none" of seven specified "grounds for denying approval" apply, then FDA will approve the drug for use. 21 U.S.C. § 355(c)(1)(A), (d).

Congress also gave FDA statutory authority over REMS, which may be required as part of an initial application approval or added after that initial approval, and which FDA may modify later when approving a Supplemental New Drug Application. *See id.* § 355-1. REMS focus on preventing and managing risks associated with a particular drug's use—for example, by

reinforcing specific practices among providers and patients. FDA's authority over REMS includes requiring modifications 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.* § 355-1(g)(4)(B)(i), (ii). Drug application holders must periodically submit assessments of REMS to assist FDA in "evaluat[ing] whether the approved [REMS] should be modified." *Id.* § 355-1(g)(2)(C). And application holders may also propose REMS modifications through Supplemental New Drug Applications based on "adequate rationale[s]" that support the changes. *Id.* § 355-1(g)(4).

After approving a New Drug Application or Supplemental New Drug Application, FDA manages a robust monitoring regime to track the approved drug's safety profile, as mandated by statute. *See id.* § 355(k)(1), (5). This regime is facilitated by the FDA Adverse Event Reporting System ("FAERS"), through which FDA collects, reports, and publicizes adverse event data received from a variety of sources, including manufacturers, healthcare providers, and patients. *See id.* §§ 352(n), 355(k)(1), (5). Manufacturers are required to submit adverse event reports that they receive in accordance with timelines and procedures established by FDA regulation. *See* 21 U.S.C. § 355(k), 21 C.F.R. § 314.80.

FAERS has long provided a source of information for FDA to monitor an approved drug's safety after it enters the market. *See* FDA, *FDA Adverse Event Reporting System (FAERS) Public Dashboard* (Dec.

2023).[10] FDA's management of FAERS, like the rest of FDA's statutory mandate, reflects Congress's determination that the expert agency is best positioned to monitor safety information and assess if certain action may be warranted.

B. The Fifth Circuit's Ruling Supplants FDA's Science-Based Approval Decisions with Its Own Judge-Made Requirements.

The Fifth Circuit usurped FDA's congressional mandate by imposing unworkable, extra-statutory requirements and misapprehending critical features of the FDCA's governing statutory framework. Although the Fifth Circuit's analysis purported to limit itself to the 2016 Amendments and 2021 Non-Enforcement Decision, its reasoning could have far-reaching implications for initial and supplemental drug approvals alike.

1. Congress Did Not Require That All Changes to Conditions of Use Be Assessed in a Single Controlled Study.

In 2016, FDA approved a Supplemental New Drug Application to change various conditions of use for the drug at issue (*e.g.*, allowing prescriptions by licensed non-physician providers, adjusting the dosage, increasing the time under which to prescribe, and modifying the method of administration). At the time, FDA concluded that the scientific evidence gathered over decades of use supported the 2016 Amendments—and in making this determination, FDA

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[10] https://perma.cc/7YB9-2PNG (archived Jan. 29, 2024).

considered at least three studies that tested the same or similar changes that it then implemented in the 2016 Amendments. *See, e.g.*, J.A. 299 nn.1, 3 & 4 (FDA Summary Review, Mifeprex REMS Changes (Mar. 29, 2016)).

Nevertheless, the Fifth Circuit determined that FDA's approval decision "was likely arbitrary and capricious," and thus invalid, because FDA allegedly "did not consider the cumulative effect of the 2016 Amendments" given that "[n]one of the studies [FDA] relied on examined the effect of implementing all of those changes together." FDA Pet. App. 53a; *see also id.* 235a (stay ruling)[11] (faulting FDA for citing "zero studies that evaluated the safety-and-effectiveness consequences of the 2016 [Amendments] *as a whole*"). In other words, the Fifth Circuit effectively imposed a requirement that *all* proposed changes to a medication's conditions of use in the context of a Supplemental New Drug Application be assessed together in a single controlled study.

