Nos. 25A1207, 25A1208

In the Supreme Court of the United States

DANCO LABORATORIES, LLC

Applicant,

v.

THE STATE OF LOUISIANA, ET AL.,

Respondents.

GENBIOPRO, INC.,

Applicant,

v.

THE STATE OF LOUISIANA, ET AL.,

Respondents.

ON APPLICATIONS TO STAY OR VACATE THE STAY PENDING APPEAL OF 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 APPLICANTS

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INTEREST OF *AMICUS CURIAE*[1]

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading innovative biopharmaceutical research companies, which are focused on developing innovative medicines that transform lives and create a healthier world. Together, we are fighting for solutions to ensure patients can access and afford medicines that prevent, treat, and cure disease. PhRMA member companies have invested more than $850 billion in the search for new treatments and cures over the last decade, supporting nearly five million jobs in the United States. Although a return on these substantial investments is never guaranteed because of the risks inherent in scientific innovation and discovery, reliability and scientific rigor in the process for drug approvals and post-approval determinations 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 the United States Food and Drug Administration's ("FDA") drug approvals and post-approval determinations. The thorough and rigorous framework Congress established in the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355, *et seq.*, is designed to assure patients, healthcare providers, drug and device developers, and drug and device manufacturers that the drugs approved and regulated by FDA are safe and effective for their intended uses. This Court should

[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.

stay or vacate the Fifth Circuit's order 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 conduct detailed and science-based evaluations of the safety and efficacy of the Nation's drugs. And for decades, biopharmaceutical companies, healthcare providers, patients, and other stakeholders have relied on the predictable regulatory environment created by FDA's established evidence-based framework. Against that regulatory backdrop, biopharmaceutical companies invest tens of billions of dollars every year and undertake the extraordinarily risky, time-consuming, and capital-intensive process of developing new medicines.

Louisiana's lawsuit and the Fifth Circuit's order threaten to upend that system, which Congress intended to be settled and predictable. By permitting a State to invoke an expansive theory of standing to obtain extraordinary relief that would circumvent Congress's carefully considered regime and allow States to sidestep FDA, the Fifth Circuit has introduced a profoundly destabilizing force into the Nation's drug regulatory regime. The consequences extend far beyond the particular drug or regulatory action at issue here. The Court should not permit a collateral attack by unregulated parties seeking to skip FDA engagement to supplant the judgment of the agency with their own—whether an initial approval or a later modification grounded in new evidence. That regime would not only distort the administrative process

Congress carefully designed but also undermine the reliance interests that make biomedical innovation possible.

Amicus submits that the Court should stay or vacate the Fifth Circuit's order for four interrelated reasons.

First, Louisiana's lawsuit—and the Fifth Circuit's endorsement of it—jeopardizes the predictability and consistency that are essential to the biopharmaceutical industry. Congress established a comprehensive, science-driven process for evaluating drug safety and effectiveness. Allowing States to leapfrog over the administrative process to invoke the judicial process would inject instability into that framework, forcing manufacturers to navigate conflicting obligations and undermining the settled expectations that enable the development and distribution of medicines.

Second, Louisiana's claims rest on an overbroad theory of standing that would permit unregulated entities to bring sweeping challenges to FDA's actions. Allowing States to establish standing by alleging downstream costs and attenuated sovereign interests could risk opening the courthouse doors to virtually any State—or similarly situated entity—to challenge any drug approval or post-approval determination. That expansion of standing doctrine would subject routine regulatory decisions to pervasive litigation risk, thereby threatening the substantial investments necessary to sustain innovation in the biopharmaceutical sector.

Third, Louisiana's (and the Fifth Circuit's) approach would interfere with the statutory processes governing Risk Evaluation and Mitigation Strategies ("REMS"),

which Congress designed to allow FDA and manufacturers to respond flexibly to emerging safety information. REMS modifications are an integral part of FDA's lifecycle regulation of drugs, enhancing patient safety, and facilitating access based on evolving evidence. Permitting state-initiated litigation to override or freeze those modifications would distort this carefully calibrated process, converting a scientific and regulatory mechanism into a source of ongoing legal uncertainty and burdening both providers and patients.

