No. 23-10362

IN THE UNITED STATES COURT OF APPEALS
FOR THE FIFTH CIRCUIT

ALLIANCE FOR HIPPOCRATIC MEDICINE, et al.,

Plaintiff-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION, et al.,

Defendant-Appellants,

and

DANCO LABORATORIES, LLC,

Intervenor-Appellant.

On Appeal from the United States District Court for the
Northern District of Texas, Amarillo Division
Case No. 2:22-cv-00223-Z, Judge Matthew J. Kacsmaryk

AMICUS BRIEF OF PATIENT AND PROVIDER ADVOCACY ORGANIZATIONS IN SUPPORT OF REVERSAL

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CERTIFICATE OF INTERESTED PERSONS

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

The undersigned counsel of record certifies that—in addition to the persons and entities listed in the Certificates of Interested Persons filed in this matter—the following listed persons and entities, as described in the fourth sentence of Fifth Circuit Rule 28.2.1, have an interest in the outcome of this case. These representations are made in order that the Judges of this Court may evaluate possible disqualification or recusal.

Amici[1]
The Leukemia & Lymphoma Society
American Cancer Society
American Cancer Society Cancer Action Network
American Childhood Cancer Organization
American Society of Clinical Oncology
American Society of Hematology
American Urological Association
Arthritis Foundation
Cancer*Care*
Cancer Support Community
Council of Medical Specialty Societies
Epilepsy Foundation
Friends of Cancer Research
Hemophilia Federation of America
Muscular Dystrophy Association
National Patient Advocate Foundation
National Multiple Sclerosis Society
National Organization for Rare Disorders
RESOLVE: The National Infertility Association
WomenHeart: The National Coalition for Women with Heart Disease

[1] A description of each *Amicus* is set forth in the Appendix.

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Respectfully submitted,

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INTEREST OF *AMICI CURIAE*

The Leukemia & Lymphoma Society and additional patient and provider advocacy organizations listed in the Appendix represent millions of patients across the United States who have serious health conditions and depend on drugs approved by the Food and Drug Administration ("FDA") for treatment. For many of these patients, their very lives depend on the availability of those medications.

In this brief, *Amici* explain patients' reliance on FDA's expert and detailed drug approval and market removal processes, as established by Congress, and the clinical risks presented by injecting uncertainty into the ongoing availability of FDA-approved drugs. These patient interests are an important part of the public interest component of the preliminary injunction analysis. *Amici* respectfully submit, therefore, that an explanation of the impact of the district court's preliminary injunction ruling on those interests, not only vis-à-vis Mifepristone but as to all FDA approved drugs, will assist this Court in deciding the appeal of the ruling under review.

Amici submit this brief pursuant to Rule 29(a) of the Federal Rules of Appellate Procedure and Fifth Circuit Rule 29.

No party's counsel authored this brief in whole or in part. No party or its counsel contributed financial support intended to fund the preparation or submission of this brief. No individual or organization other than *Amici*, their members, and

their counsel contributed financial support intended to fund the preparation or submission of this brief.

SUMMARY OF ARGUMENT

The district court's preliminary injunction ruling and the flawed rationale underlying it jeopardize patients' access to drugs on which their health and, in some cases, their lives depend. Absent reversal, the ruling would render the drug Mifepristone largely unavailable to patients. But the adverse implications of the district court's decision extend far beyond one drug. If allowed to stand, this decision would cast uncertainty over the continued availability of *all* FDA-approved drugs, any of which could be challenged by litigants who disagree that patients should have access to the drug, whether for business reasons, ideological reasons, or actual clinical disagreement with FDA.

If the standard for second-guessing an FDA approval decision were as low as the district court presumed, hosts of future litigants could be expected to follow Plaintiffs' path to the courthouse door with challenges to the continued availability of a wide range of approved therapies, or even to new drugs that are still in the FDA review process. Patients would be at risk of suddenly losing access to the therapies on which their health depends. They would no longer have the security of knowing that determinations about drug safety and effectiveness rest with FDA experts in science and medicine. Further, patients would be less likely to benefit from new

therapies because uncertainty about the reliability and durability of an FDA approval would discourage investments in research and development of new drugs.

The district court's undue interference with FDA's authority regarding drug safety and effectiveness presents a grave and, in some cases deadly, risk for patients. *Amici* urge this Court to reverse the preliminary injunction ruling.