Contrary to the Fifth Circuit's ruling, the FDCA does not require FDA to evaluate a single controlled study testing the cumulative impact of changes proposed in a Supplemental New Drug Application before approving such changes. *See generally* 21 U.S.C. §§ 355, 355-1. In outlining the procedures for approving New Drug Applications and Supplemental New

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[11] The Fifth Circuit's order granting a stay in part is not published in the Federal Reporter but is available at 2023 WL 2913725. For consistency, this brief cites to FDA's Appendix to the Petition for a Writ of Certiorari filed in No. 23-235. FDA Pet. App. 196a–244a.

Drug Applications, Congress required that applicants submit an extensive set of information, including "full reports of investigations which have been made to show whether such drug is safe [and effective] in use," research into pediatric uses (if required by 21 U.S.C. § 355c), and plans for future clinical trials. *Id.* § 355(b)(1), (5). FDA approves an average of 200 supplemental applications annually, permitting new uses, expanding treatment to different patient populations, and modifying conditions of use. *See* FDA, *Report of Summary Level Review Under Section 3031 of 21st Century Cures* (2023).[12]

The same is true of the initial imposition of a REMS or a REMS modification. When considering whether to impose a REMS, FDA must look at factors such as population, the seriousness of the targeted disease or condition, and the expected benefits and risks of the drug. If a drug has been approved without a REMS, FDA can nevertheless later decide to impose one based on "new safety information . . . derived from a clinical trial, an adverse event report, a postapproval study . . . , or peer-reviewed biomedical literature." 21 U.S.C. § 355-1(a)(1), (b)(3). If a manufacturer later seeks to modify a REMS, the FDCA mandates that such modification be supported by "an adequate rationale," *id.* § 355-1(g)(4)(A), which "*may* include . . . 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) (emphasis added).[13]

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[12] https://perma.cc/E7QB-G6HA (archived Sept. 29, 2023).

[13] https://perma.cc/R42Y-7WUT (archived Apr. 14, 2023).

But Congress did *not* require FDA to cite a controlled study, let alone a controlled study that tests the proposed changes together. *See* 21 U.S.C. § 355-1.

The Fifth Circuit's novel requirement that FDA examine the effect of all proposed changes through a single controlled study could seriously harm healthcare providers, patients, and pharmaceutical innovation. Such a study would be at minimum impractical and at worst impossible to effectuate. The economic and temporal costs of such a study, not to mention its practical complexity, would likely render it infeasible. And even if commissioned, such a study would consume valuable years and resources. Important changes to conditions of use for medicines could happen slowly or not at all. Such a regime could also freeze in place various REMS restrictions that are unwarranted by current data, thus burdening drug manufacturers and healthcare providers and impeding patients' access to safe and effective medicines.

2. The Fifth Circuit Fundamentally Misunderstood Adverse Event Reporting.

The Fifth Circuit held that the 2021 Non-Enforcement Decision (which halted enforcement of the in-person dispensing requirement during the COVID-19 pandemic) was arbitrary and capricious in part because, in the Fifth Circuit's view, FDA "no longer had access to perhaps the best source of [adverse event] data: the prescribers." FDA Pet. App. 59a. That reasoning stemmed from a flawed understanding of the adverse event reporting data available to FDA.

Congress provided for a robust adverse event reporting system, which FDA implements primarily through FAERS, to facilitate decisions of whether to withdraw drug approvals. *See* 21 U.S.C. § 355(k). Congress further mandated that FDA's recordkeeping and reporting framework have "due regard for the professional ethics of the medical profession and the interests of patients." *Id.* Consistent with these congressional directives, FDA has instituted and implemented a framework comprising mandatory adverse event reporting from drug application holders and voluntary reporting from providers and patients, all captured in FAERS.

Adverse event reporting responsibilities start with drug application holders—often drug manufacturers. Federal law *mandates* that a drug application holder maintain records and report information relating to clinical experience and other data the manufacturer receives or obtains to FDA as prescribed by regulation so that FDA can determine whether grounds exist for withdrawing a drug approval under 21 U.S.C. § 355(e). 21 U.S.C. § 355(k)(1). FDA's implementing regulations in turn require drug application holders to report all adverse events to FDA. *See* 21 C.F.R. §§ 314.98, 314.80, 314.81. A drug application holder must promptly review all adverse event information obtained directly and indirectly from any source, including healthcare providers, patients, postmarketing clinical investigations, epidemiological surveillance studies, scientific literature, and unpublished scientific papers, and must establish procedures for the surveillance, receipt, evaluation, and reporting of adverse events to FDA. *See id.* § 314.80(b). Once a drug application holder has received and reviewed adverse

event information, it *must* submit reports to FDA. *Id.* § 314.80(c).