Fourth, the concerns Louisiana invokes regarding drug safety are based on a fundamental misunderstanding of the adverse-event reporting system that Congress created and FDA now administers. Through mandatory manufacturer reporting and voluntary submissions from healthcare providers and patients, FDA maintains a comprehensive, nationwide system for monitoring and evaluating drug safety. If a State has concerns about the safety profile of a drug, it has mechanisms to raise those concerns with FDA before rushing to court, such as filing a citizen petition. But allowing States to bypass established administrative processes in favor of judicial intervention risks subverting the system Congress created and industry relies on.

Taken together, these errors would destabilize the regulatory framework that underpins the development and marketing of safe and effective medicines. The Court should restore that framework by granting the Applicants' requests for a stay.

ARGUMENT

I. Louisiana's Lawsuit Jeopardizes the Predictability and Consistency That Is Essential for the Biopharmaceutical Industry to Operate.

Congress has created a comprehensive, scientific, and evidence-based system whereby FDA evaluates, approves, and regulates drugs. 21 U.S.C. § 355; *see FDA v. Alliance for Hippocratic Med.*, 602 U.S. 367, 375 (2024). Louisiana's lawsuit and the Fifth Circuit's order granting Louisiana's request to stay FDA's 2023 REMS under 5 U.S.C. § 705 upend the statutory framework and create instability for industry participants writ large.

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

Congress directed that approval and post-approval decisions about drug safety and effectiveness be made through a rigorous, science-based process grounded in evidence, rather than policy preference or litigation outcomes. When a company files a New Drug Application ("NDA"), an FDA review team is required to thoroughly evaluate the scientific and clinical evidence to assess whether the studies submitted show that the drug is safe and effective for its intended use. "Safe" in this context means that the benefits of the drug outweigh the known risks, *see* 21 U.S.C. § 355(d), as essentially no drug has zero risk of adverse events. When particular safety concerns are identified pre-approval, a REMS may be required to help ensure that the benefits of the medication outweigh its risks. *See id.* § 355-1. REMS may range in complexity, and can include, for example, a communication plan for sharing information with healthcare providers. *See id.* § 355-1(e). When a drug is shown to be effective, but is associated with a specific serious risk, a REMS may further include

"elements to assure safe use," such as patient-specific monitoring or prescriber certification requirements. *See id.* § 355-1(f)(3).

FDA's findings of effectiveness regarding a drug must be based on "substantial evidence"—*i.e.*, "evidence consisting of adequate and well-controlled investigations." *Id.* § 355(d); *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 613 & n.3, 617 (1973) (FDA must "refuse approval" of an NDA "if 'substantial evidence' that the drug is effective for its intended use is lacking" (citation omitted)). Consistent with this mandate, FDA must "promptly and efficiently review[] clinical research and tak[e] appropriate action on the marketing of regulated products." 21 U.S.C. § 393(b)(1). Congress further required that FDA carry out its obligations to grow and develop its expertise by "consult[ing] with experts in science, medicine, and public health." *Id.* § 393(b)(4).

FDA's review system does not end after initial approval. Congress recognized that scientific knowledge develops over time and therefore defined post-approval mechanisms, such as Supplemental New Drug Applications, labeling updates, and REMS assessment and modifications, to allow recalibration in light of accumulated evidence. *Id.* § 355-1(g); 21 C.F.R. § 314.70. In particular, REMS focus on preventing and managing risks associated with a particular drug's use—for example, by reinforcing specific practices among providers and patients—while remaining responsive to evolving data and post-market experience. *See* 21 U.S.C. § 355-1.

Review of scientific and clinical evidence is central to this regulatory process. FDA's evaluation of the safety of a drug therefore relies on multiple, complementary

sources. First, drug application holders provide ongoing safety information through required safety reports and periodic REMS assessments, which allow FDA to "evaluat[e] whether the approved [REMS] should be modified." *Id.* § 355-1(g)(2)(C).

Second, Congress created a monitoring regime to track an approved drug's safety profile. *See id.* § 355(k)(1), (5). This regime is facilitated by the FDA Adverse Event Reporting System ("FAERS"), which 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 id.* § 355(k), 21 C.F.R. § 314.80.

Third, FDA evaluates peer-reviewed scientific literature, epidemiological studies, and other scientific and medical evidence that emerges independently of sponsor submissions or adverse event submissions.

B. Louisiana's Lawsuit Upends the Regular and Predictable Evidence-Based Process for Regulating Biopharmaceuticals.

Louisiana's lawsuit disrupts the administrative process by which biopharmaceuticals are regulated. Louisiana effectively seeks to use judicial process to impose its own view of a drug's safety profile on the entire Nation, without first engaging with FDA through its established administrative processes. But States cannot make safety-based determinations on behalf of the country and the Fifth Circuit erred by adopting one State's assessment of the risks.

