Nos. 23-235, 23-236

In The

Supreme Court of the United States

FOOD AND DRUG ADMINISTRATION, ET AL.,

Petitioners,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

DANCO LABORATORIES, L.L.C.,

Petitioner,

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.

ON PETITIONS FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

BRIEF OF PATIENT AND PROVIDER ADVOCACY ORGANIZATIONS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

Aileen M. McGrath
AKIN GUMP STRAUSS HAUER & FELD LLP
100 Pine Street, Suite 3200
San Francisco, CA 94111

Craig B. Bleifer
AKIN GUMP STRAUSS HAUER & FELD LLP
One Bryant Park
New York, NY 10036

Caroline L. Wolverton
Counsel of Record
Nathan A. Brown
Emily I. Gerry
Caroline D. Kessler
Jenna H. Becker
AKIN GUMP STRAUSS HAUER & FELD LLP
2001 K Street, NW
Washington, DC 20006
(202) 887-4000
cwolverton@akingump.com

Counsel for Amici Curiae

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES:

STATUTES AND REGULATIONS:

RULES

OTHER AUTHORITIES

INTEREST OF *AMICI CURIAE*[1]

The Leukemia & Lymphoma Society, American Cancer Society, American Cancer Society Cancer Action Network, American Society of Clinical Oncology, American Society of Hematology, Cancer*Care*, Cancer Support Community, Hemophilia Federation of America, Muscular Dystrophy Association, National Organization for Rare Disorders, and WomenHeart: The National Coalition for Women with Heart Disease represent millions of patients across the United States who have serious health conditions and depend on drugs approved by the U.S. Food and Drug Administration ("FDA") for treatment. For many of these patients, their very lives depend on the reliability of FDA's approvals of those medications and their approved conditions of use. The Fifth Circuit's opinion partially affirming the district court's preliminary injunction jeopardizes patients' and providers' ability to rely on FDA's expert process to deem drugs and their conditions of use safe and effective, and therefore available for treatment.

INTRODUCTION AND SUMMARY OF ARGUMENT

This case carries significant implications for patients' access to drugs on which their health, and in many cases their lives, depend. The Fifth Circuit's

---

[1] Pursuant to Supreme Court Rule 37.2, *amici curiae* state that they provided timely notice to all counsel of their intent to file a brief. Pursuant to Supreme Court Rule 37.6, *amici curiae* state that no counsel for any party authored this brief in whole or in part and no entity or person, aside from *amici curiae*, their members, or their counsel, made any monetary contribution intended to fund the preparation or submission of this brief.

reasoning below undermines FDA's drug approval and review process, leaving patients and their providers uncertain whether they can rely on FDA approval of a drug and its conditions of use to mean that the drug's availability will not suddenly be called into question absent an expert-driven deliberation about benefits and risks. The ramifications extend far beyond the single drug that is the subject of this case, because the Fifth Circuit's reasoning disregards FDA's expertise-based risk-benefit assessment and instead employs an approach unfaithful to the Federal Food, Drug, and Cosmetic Act ("FDCA") and FDA's implementing regulations.

Many of the drugs approved to treat the most serious conditions afflicting patients across the country—from rare cancers to crippling genetic disorders—are not risk-free. Their approvals usually result from a careful risk-benefit analysis conducted by scientific and medical experts at FDA. Approval of a drug and its conditions of use requires a determination by those experts that the benefits of the drug under its conditions of use outweigh the potential risks. Take, for example, some of the therapies on which cancer patients rely. Many require drug treatments the risks of which would not be tolerated in other circumstances. And yet, these FDA-approved drugs can represent the best-known treatment or even a last-hope therapy for a particular type or stage of cancer.

The reasoning in the decision below subverts this expertise-based process. It substitutes a single court's views—based on an incomplete record and not even citing any robust literature, Danco. Cert. Pet. 13, 31—

regarding risks and benefits for the FDA's considered analysis of those same factors. It disregards the FDA's unparalleled expertise in assessing and explaining why a particular drug is safe and effective under the prescribed conditions of use. And it impairs and potentially eliminates access for a wide class of patients to a drug that FDA has determined to be safe and effective.