ARGUMENT

I. PATIENTS RELY ON, AND CONTRIBUTE TO, THE FDA DRUG APPROVAL PROCESS

FDA is the expert agency Congress charged with evaluating the scientific and clinical merits of all drugs for human use submitted for marketing approval in the United States. 21 U.S.C. §§ 355, 393. The agency possesses both the depth and breadth of knowledge necessary to balance the relative benefits and risks of drugs, as it is staffed with experts in multiple scientific specialties including various disciplines of medicine, biochemistry, chemical engineering, manufacturing, biostatistics, toxicology, epidemiology, pharmacology, social and behavioral science, and biology.[2] As detailed below, patients and their clinicians rely on FDA's pre-market and post-market evaluation of drugs, which draws on evidence regarding a drug's risk profile, its potential benefits, the therapeutic context in which the drug will be used, information about the conditions it can treat or prevent, existing

[2] *See, e.g.*, U.S. Food & Drug Admin. ("FDA"), *FDA Organization* (Jan. 17, 2020), https://www.fda.gov/about-fda/fda-organization (linking to FDA components).

alternative treatment options, the patients to whom it is to be administered, and any other information about the therapy and associated risks.[3] A drug's safety profile, and its efficacy profile, are not evaluated in the abstract: they are weighed in the context of the intended patient population and the relative benefit and risk in light of viable alternative clinical options. For example, the acceptable level of risk of a drug for a lethal cancer will differ from that of a drug for a less serious condition because of the inherent differences in risk of mortality or morbidity of the disease being treated. Importantly, every facet of this analysis involves an intensive and technical analysis by FDA's scientific and medical experts, as well as outside experts.

A. FDA's Approval Process Incorporates Patient and Clinician Input

The Federal Food, Drug, and Cosmetic Act ("FDCA") authorizes FDA to determine the safety and effectiveness of a new drug for its intended use before the drug can be marketed and distributed in the United States. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq*.). Charged by Congress as the expert agency for drug approvals, FDA will approve a New Drug Application ("NDA") only if the application includes "substantial evidence" of

[3] *See, e.g.*, FDA, *Benefit-Risk Assessment for New Drug and Biological Products Guidance for Industry: Draft Guidance* (Sept. 2021) (hereinafter "*FDA Benefit-Risk Assessment*"), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products.

safety and effectiveness from "adequate and well-controlled investigations." 21 U.S.C. § 355(c)(1)(A) and (d); *see also id*. §§ 321(p), 331(d), 355(a).[4]

To obtain FDA approval of a new drug, the drug's sponsor undergoes a lengthy and resource intensive development process that includes: laboratory testing; preclinical (animal) testing; several phases of clinical studies; chemistry, manufacturing, and controls; and product labeling information for prescribers.[5] Drug sponsors must show that the drug's benefits outweigh any potential risks. Under 21 U.S.C. § 355(d), the agency "shall 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."[6]

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[4] "Well-controlled clinical investigations" include "clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts 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 labeling or proposed labeling thereof." 21 U.S.C. § 355(d). Medications that are considered to be biologics are subject to licensure by FDA under the Public Health Service Act. *See* 42 U.S.C. § 262(j). A biologic is defined as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings." 21 U.S.C. § 355(i). FDA considers biologics to be a subset of drugs, and for purposes of this brief, we refer to both drugs and biologics as "drugs" for simplicity.

[5] *See* 21 C.F.R. § 314.50; *see also* FDA, *FDA's Drug Review Process: Continued* (Aug. 24, 2015), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-continued.

[6] FDA must also consult patient advocacy groups during the periodic reauthorizations of the user fee programs that fund the majority of the drug review process. *See* 21 U.S.C. §§ 379h–2(f)(1) &

FDA recognizes the central role that patients play in this balancing:

> [I]t is important to maximize the potential for such clinical trials to provide interpretable scientific evidence about the drug's benefits and risks beginning from the earliest stages of drug development. Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features such as randomization, blinding, enrichment procedures, and adequate trial duration.[7]

The agency has long utilized multiple avenues to incorporate patient and physician input in the drug review process.[8] For example, it consults with expert advisory committees that include patients and physicians to obtain independent advice and recommendations on marketing approval of drug products.[9] Indeed, patients and physicians affiliated with *Amici* frequently share their perspectives on drug applications through these mechanisms.

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(3); 379j–43(f)(1) & (3); & 379j-53(f)(1) (requiring agency consultation with representatives of patient and consumer advocacy groups in developing recommendations for the every-five-year reauthorization of the Prescription Drug User Fee Act ("PDUFA"), the Generic Drug User Fee Amendments ("GDUFA"), and the Biosimilar User Fee Act ("BsUFA")).