The biopharmaceutical industry depends on the predictability of FDA's review process. At the end of the process, sponsors can seek judicial review if they disagree

with FDA's decision. But the FDCA does not contemplate that a State or other allegedly interested party can throw overboard the agency's evidence-based determinations by substituting its own views on drug safety or efficacy. As the district court acknowledged, Louisiana's gambit here "risks 'rushed, high-stakes, and low-information' decision-making." App. 50a (quoting *Trump v. CASA, Inc.*, 606 U.S. 831, 855–56 (2025)) (alteration adopted).[2]

Allowing the type of gamesmanship that Louisiana attempts here would disrupt the science-based process through which drug safety profiles and conditions of use are evaluated and calibrated over time, introducing chaos into pharmaceutical regulation and broadly undermining patients' access to medicine. Drug sponsors and FDA would have to continuously look over their shoulders to determine whether someone is going to try to seek an injunction to undo science- and evidence-based determinations. If the Fifth Circuit's order is allowed to stand, it would inject instability into the post-market regulatory system, undermine reliance interests, and ultimately harm manufacturers, pharmacies, providers, and patients. Patients would ultimately bear the brunt of the harm as the uncertainty surrounding post-approval modifications generated by actions like the Fifth Circuit's and efforts like Louisiana's would have the effect of restricting access to important drugs and reducing incentives to pharmaceutical innovation.

[2] Appendix citations reference the Appendix filed in Case No. 25A1207.

II. Louisiana's Overbroad Standing Theory Threatens to Stifle Biopharmaceutical Innovation.

Innovation by companies in the biopharmaceutical industry depends on a predictable regulatory framework. By allowing one State to wipe away agency action with assertions of attenuated harm, the Fifth Circuit's ruling undermines the reliability and stability of the regime that Congress established and that companies rely on. The result will be harm to investment-backed expectations and a stifling of innovation, all to the detriment of patients throughout the country.

A. The Fifth Circuit's View of Standing Cannot Be Reconciled with This Court's Decision in *Alliance*.

In concluding that Louisiana is likely to establish standing, the Fifth Circuit credited the State's assertion of two harms: sovereign injury and financial injury. Neither theory of harm can be reconciled with this Court's decision in *Alliance* or with the many standing decisions that preceded it.

First, the Fifth Circuit erred in concluding that Louisiana has standing because "the agency's 2023 REMS causes 'federal interference with the enforcement of [Louisiana] law.'" App. 10a–11a (quoting *Texas v. United States*, 809 F.3d 134, 153 (5th Cir. 2015)). The court credited Louisiana's theory that the 2023 REMS allowed out-of-state providers to prescribe the drug to women in Louisiana for uses that violate state law. *Id.* That type of "attenuated chain of possibilities," *Clapper v. Amnesty International USA*, 568 U.S. 398, 410 (2013), all of which "depend[] on the unfettered choices made by independent actors not before the courts," *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 562 (1992), cannot support standing. This Court rejected essentially the same attenuated theory in *Alliance* where the plaintiffs did

"not prescribe or use" the drug, "FDA ha[d] not required the plaintiffs to do anything or to refrain from doing anything," and the plaintiffs "suffer[ed] no direct monetary injuries from FDA's actions relaxing regulation" of the drug because they did "not prescribe, manufacture, sell, or advertise" it or sponsor a competing drug. 602 U.S. at 385–86. Because Louisiana also does none of these things, it too lacks standing.

Indeed, Louisiana's status as a State does not eliminate the ordinary requirements of injury, traceability, and redressability. *See United States v. Texas*, 599 U.S. 670, 676 (2023). And here, the State's asserted injuries depend on independent choices by third parties not before the Court, including prescribers, pharmacies, patients, and treating providers. That is precisely the kind of attenuated causal chain that *Alliance* rejected. *See* 602 U.S. at 391–92. A State may not convert every alleged downstream regulatory cost into standing to displace FDA's national scientific judgment.

The fact that the 2023 REMS allegedly makes it easier for third parties to prescribe a drug in Louisiana does not give the State standing to vacate FDA's decision at all, let alone for the entire country. Louisiana does not allege that FDA is violating state law, nor could it. And the State would have no authority to sue to block individuals and entities outside its territory from engaging in activity that is legal where it occurs. As this Court explained in *Alliance*, Louisiana does "not have standing to sue simply because *others* are allowed to engage in certain activities." 602 U.S. at 393. Like any other State, Louisiana has ample avenues to enforce its own statutes—but enjoining FDA's determinations about drug safety and efficacy

after a scientifically rigorous evaluation of the totality of the scientific and medical evidence is not one of them.