The potential negative ramifications of this reasoning are vast. If FDA's risk-benefit assessments are vulnerable to the kind of short-sighted challenges and second guessing at the root of the Respondents' claims and validated by the decision below, the resulting uncertainty about the ongoing authoritativeness of FDA's approval process will cause grave harm to patients. The decision risks rendering needed treatments suddenly unavailable, resulting in physical harm and psychological turmoil. Patients will also be less likely to benefit from innovative treatments made possible by new drugs and new indications of use. Why? Because this new, unprecedented uncertainty about the reliability of FDA approval disincentivizes drug manufacturers from making the huge investments of funds in research and development and manufacturing required to bring to market cutting-edge drugs and improved therapies that benefit patients.

The detrimental implications for patients call for this Court's review.

ARGUMENT

I. THE FIFTH CIRCUIT'S DECISION IMPLICATES SUBSTANTIAL PATIENT RELIANCE INTERESTS

A. Patients and Providers Rely on FDA's Expertise-Based Approval Process

Approval of pharmaceutical treatments in this country is entirely dependent on FDA's pre-market and post-market evaluations. 21 U.S.C. §§ 355, 355-1. FDA is the expert agency long-entrusted by Congress with ensuring that human drugs in the United States are safe and effective. *See* FDCA, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq*.). The agency, staffed with scientific experts across a broad range of fields,[2] is well-equipped to evaluate drug safety and effectiveness. By statute, FDA may approve a new drug application only if the application includes "substantial evidence" of safety and effectiveness from "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved[.]" 21 U.S.C. § 355(c)(1)(A) and (d); *see also id*. §§ 321(p), 331(d), 355(a).

FDA's evaluation process involves an intensive quantitative and qualitative assessment of the benefits and risks of a drug and of the conditions under

---

[2] *See, e.g.*, FDA, *Meet the Faces Behind FDA Science* (last updated Jun. 9, 2022), https://www.fda.gov/science-research/fda-stem-outreach-education-and-engagement/meet-faces-behind-fda-science.

which it may be used. 21 U.S.C. § 355(d) (requiring the agency to "implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs" and to evaluate whether "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"). In accordance with the agency's statutory authority, FDA experts examine multiple factors, including: extensive evidence of safety and effectiveness submitted in the drug's premarket application and/or available in a post-market setting; the therapeutic context in which the drug will be used; the nature and severity of the condition the drug is intended to treat or prevent; uncertainties regarding the drug's benefits and risks; the benefits and risks of other available therapies for the condition; and any risk management tools necessary to ensure that the benefits of the drug outweigh its risks. *See id.* § 355; FDA, *Benefit-Risk Assessment for New Drug and Biological Products* (Sept. 2021).[3]

After a drug is approved, FDA continues to monitor its real-world performance to ensure that the drug remains safe and effective for its intended uses. If a sponsor wishes to change the approved conditions

[3] *Available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products.

of use in a way that could have a moderate or substantial impact on safety or effectiveness, the sponsor must submit a supplemental application, which is subject to the same standards as the initial application. 21 C.F.R. §§ 314.70, 314.71. And when FDA learns of new information bearing on safety or efficacy, it evaluates the drug's approval status, the conditions it is intended to treat, and the patient population reliant on the therapy. FDA, *Benefit-Risk Assessment for New Drug and Biological Products* (Sept. 2021). For an approved drug, FDA also considers how a change in indication or removal from the market would impact clinical practice and patient care.[4] FDA may determine that an additional warning or precaution is appropriate or require a change in the labeling. *See* FDA, *Guidance for Industry Safety Labeling Changes -- Implementation of Section*

[4] For instance, when FDA Advisory Committees—panels of experts who provide scientific advice and recommendations on drug approvals, *see* 21 U.S.C. § 355(n)—assess whether to recommend that a drug be removed from the market, they weigh evidence regarding not only the drug's risk-benefit profile, but also the importance of the drug to the medical and patient communities and the risk of negative health outcomes if the product is removed. *See, e.g.*, Covis Pharma GmbH, *Covis Pharma GmbH's Briefing Materials In Response To The Center for Drug Research and Evaluation's Notice Of Opportunity For A Hearing And Proposal To Withdraw Approval Of MAKENA® (hydroxyprogesterone caproate injection) 250 mg/mL (NDA No.: NDA 21-945)*, Docket No. FDA-2020-N-2029 (Sept. 16, 2022), https://www.fda.gov/media/162247/download; Center for Drug Evaluation and Research (CDER), FDA, *Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena*, Docket No. FDA-2020-N-2029 (Sept. 16, 2022), https://www.fda.gov/media/162246/download.

505(o)(4) of the FD&C Act 4–5 (July 2013).[5] Or, where it appears to FDA that the risks of a drug to patients outweigh the benefits, even with appropriate labeling and other protections, FDA has the authority to initiate an action to withdraw its approval of the drug. *See* 21 U.S.C. § 355(e); 21 C.F.R. §§ 314.150, 314.151.