[7] *See FDA Benefit-Risk Assessment*, *supra* note 3, at 11.

[8] *See* FDA, *Development & Approval Process | Drugs* (Aug. 8, 2022), https://www.fda.gov/drugs/development-approval-process-drugs.

[9] *See* FDA, *New Drug Application (NDA)* (Jan. 21, 2022), https://www.fda.gov/drugs/types-applications/new-drug-application-nda. Similarly, the agency's Patient Focused Drug Development ("PFDD") initiative facilitates programs such as public meetings that allow patients, caregivers, and other stakeholders to share their perspectives and further inform the drug development process. *See* FDA, *FDA-led Patient-Focused Drug Development (PFDD) Public Meetings* (Feb. 23, 2023), https://www.fda.gov/industry/prescription-drug-user-fee-amendments/fda-led-patient-focused-drug-development-pfdd-public-meetings.

B. FDA's Withdrawal Procedure Is a Careful, Reasoned Process Heavily Focused on Patient Impact

After a drug is approved, FDA continues to monitor its real-world performance, including safety, to ensure that the drug remains safe and effective for its intended uses according to the conditions under which it was approved.[10] Patients, in particular, play a critical role in the agency's monitoring process. For example, patients and their clinicians are the principal source of post-approval adverse drug experience reports and are therefore crucial to the agency's ongoing understanding of a drug's safety and efficacy. Moreover, patient participation in post-approval clinical studies directly informs the agency's determination of any drug-specific post-approval requirements and conditions, including post-approval studies, labeling warnings, and other protections necessary to ensure safe and effective use of the drug.[11]

When FDA becomes aware of new information about a drug—either through post-approval studies or reports from patients, clinicians, or manufacturers—the agency assesses the information through a multi-step analysis tailored to the particular drug. Under that analysis, the agency considers the drug's approval status,

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[10] Sponsors also sometimes seek supplemental approval for a new indication, labeling change, or change to the drug itself or its manufacturing process, quality controls, or other changes that "may relate to the safety or effectiveness of the drug product." 21 C.F.R. § 314.70.

[11] *See* 21 U.S.C. § 356b; *see also* FDA, *FDA Patient Engagement Overview* (Sept. 14, 2020), https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-engagement-overview (providing an overview of FDA's patient engagement initiatives).

the conditions it is intended to treat, and the patient population reliant upon the therapy. When a drug is already on the market, FDA gives additional weight to how a change in indication, or removal of the drug from the market, would impact clinical practice and patient care. Depending on the agency's analysis of new information, it may determine that an additional warning or precaution is appropriate.[12] In other cases, FDA might require a change in the labeling to narrow the use of the drug.

Where it appears to FDA that the risks of a drug to patients outweigh the benefits, even with appropriate labeling and other protections,[13] FDA initiates an action to withdraw its approval of the drug. *See* 21 U.S.C. § 355(e); 21 C.F.R. §§ 314.150–314.151.[14] Even where a manufacturer voluntarily removes a drug from the market, FDA will determine whether the drug is "safe and effective" in order to permit or prevent generic versions from entering the market.[15]

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[12] *See, e.g.*, FDA, *Postmarket Drug Safety Information for Patients and Providers: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications* (Feb. 5, 2018), https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications.

[13] *See* FDA, *Guidance for Industry Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* 4–5 (July 2013), https://www.fda.gov/media/116594/download.

[14] In addition, FDA may initiate a withdrawal procedure if a sponsor either fails to undertake required post-market studies or new evidence comes to light that contradicts the data in the original new drug application. 21 U.S.C. § 355(e)(1)–(3); 21 C.F.R. § 314.150(a)(2). FDA has withdrawn approved indications for certain drugs while leaving them on the market to treat other conditions. For example, in 2011, FDA announced that it was withdrawing the breast cancer indication for Bevacizumab, but the drug was still indicated for metastatic colorectal cancer and other conditions, and remained on the market for those other indications. *See* Larry Sasich, et al., *The US FDA's withdrawal of the breast cancer indication for Avastin (bevacizumab)*, 20 Saudi Pharm J. 381 (2012).

[15] 21 C.F.R. § 314.161.