Second, the Fifth Circuit further erred in concluding that the $92,000 Louisiana allegedly paid "in Medicaid costs" was sufficient to establish standing. App. 11a. As in *Alliance*, the number of links in the chain between FDA's regulatory action and Louisiana's expenditure is far too many to create Article III standing. *See Alliance*, 602 U.S. at 390–91. Between FDA and that expenditure are a patient who sought care from an out-of-state provider, a provider who prescribed a drug, a pharmacy that mailed the drug to the patient, a patient who ingested the drug, and a medical complication that may or may not have been attributable to the drug. At each step, the chain of causation becomes more speculative and attenuated—and cannot stand under this Court's decision in *Alliance*.

Indeed, Louisiana's theory of financial injury is as attenuated as the failed theory of standing in *Alliance* but even more boundless. *See Alliance*, 602 U.S. at 392–93. Louisiana asserts that any unregulated party that spends "even one dollar's worth" on downstream consequences can challenge a regulation. App. 43a. Because essentially no drug has zero risks or potential side effects, the universe of potential plaintiffs who could assert standing to challenge drug approvals or post-approval modifications because they spent money to treat or mitigate such effects would be mind-boggling under the theory advanced by Louisiana and adopted by the Fifth Circuit. Such a "limitless approach" cannot satisfy Article III: "The chain of causation is simply too attenuated." *Alliance*, 602 U.S. at 391.

Alliance confirms that Louisiana's attenuated theory of standing cannot satisfy Article III. And the consequences of embracing such a capacious view of when plaintiffs can seek to substitute their own judgment for FDA's would be disastrous, eroding incentives to invest in drug development and stifling innovation.

B. Biopharmaceutical Research and Development Will Suffer if Louisiana Is Allowed to Proceed.

Biopharmaceutical research and development is expensive, time-consuming, and risky. Biopharmaceutical companies already invest enormous sums to develop new medicines without knowing whether their efforts will bear fruit. If such a capacious theory of standing is allowed, the risk involved in researching and developing safe and effective, life-saving and life-improving drugs will increase and deter future investment.

The biopharmaceutical sector is among the Nation's most research- and development-intensive industries. Cong. Budget Off., *Research and Development in the Pharmaceutical Industry* at 5 & fig. 1 (Apr. 2021) ("CBO Report").[3] From drug discovery through FDA approval, developing a new medicine costs $2.6 billion on average. PhRMA, *Research & Development: Clinical Trials*.[4] In 2024 alone, PhRMA members invested $104.3 billion to develop novel treatments and cures and spent approximately 20.4% of their domestic sales revenue on research and development. PhRMA, *Annual Membership Survey* at 3 tbl. 1 (2025);[5] *id.* at 4 tbl. 2. By contrast,

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

[4] https://perma.cc/EMP4-RQLY.

[5] https://perma.cc/82SC-X24R.

the average percentage spent on research and development across all industries "typically ranges between 2 percent and 3 percent." CBO Report at 3.

The expensive and resource-intensive process is lengthy: PhRMA members take an average of ten years to bring a new drug from discovery to FDA approval. PhRMA, *Research & Development: Clinical Trials*, *supra*. Even once a new medicine is on the market, PhRMA members engage in additional research and development to improve patient care, including the identification and development of new uses, new formulations, new dose regimens, and better manufacturing processes for quality control of already-approved medicines. In 2024, 7.7% of PhRMA members' $104.3 billion research and development expenditures supported post-approval research and development. PhRMA, *Annual Membership Survey*, *supra*, at 4 tbl. 3.

These investments are made against heavy odds: 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*, *supra*. 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, *Advancing Health Through Innovation: New Drug Therapy Approvals 2023* at 6 (Jan. 2024).[6]

[6] https://perma.cc/U4NJ-HG5C.