Patients and providers, as well as drug developers and manufacturers, rely on this extensive scientific and regulatory process with the reasonable expectation that changes to the drug's approval status will be based on the FDA's existing deliberative process and procedural safeguards in the FDCA. For all patients, access to safe and effective drugs that treat their conditions is a matter of supreme importance. But for some patients, including cancer patients and others with life-threatening illnesses whom *amici* represent, that access can be a matter of life or death. Patients, and their treating providers, expect that access to drugs will be determined pursuant to FDA's congressionally authorized procedures and scientific and technical expertise.

B. The Fifth Circuit's Reasoning Threatens Patients' Ability to Rely on the FDA Approval Process

The Fifth Circuit's analysis undercuts FDA's established processes for approval and post-market surveillance of drugs and conditions of use. In evaluating whether FDA's 2016 and 2021 mifepristone

---

[5] *Available at* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-labeling-changes-implementation-section-505o4-federal-food-drug-and-cosmetic-act.

actions were arbitrary and capricious, the court effectively "substitute[d] its own policy judgment for that of the agency," *FCC v. Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). Despite ample evidence that FDA exercised its judgment as contemplated by its statutory authority in approving modifications to mifepristone's conditions of use, *see* FDA Cert. Pet. 4-7, the Fifth Circuit, among other errors: (i) imposed its own requirement, untethered from the FDCA or FDA regulations, for how FDA must consider the effect of changes in a drug's conditions of use; (ii) faulted FDA for not maintaining heightened reporting requirements that the agency determined were unnecessary; and (iii) rejected FDA's judgment about the sufficiency of adverse event reports for monitoring safety. FDA Cert. Pet. 22–27.

The willingness to second-guess FDA's expertise-based judgment reflected in the decision below jeopardizes the confidence patients and providers can and should have that pre- and post-market determinations about drug safety and efficacy are made by medical and scientific experts using prescribed deliberative processes. Under the Fifth Circuit's approach, in evaluating a potential treatment modality, and the benefits and risks of that modality for that patient, a patient and their provider cannot depend on FDA's approval processes as the determinants of safety and efficacy. Nor can they expect that, once approved, a treatment modality will remain approved absent change through FDA's congressionally authorized procedures and scientific and technical expertise. Instead, under the Fifth Circuit's rationale, courts are free to upend the FDA

approval process, with little notice and without consideration of impact on patients, the availability of alternative treatments, and other factors that comprise the statutorily based risk-benefit determination. Patients and providers in this landscape would struggle to determine appropriate courses of treatment for critical conditions, uncertain if approval of drugs and conditions of use could be suddenly enjoined through litigation brought by groups who object to a medical treatment on moral grounds, or by companies seeking to remove competing products for commercial gain.

C. Drug Developers' Investment Decisions Depend on the FDA Approval Process

Manufacturers invest significant time, effort, and money to develop cutting-edge medicines to improve and save the lives of patients in the U.S. and across the globe. In 2019, the pharmaceutical industry spent $83 billion on research and development.[6] This spending has brought us to the cusp of what one journalist referred to as a "golden age for medicine."[7] And while the cures for cancers and other conditions once thought to be a death sentence appear closer than ever, the decision below threatens to destabilize the

---

[6] CBO Report, Research and Development in the Pharmaceutical Industry (Apr. 8, 2021), https://www.cbo.gov/publication/57025.

[7] David Wallace-Wells, *Suddenly, It Looks Like We're in a Golden Age for Medicine*, N.Y. Times Magazine (June 23, 2023), https://www.nytimes.com/2023/06/23/magazine/golden-age-medicine-biomedical-innovation.html.

regulatory system upon which current treatments and those yet to come rely.

As with any economic venture, manufacturers must be able to predict, to a reasonable degree, the risks associated with investing in drug development and in maintaining sufficient supply of product under current Good Manufacturing Practices.[8] Though failed studies and adverse reactions are always a possibility, they are a long-understood part of the development process. The impact of judicial rulings upending decisions made by FDA scientists in accordance with FDA's congressionally mandated drug approval process, however, is not.