The district court disregarded this robust and well-established process through which drugs are reviewed for marketing approval, necessary adjustments are made to labeling or other conditions of distribution as needed, and drugs are removed from the market by FDA when warranted. The court also failed to account for the fact that FDA specialists with technical expertise in their respective fields undertake this balancing of complex scientific data bearing on drug safety and effectiveness pursuant to a specific grant of authority by Congress.

II. INJECTING UNCERTAINTY INTO THE STATUS OF APPROVED DRUGS WOULD HARM PATIENTS

Amici are extremely concerned that if the district court's decision is allowed to stand, it will encourage private litigants to bring additional lawsuits that second-guess FDA's scientifically-based approval decisions. Compounding this concern, under the lower court's reasoning, the bar for overturning FDA approvals would be improperly low. The adverse impact on patients of such a regime would be strongly contrary to the public interest.

Because Article III judges are not equipped to undertake the clinical and scientific assessment of a drug's risks and benefits, the bar for a court to take the drastic step of effectively removing a drug from the market should be extremely

high.[16] Lowering that bar, as the district court has done in this case, would inject uncertainty into the status of approved drugs, which would jeopardize treatment for patients.

A. Sudden Loss of Access to Needed Drugs Jeopardizes Patients

While the district court's decision applies to one drug and was driven by the agenda of one group of plaintiffs, the decision leaves no meaningful limiting principle on the ability of future plaintiffs to challenge the approval of other drugs and threaten their availability for patients other than themselves. Future plaintiffs might seek injunctions blocking approval of a drug based on, for example, a different view of the drug's safety profile, belief the drug is too expensive or encourages undesired behavior, the plaintiffs' religious or moral beliefs, or business interests that would benefit from removal of the drug from the market. Injunctions effectively reversing an FDA drug approval like the one entered by the district court could result in immediate removal of a drug from the market. Patients taking the drug would lose access with little or no warning, which could pose serious or life-threatening health risks. Even the threat of such loss would create uncertainty for patients and their clinicians. A drug approved as long as twenty years ago (such as Mifepristone) could be removed. Where the continued availability of a drug is threatened by the

[16] *See, e.g.*, *Sierra Club v. EPA*, 939 F.3d 649, 680 (5th Cir. 2019) ("A reviewing court must be 'most deferential' to the agency where, as here, its decision is based upon its evaluation of complex scientific data within its technical expertise.").

prospect of litigation, physicians and patients would potentially need to consider starting a course of treatment based on which drug they predict is least likely to be removed from the market rather than on the best clinical interests of the patient.

The risks of sudden loss of access to therapies are especially high for patients who are undergoing treatment for life-threatening conditions. The harm from lost access to prescribed drugs has been well-studied in the context of drug shortages, and these studies provide a useful analogy for considering the impact of a potential disruption in access to a critical drug as a result of litigation.[17] When a medication is unavailable to a patient who requires treatment, "regardless of the reason, the patient will either have to go without treatment, choose an alternative treatment, delay treatment, or incur some difficulty by trying to obtain treatment via another source."[18] Studies have found that sudden lack of drug availability due to shortage caused severe harms, including significant rates of delay and cancellation in

[17] FDA defines a "drug shortage" as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug." 21 C.F.R. § 314.81(b)(3)(iii)(f).

[18] Jonathan Minh Phuong et al., *The impacts of medication shortages on patient outcomes: A scoping review*, PLoS One (May 3, 2019), at 2.

treatment and surgical intervention[19], increased medication errors[20], and serious adverse outcomes—including death.[21] Congress has responded to the detrimental impact of drug shortages by granting FDA multiple tools to avoid disruption to the supply of a drug and to quickly increase alternative sources so patients are not left without treatment options.[22] The sudden overturning of a drug's approval would be equivalent to a dramatic shortage event.

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[19] *See, e.g.*, *id*. 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"), *AHA Survey on Drug Shortages* (Jun. 12, 2011), https://www.aha.org/system/files/content/11/drugshortagesurvey.pdf.

[20] *See, e.g.*, Phuong, *supra* note 18, at 6, 12 (citing a finding in a 2003 study that in 54% of shortages, "clinicians may be unfamiliar with the alternative product regarding its mechanism of action, adverse effects, or interactions"); McBride, *supra* note 19, at e1291; McKeever, *supra* note 19, at 491; McLaughlin, *supra* note 19, at 785.