This reliable system—established by Congress and administered by FDA—provides drug developers a measure of predictability in their investments. But, if Louisiana, or another State or other unregulated entity, can substitute its own views for FDA's evidence-based assessment of the benefits and risks of a medicine, then those investments become much riskier. Industry could face an increased threat of litigation for potentially any federal review or approval, and States could wield the threat of litigation as leverage against industry. Opening the door to state-by-state second-guessing of drug regulation would place sponsors in an untenable position between potentially conflicting state positions. The risk that States may try to interfere or reverse science-based regulatory actions based on attenuated theories like Louisiana's could impact the pharmaceutical industry's decision-making in a manner that hurts innovation and public health. Congress has authorized FDA, not the States, to conduct an evidence-based drug approval process. Louisiana's theory of standing would permit States to undermine that system by creating a "boundless theory of standing—in which all peripheral costs imposed on States by actions of the [executive branch] create a cognizable Article III injury." *Arizona v. Biden*, 40 F.4th 375, 386 (6th Cir. 2022).

This case does not require the Court to decide the full scope of States' authority over medical practice, the regulation of pharmacies, or the administration of Medicaid. The only question is whether a State may obtain emergency judicial relief displacing FDA's national REMS determination based on attenuated downstream injuries. If the Fifth Circuit's ruling is allowed, 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.

C. Louisiana's Theory of Standing Puts Patients at Risk.

Louisiana's theory has downstream effects that would harm patients by creating unpredictability and limiting access to essential medications. Even after an iterative, multi-year assessment of a drug's conditions of use, States could initiate litigation to challenge or suspend evidence-based changes. This instability could delay or deter evidence-based updates, including those intended to increase patient access or reduce burdens on healthcare providers.

Patients would lose out on the benefits of removal of REMS requirements when evidence shows that the requirements are no longer necessary. REMS are not designed to freeze the most restrictive conditions ever imposed on a drug. Congress required FDA to calibrate REMS to the evidence, including by modifying or eliminating elements when they are no longer necessary to assure safe use or when they impose unnecessary burdens on the healthcare system. Patient access to important drugs may be unnecessarily limited if States are permitted to use the courts to intervene in the evidence-based process for considering modifications or removal of REMS.

III. The Biopharmaceutical Industry Has an Interest in Implementing REMS Without State Interference.

REMS are a controlled, statutory process that allows drug developers to respond agilely to emerging safety information with additional safety measures when appropriate. REMS focus on preventing, monitoring, and managing risks associated

with a drug, by providing targeted information to providers and patients and by reinforcing particular practices among providers and patients. REMS permit 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]." 21 U.S.C. § 355-1(g)(4)(B)(i), (ii).

Section 505-1, which describes the drug approval process, expressly contemplates that manufacturers will work within an iterative framework to make modifications over time based on evolving scientific and clinical evidence. REMS may be required as part of an initial application approval or added after that initial approval. *See id.* § 355-1. 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). Indeed, this is the only requirement applicable to all REMS. 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). And manufacturers may propose a REMS modification "at any time." *Id.* This statutory framework enabling evidence-based modifications to a REMS contributes to patient safety and access, eases burdens on the healthcare system, and helps assure the benefits of a drug outweigh its risks over time. Allowing suits like Louisiana's to proceed would disrupt the REMS system established by Congress with no apparent benefit.

In addition to the evidence-based process, Congress has created a clear set of requirements for REMS that are not compatible with state efforts to substitute their

own theories for FDA's evidence-based decision-making. For example, REMS modifications require a benefit-risk assessment. *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.").[7] And, REMS are designed to optimize uniformity. The regulation for drugs requiring REMS provides that the safe use elements should—"to the extent practicable, so as to minimize the burden on the health care delivery system—(i) *conform with elements to assure safe use for other drugs with similar, serious risks*; and (ii) be designed to be compatible with established distribution, procurement, and dispensing systems for drugs." 21 U.S.C. § 355-1(f)(2)(D) (emphasis added). Regulated parties have pathways for objecting or contributing within the process, and any party can submit safety information to FDA at any time. State-by-state interference with REMS based on disfavor of particular drugs undermines the regulatory scheme's focus on consistency, to the detriment of drug developers, healthcare providers, and patients.

Congress anticipated that REMS elements would change over time in response to new information and post-market experience and created a statutory framework

[7] https://perma.cc/EV8A-86YV.

that allows its chosen process to unfold *absent interference*. Injecting state-initiated litigation into the process threatens to replace scientific and medical judgment with unscientific extra-statutory standards. Allowing state interference through litigation could 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. So too, undermining Congress's regulatory scheme would disincentivize investments in medical and pharmaceutical research by making the investments riskier. The incentives for biopharmaceutical companies to make enormous investments in drug development would be reduced if they no longer have a reasonable expectation that they will be able to recoup their research and development costs after they obtain FDA approval. Industry has an interest in being able to implement REMS without interference from States that did not even bother to engage with FDA about their views on the safety profile of the drug.