Federal law also encourages other stakeholders, such as physicians and patients, to voluntarily report adverse events. *See* 21 U.S.C. § 352(n) (providing that a prescription drug shall be deemed misbranded, subject to limited exceptions not applicable here, unless published direct-to-consumer advertisements contain the following statement: "You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1–800-FDA-1088."); *see also* 21 C.F.R. § 201.57(a)(11)(ii) (requiring that prescription drug product labels contain contact information for the manufacturer and FDA for reporting).[14]

Stakeholders have a strong incentive to report adverse events to application holders to improve patient healthcare. *See, e.g.*, Gerald J. Dal Pan et al., *Postmarketing Spontaneous Pharmacovigilance Reporting Systems*, in *Textbook of Pharmacoepidemiology* 115, 118 (Brian L. Strom et al. eds., 3d ed. 2021). In fact, 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

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[14] Healthcare providers and patients can easily report adverse events on FDA's MedWatch website. *See* https://perma.cc/3M5H-JLZ5 (archived Jan. 29, 2024).

> Web address for voluntary reporting of adverse reactions).

21 C.F.R. § 201.57(a)(11)(ii).

FDA then collects all adverse event reports received from all sources—including drug application holders, healthcare providers, and patients—into FAERS. *See, e.g.*, FDA, *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)* (June 4, 2018).[15]

The 2016 Amendments removed only *one* atypical REMS-imposed reporting measure for the drug: The requirement that healthcare providers report non-fatal events. Mandatory reporting of non-fatal adverse events by healthcare providers is not a requirement for most FDA-approved drugs. Contrary to the Fifth Circuit's assumption, *see* FDA Pet. App. 59a, FDA did not lack "access" to adverse event reports from prescribers. Even after the 2016 Amendments, healthcare providers were still required to report any fatal adverse events (in the exceedingly rare instance that such an event were to occur). And the manufacturers were also still subject to mandatory reporting requirements for *all* adverse events (fatal or non-fatal) under the regulations described above. Moreover, it remained the case that healthcare providers and others could voluntarily submit reports about *any* adverse events to FDA. Thus, even after the 2016 Amendments, FDA continued to receive adverse event

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[15] https://perma.cc/Y25N-VZ67 (archived Jan. 29, 2024); *see also* s*upra* note 10.

reports from multiple sources, just as it does for every FDA-approved drug.[16]

Indeed, even after the 2016 Amendments, the drug at issue remains subject to adverse event reporting requirements that exceed those of most other drugs on the market. Thus, FDA did not behave arbitrarily and capriciously by relying on a "thorough scientific review" of the "available clinical outcomes data and adverse event reports" when issuing its 2021 Non-Enforcement Decision. J.A. 377, 397–408 (FDA Denial Letter, 2019 Citizen Petition (Dec. 16, 2021)). Importantly, if this Court deems FAERS and other safety data evaluated by FDA "insufficient" to ground FDA's safety determinations here, FDA Pet. App. 59a–60a, the ramifications could extend beyond the drug at issue. Such a holding would drastically impinge on FDA's fulfillment of its congressionally directed mission to protect and promote public health by inviting lawsuits challenging FDA's reliance on the safety information in FAERS to evaluate drug safety profiles.

III. THE EXTRAORDINARY REMEDY HERE FURTHER AGGRAVATES THE POTENTIAL FOR HARM TO THE BIOPHARMACEUTICAL INDUSTRY AND PATIENTS.

The Fifth Circuit's ruling was unprecedented—and harmful to the drug industry and patients—in yet another respect: The court awarded extraordinary preliminary relief, contrary to Congress's statutory

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[16] This is in addition to the adverse event reports compiled during the more than fifteen years that the drug was subject to mandatory reporting from physicians and the manufacturer.

scheme and without affording FDA a chance to further explain its assessments.