[21] *See, e.g.*, Phuong, *supra* note 18, at 5-10 (citing eight studies linking drug shortages to patient deaths); Kehl, *supra* note 19, at e157; McKeever, *supra* note 19, at 491 (citing studies linking patient deaths to delays or cancellations in oncology treatment or drug substitutions); McLaughlin, *supra* note 19, at 785 (noting 41.4% of directors of pharmacy reported possible or probable adverse events from drug shortages); AHA, *supra* note 19, 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).

[22] *See, e.g.*, 21 U.S.C. §§ 356c(a) (requiring manufacturer notification to FDA of a permanent discontinuance of certain drugs or of an interruption that is likely to lead to a meaningful disruption in the drug's supply), 356e (providing for FDA to maintain a drug shortages list), 356f (providing for hospital repackaging of a drug in shortage), 353b (providing for outsourcing facilities to compound drugs on the shortage list, notwithstanding if such drug would otherwise be prohibited from compounding as "essentially a copy" of an approved drug). FDA also takes a variety of steps to help facilitate increases in supply or to identify alternative manufacturing sources to avoid and mitigate drug shortages. *See* FDA, *Frequently Asked Questions about Drug Shortages* (Apr. 6,

These consequences of lost access to therapies are devastating for all patients, but they are particularly devastating for cancer patients.[23] Cancer patients who lose access to a prescribed drug must switch to treatments that are more toxic[24] and/or less efficacious and may result in worse prognoses.[25] In addition, health plan formularies frequently cover only one therapy in a class, meaning that an alternative treatment, even if legally marketed, is not available to a patient until the health plan updates its coverage policy. For some diseases or conditions, including a number of cancers, there are *no* legally marketed alternative treatments. For these diseases and conditions, removal of a drug from the market could, in effect, be a death sentence.[26]

2023), https://www.fda.gov/drugs/drug-shortages/frequently-asked-questions-about-drug-shortages.

[23] *See, e.g.*, McBride, *supra* note 19, at e1289; Kehl, *supra* note 19, at e154; McKeever, *supra* note 19, at 490; Gogineni, *supra* note 19, at 2463-64; Hanna, *supra* note 21; *see also* Yoram Unguru, *Second Opinion: In Short Supply*, Hopkins Med. (Winter 2020), https://www.hopkinsmedicine.org/news/publications/hopkins_medicine_magazine/forum/in-short-supply ("Drug shortages have directly harmed countless patients, and those with cancer are particularly vulnerable.").

[24] *See, e.g.*, Daniel J. Becker, et al., *Impact of Oncology Drug Shortages on Patient Therapy: Unplanned Treatment Changes*, 9 J. Oncology Practice e122, e124 (2013); McKeever, *supra* note 19, at 493; 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, 2461 (2012); *see also* McBride, *supra* note 19, at e1293.

[25] *See* Metzger, *supra* note 24, at 2462; *see also* Unguru, *supra* note 22 ("Chemotherapy shortages force my colleagues and me to delay treatments, skip or reduce doses, and select less effective and familiar alternatives."); Kehl, *supra* note 19, at e157; Becker, *supra* note 24, at e125.

[26] 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* Metzger, *supra* note 24, at 2463; McKeever, *supra* note 19, 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 midtreatment" because the drug suddenly became unavailable due to manufacturing issues).

The risks to pediatric cancer patients are especially severe. For many pediatric cancers, there is only one FDA-approved treatment available.[27] For others, approved alternatives to standard treatment are inferior—often leading to significantly worse outcomes. 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%).[28] The study authors concluded that the unavailability of agents used in pediatric cancer treatment regimens is "likely to have devastating effects on patients with cancer," and that "what might appear to be a suitable alternative regimen may result in an inferior outcome—an intolerable situation for young people with curable diseases."[29]

It is no wonder that drug shortages lead patients, and their family members, to experience serious anxiety in the face of uncertainty about their treatment. 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

[27] *See* Metzger, *supra* note 24, at 2463 ("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.").

[28] *Id.* at 2462.

[29] *Id*. at 2463.

therapy regimen for acute lymphoblastic leukemia, "It is terrifying as a mom that a drug your child needs is not available." [30]

Uncertainty about the prospect of lost access to a drug as a result of a lawsuit or lawsuits seeking to remove it from the market—which a decision upholding the district court would encourage—would be an added source of anxiety for patients and families already grappling with battling life-threatening diseases and other conditions.