IV. The Fifth Circuit Fundamentally Misunderstood FDA's Adverse-Event Reporting System.

As it did in *Alliance*, the Fifth Circuit fundamentally misunderstood how the federal adverse-event-reporting system operates. Both the district court and the Fifth Circuit panel relied on the court of appeals' earlier misunderstanding of adverse-event reporting in *Alliance*, repeating the inaccurate conclusion that removing the requirement that healthcare providers report non-fatal adverse events had dramatically curtailed FDA's access to information about adverse events related to the drug. *Alliance for Hippocratic Med. v. FDA*, 78 F.4th 210, 249 (5th Cir. 2023),

rev'd, 602 U.S. 367 (2024); App. 13a, 26a. But under the 2023 REMS, as explained below, healthcare providers are still required to report fatal adverse events (in the exceedingly rare instance that such an event were to occur), and the manufacturers are still subject to mandatory reporting requirements for *all* adverse events (fatal or non-fatal). Moreover, healthcare providers and others remain free to voluntarily submit reports about any adverse events to FDA. It is thus simply untrue that FDA had cut off its own ability to collect and access information about adverse events.

Congress authorized the creation of a system to report adverse events from drugs to ensure the continued safety of drugs that have been approved for the market. 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 created FAERS, which collects adverse-event information through mandatory reporting requirements imposed on drug application holders and through voluntary reporting from providers and patients.

Federal law mandates that a drug application holder (often a drug manufacturer) maintain records and report to FDA information relating to clinical experience and other data the manufacturer receives or obtains 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 regulations require application holders to maintain systems for surveillance, receipt, evaluation, and reporting of adverse drug experience information, including expedited reporting for serious and unexpected

adverse drug experiences and periodic reporting of other reportable information. *See* 21 C.F.R. §§ 314.80, 314.81, 314.98. 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. *See id.* § 314.80(b).

Federal law also encourages other stakeholders, including 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)-(iii) (requiring that prescription drug product labels contain contact information for reporting suspected adverse reactions to the manufacturer).[8] Stakeholders have a strong incentive to report adverse events to application holders to improve patient healthcare. *See, e.g.*, Gerald J. Dal Pan, Marie Lindquist & Kate Gelperin, *Postmarketing Spontaneous Pharmacovigilance Reporting Systems*, in *Textbook of Pharmacoepidemiology* 115, 118 (Brian L. Strom, Stephen E. Kimmel & Sean Hennessy eds., 3d ed. 2021).

[8] Healthcare providers and patients can easily report adverse events on FDA's MedWatch website. *See* FDA, *MedWatch Online Voluntary Reporting Form*, https://perma.cc/3M5HJLZ5.

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).[9]

If a State has concerns about the safety profile of a drug, it has several ways to convey that information to FDA. For instance, the State could file a citizen petition requesting that FDA take certain action, such as conducting additional safety testing. *See* 21 C.F.R. § 10.30. Indeed, FDA's regulations *require* that any request for FDA to "take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a [citizen] petition" before a lawsuit is filed, 21 C.F.R. § 10.45(b)—a requirement that Louisiana did not fulfill here. A State could also participate in FDA's rulemaking procedures and provide FDA with data to use during its safety reviews. Rather than participate in the system FDA established pursuant to congressional authorization, Louisiana filed this suit, seeking to impose its views on the Nation as a whole.

FDA's decision to remove the requirement that healthcare providers report non-fatal adverse events aligned with the requirements FDA has for the vast majority of approved drugs, under which healthcare providers are not required to report non-fatal adverse events—though they remain free to voluntarily report such events and routinely do so. Mandatory reporting of adverse events by healthcare providers is

[9] https://perma.cc/Y25N-VZ67.

required only in exceptional events; notably, even fatal events are usually not subject to mandatory reporting by healthcare providers.

Louisiana and the Fifth Circuit should not be permitted to circumvent Congress's decision to entrust evidence-based decisions about drug safety and efficacy to FDA after scientifically rigorous evaluation—particularly when their own understanding about FDA's methods of collecting and evaluating safety data are ill-informed and the State did not engage with the Agency on its views.

CONCLUSION

The applications should be granted.

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