II. UNDERMINING THE RELIABILITY OF THE FDA DRUG APPROVAL PROCESS HARMS PATIENTS

The reasoning employed by the Fifth Circuit invites immediate challenge to a wide range of drugs and their conditions of use because it disregards FDA's exercise of scientific judgment and evaluation of clinical data in accordance with the statutory authority that Congress has granted it. It opens the courthouse doors to advocacy groups that disfavor particular drugs for any number of reasons not based in the FDCA or FDA regulations. The evidence for many cutting-edge drugs is often heavily debated by experts; the approval decision frequently comes down to an assessment of the overall benefits versus the

---

[8] *See* CBO Report, *supra* note 6; The Pew Charitable Trusts and the Int'l Soc'y for Pharm. Eng'g, *Drug Shortages* (Jan. 2017), https://www.pewtrusts.org/-/media/assets/2017/01/drug_shortages.pdf.

overall potential risks to the intended patient population. If courts hearing such challenges substitute their judgment for FDA's expert process, like in the decision below, the availability of countless drugs could be undermined by uncertainty, given the potential for adverse court decisions, appeals, and conflicting decisions in different jurisdictions. The bar to roll back approved conditions of use that have been carefully determined and modified by FDA would be dangerously low. The factors endorsed by the Fifth Circuit are not even set forth in the FDCA or implementing regulations. The resulting destabilization would harm patients and providers who depend on FDA's determinations and the ongoing availability of a drug approved for use on the terms that FDA has established.

Disruptions in drug availability undermine patient care. Hence, consistent market availability of drugs is critical for patient care. Even a temporary lack of access to certain drugs can lead to serious patient harm. If long-approved drugs are removed from the market, or if conditions of use rolled back, providers may be forced to prescribe medications that are less safe or effective for a particular patient or adjust their standard of care in a manner contrary to scientific evidence. Even the threat of removal can disrupt patient care and harm patients. Providers expecting long-term or short-term disruptions to the availability of certain drugs may decide to prescribe drugs they expect to be less likely to experience disruptions, even if those drugs are less effective for the patient's disease or condition or cause worsened side effects.

The devastating medical and psychological impacts of the sudden lack of availability of pharmaceutical drugs have been studied extensively in the context of drug shortages. Studies have found that sudden loss of access to drugs causes severe harms, including significant rates of delayed and cancelled treatment and surgical intervention, [9] increased medication errors [10], and serious adverse patient outcomes—including death. [11] The

---

[9] See, e.g., Jonathan Minh Phuong et al., The impacts of medication shortages on patient outcomes: A scoping review, PLoS One (May 3, 2019), at 6-8; Ali McBride et al., National Survey on the Effect of Oncology Drug Shortages, in Clinical Practice: A Hematology Oncology Pharmacy Association Survey, 18 JCO Oncology Practice e1289, e1291 (2022); Kenneth L. Kehl et al., Oncologists' Experiences With Drug Shortages, 11 J. Oncology Practice e154, e157 (2015); Keerthi Gogineni & Katherine L. Shuman, Correspondence: Survey of Oncologists about Shortages of Cancer Drugs, 360 New Eng. J. Med. 2463, 2464 (2013); Amy E. McKeever et al., Drug Shortages and the Burden of Access to Care: A Critical Issue Affecting Patients With Cancer, 17 Clinical J. Oncology Nursing 490, 490-93 (2013); Milena McLaughlin et al., Effects on Patient Care Caused by Drug Shortages: A Survey, 19 J. Managed Care Pharmacy 740, 786 (2013); American Hospital Association, AHA Survey on Drug Shortages (July 12, 2011), https://www.aha.org/system/files/content/11/drugshortagesurvey.pdf.

[10] *See, e.g.*, Phuong, *supra* note 9, at 6, 12 (citing a study's finding that in 54% of drug shortages, "clinicians may be unfamiliar with the alternative product regarding its mechanism of action, adverse effects, or interactions"); McBride, *supra* note 9, at e1291; McKeever, *supra* note 9, at 491; McLaughlin, *supra* note 9, at 785.

[11] *See, e.g.*, Phuong, *supra* note 9, at 5-10 (citing eight studies linking drug shortages to patient deaths); Kehl, *supra*

consequences of lost access to therapies are detrimental for all patients undergoing treatment of life-threatening disease, but they are particularly devastating for cancer patients, for whom removal of a drug from the market could be the equivalent of a death sentence.[12] The unavailability of agents used in pediatric cancer treatment regimens, for example, is "likely to have devastating effects on patients with cancer."[13] Even when alternative regimens may be available, "what might appear to be a suitable alternative regimen may result in an inferior outcome—an intolerable situation for young people

---

note 9, at e157; McKeever, *supra* note 9, at 491 (citing studies linking patient deaths to delays or cancellations in oncology treatment or drug substitutions); McLaughlin, *supra* note 9, at 785 (noting 41.4% of directors of pharmacy reported possible or probable adverse events from drug shortages); AHA, *supra* note 9, at 8; *see also* Timothy P. Hanna et al., *Mortality due to cancer treatment delay: systematic review and meta-analysis,* BMJ (Oct. 16, 2020), at 1-11 (finding significant association between treatment delay and increased mortality).