In addition to the authority to approve drugs, evaluate subsequent changes, and administer REMS, Congress vested FDA with the exclusive authority to withdraw approval of a New Drug Application or a Supplemental New Drug Application. FDA can withdraw an approval if it finds that "experience," "tests," "scientific data," or other "new evidence" show that the drug "is unsafe for use under the conditions" for which it was approved. 21 U.S.C. § 355(e). As part of this process, Congress required FDA to provide the drug application holder "due notice and opportunity for hearing" before withdrawing or suspending approval. *Id.* Nevertheless, if FDA makes a series of findings that "there is an imminent hazard to the public health," it can suspend a drug approval "immediately," although it must provide the drug application holder with an opportunity for an expedited hearing after suspension. *Id.*

All these procedures—which involve due notice and opportunity for hearing to the applicant—are mandated by statute. They serve, in part, to protect the sizeable investments that make the approval, marketing, and distribution of drugs possible; to prevent shocks to the U.S. biopharmaceutical market; and to ensure that any safety concerns are promptly and thoroughly addressed. *See* 21 U.S.C. § 355(e); 21 C.F.R. § 314.150.

Yet the decisions below worked an end-run around this statutory process. The district court stayed the two-decade-old drug approval under 5 U.S.C. § 705—

a provision directed at "postpon[ing]" the effective date of an agency action pending judicial review—and the Fifth Circuit endorsed that approach as it applied to the 2016 and 2021 post-approval actions (even while finding that the 2000 approval decision was time-barred). Circumventing the FDCA's withdrawal requirements with a dubious use of the Administrative Procedure Act's stay provision deprives drug application holders of their property interests without proper notice or hearings. That in turn diminishes their incentives to invest in the development of drugs in the first place.

The remedy fashioned by the lower courts was misguided in another key respect: It vacated the 2016 and 2021 actions *before* affording FDA an opportunity to further explain itself. Even if the lower courts had correctly addressed the merits, the proper remedy would have been to remand to FDA for additional explanation, without vacatur of the agency action.

Remand without vacatur is often the proper course when "vacatur could cause substantial disruption." *EME Homer City Generation, L.P. v. EPA*, 795 F.3d 118, 132 (D.C. Cir. 2015) (Kavanaugh, J.). That criterion applies with special force when a drug approval is challenged. FDA's drug approval decisions implicate enormous reliance interests on the part of patients, healthcare providers, biopharmaceutical companies, and other stakeholders. The stakes could not be higher when a medication is on the market one day and off the market the next.

Nor are those reliance interests limited to FDA's initial drug approval decisions. The Fifth Circuit dismissed concerns that its decision "would destabilize the pharmaceutical industry, especially research-and-development sections," maintaining that those concerns "appl[ied] primarily (if not wholly) to the challenge to the 2000 Approval." FDA Pet. App. 69a–70a. But that reasoning was deeply flawed for two reasons: First, even though the Fifth Circuit limited its holding to supplemental actions, its underlying reasoning could apply with equal force to initial approvals, thus risking the very type of discord that the court disregarded here. Second, Supplemental New Drug Applications, including those for REMS modifications, play a critical role in FDA's overall regulatory regime. As discussed above, innovation does not stop when FDA approves a new prescription medicine. *See supra* section I.A. FDA often approves supplemental applications seeking new indications to treat further ailments, or the broadening of use parameters that ease patient access. Those decisions—just like initial drug approvals—have substantial and immediate impacts on patients, providers, and industry. And *reversing* those decisions can accordingly cause deep and immediate harm.

If endorsed by this Court, the lower courts' remedy could greenlight lawsuits seeking the reversal of certain longstanding FDA drug approvals and post-approval decisions at a preliminary stage, without even affording the agency an opportunity to supplement its reasoning. That approach would bypass the extensive drug-withdrawal procedures that Congress mandated, jeopardize investments in life-saving medicines, and ultimately undermine patient care.

CONCLUSION

The judgment below should be reversed.

Respectfully submitted,

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