[12] C. Lee Ventola, *The Drug Shortage Crisis in the United States,* 36 Pharmacy & Therapeutics 740, 751 (2011) ("[T]he shortage of cytarabine raised the possibility that drug shortages would not only cause disruptions in care but could also be a death sentence for [acute myeloid leukemia] patients."); *see also* Monika L. Metzger et al., *Perspective: The Impact of Drug Shortages on Children with Cancer—The Example of Mechlorethamine*, 367 New Eng. J. Med. 2461, 2463 (2012); McKeever, *supra* note 9, at 490 (relating story of an ovarian cancer patient whose disease progressed after her healthcare provider "informed her that her chemotherapy protocol would need to be altered mid-treatment" because the drug suddenly became unavailable due to manufacturing issues).

[13] Metzger et al., *supra* note 12, at 2463.

with curable diseases."[14] "Almost 80% of children and adolescents with cancer can be cured with current therapy. Most of the curative treatment regimens are based on chemotherapeutic agents that have been available for decades. . . . For many of these agents, no adequate substitute drugs are available."[15]

Uncertainty of access to medication also causes serious psychological harm. In the words of one mother whose biggest fear was that drug shortages would cause her 5-year-old son to lose access to vincristine, a critical medication that was part of his therapy regimen for acute lymphoblastic leukemia, "It is terrifying as a mom that a drug your child needs is not available." Dr. Sherise Rogers, *Shortage of critical cancer drug forcing some children to go without,* ABC News (Oct. 22, 2019);[16] *see also* Elizabeth Cohen & Amanda Musa, *Thousands of people can't get full treatments of a lifesaving cancer drug,* CNN (Feb. 17, 2023) (quoting patient with bladder cancer, in response to being told that due to a shortage he would not be able to receive his remaining doses of cancer drug Bacillus Calmette-Guérin, as stating, "It's a very, very frightening circumstance to realize that at that point, what they deem to be an aggressive cancer could

---

[14] *Id.* One study designed to evaluate the effect of drug shortages on children with cancer found a "dramatic difference in event-free survival" over two years between children with Hodgkin's lymphoma treated with the standard treatment (88%) and those treated with a treatment that had been touted as an alternative (75%). *See* Metzger, *supra* note 12, at 2462.

[15] *Id.*

[16] *Available at* https://abcnews.go.com/Health/shortage-critical-cancer-drug-forcing-children/story?id=66411784.

in fact come right back");[17] Brenda Goodman, *How one mom headed off a drug shortage,* CNN (Dec. 29, 2022) (quoting a 9-year-old girl with acute lymphoblastic leukemia, in response to learning she could not start cancer drug Erwinaze due to a shortage, as asking her mother, "What happens now? . . . Don't I need this to live?"); [18] Rob Stein, *How A Drug Shortage Hiked Relapse Risks For Lymphoma Patients,* NPR (Dec. 26, 2022) (quoting mother whose 10-year-old daughter with lymphoma lost access to cancer drug Mustargen due to a shortage, as expressing "When a doctor says, 'This is what you need to take.' And then all of a sudden somebody tells you, 'Well, that is what you need to take but this isn't available so we're going to try this instead,' it's very scary").[19]

---

[17] *Available at* https://www.cnn.com/2023/02/15/health/cancer-drug-shortage-bcg/index.html.

[18] *Available at* https://www.cnn.com/2022/12/29/health/drug-shortage-mom-angels-for-change/index.html.

[19] *Available at* https://www.npr.org/sections/health-shots/2012/12/26/168038307/how-a-drug-shortage-hiked-relapse-risks-for-lymphoma-patients.

CONCLUSION

For the foregoing reasons, the petitions for writ of certiorari should be granted.

Respectfully submitted.

Caroline L. Wolverton
Counsel of Record
Aileen M. McGrath
Nathan A. Brown
Craig B. Bleifer
Emily I. Gerry
Caroline D. Kessler
Jenna H. Becker
AKIN GUMP STRAUSS
HAUER & FELD LLP

October 12, 2023