B. Uncertainty About the Reliability of Drug Approvals Would Discourage Research and Development into New Therapies

In recent years, biopharmaceutical innovation has spawned research into promising, but complex, potential new therapies designed to treat chronic, serious, and rare conditions. However, developing these therapies is technically challenging

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[30] Dr. Sherise Rogers, *Shortage of critical cancer drug forcing some children to go without*, ABC News (Oct. 22, 2019), https://abcnews.go.com/Health/shortage-critical-cancer-drug-forcing-children/story?id=66411784; *see also* Elizabeth Cohen & Amanda Musa, *Thousands of people can't get full treatments of a lifesaving cancer drug*, CNN (Feb. 17, 2023), https://www.cnn.com/2023/02/15/health/cancer-drug-shortage-bcg/index.html (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 in fact come right back"); Brenda Goodman, *How one mom headed off a drug shortage*, CNN (Dec. 29, 2022), https://www.cnn.com/2022/12/29/health/drug-shortage-mom-angels-for-change/index.html (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?"); Rob Stein, *How A Drug Shortage Hiked Relapse Risks For Lymphoma Patients*, NPR (Dec. 26, 2022), https://www.npr.org/sections/health-shots/2012/12/26/168038307/how-a-drug-shortage-hiked-relapse-risks-for-lymphoma-patients (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").

as well as costly. For example, chimeric antigen receptor ("CAR") T-cell therapy—which uses a type of white blood cell (T cells) from a patient that have been modified to target and destroy cancer cells more effectively than the typical "pillars" of cancer treatment (surgery, chemotherapy, and radiation therapy)—was extremely costly and challenging to develop.[31] Companies can be expected to spend anywhere from under $1 billion to more than $2 billion on research and development ("R&D") for some of these promising new therapies.[32] The pharmaceutical industry has invested over $1.1 trillion in the development of new treatments and cures since 2000, including $102.3 billion in 2021 alone.[33] Significantly, however, these investments do not guarantee that a new therapy will ever reach the market. As documented in the Congressional Budget Office's ("CBO's") 2021 report on the pharmaceutical industry, most drugs in development never enter clinical trials, and, of those that do, only about 12 percent are ultimately approved by FDA.[34]

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[31] T cell engineering, which itself drew on decades of research, began in 1992, with the first effective CAR T cells being developed in 2002. FDA designated CD19-directed CAR T cells as a "breakthrough therapy" in 2014 and approved them for the treatment of relapsed, refractory acute lymphoblastic leukemia in children and young adults in 2017. This was the first approval of a CAR T cell therapy in the United States and represented a tremendous scientific and medical breakthrough for the treatment of cancer. *See* Memorial Sloan Kettering, *CAR T Cells: Timeline of Progress*, https://www.mskcc.org/timeline/car-t-timeline-progress (last accessed Apr. 29, 2023).

[32] Cong. Budget Office ("CBO"), *Research and Development in the Pharmaceutical Industry* (2021), https://www.cbo.gov/system/files/2021-04/57025-Rx-RnD.pdf.

[33] *See* Pharmaceutical Research and Manufacturers of America ("PhRMA"), *Annual Membership Survey* 3, tbl. 1 (2022), https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Refresh/Report-PDFs/P-R/PhRMA_membership-survey_2022_final.pdf.

[34] CBO, *supra* note 32.

Given the complexity and expense of developing a new drug, Congress and FDA actively encourage and support new drug development through a variety of financial incentives,[35] while at the same time ensuring that the relevant patient populations, who in many cases are vulnerable, are sufficiently protected.[36] For example, some new drugs qualify for a period of marketing exclusivity that reflects the significant investment in R&D.[37] Congress and FDA have also established designations to expedite development and review of drugs for particular needs, such as drugs for rare diseases.[38] Similarly, Congress has provided for priority review vouchers (entitling the voucher-holder to designate a drug application as qualifying

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[35] *See, e.g.*, FDA, *Rare Diseases: Common Issues in Drug Development Guidance for Industry: Draft Guidance* (Feb. 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-common-issues-drug-development-guidance-industry.

[36] *See e.g.*, *FDA Benefit-Risk Assessment*, *supra* note 3, at 11 ("A higher degree of uncertainty is common in drug development programs for rare diseases, where the prevalence of disease, and consequent limitations of study size, can limit the precision of safety and efficacy characterizations. FDA recognizes that . . . it is important to maximize the potential for such clinical trials to provide interpretable scientific evidence about the drug's benefits and risks beginning from the earliest stages of drug development. Patient contribution is optimized in small sample size studies by minimizing bias and maximizing precision with trial design features such as randomization, blinding, enrichment procedures, and adequate trial duration."); *see also* Liz Essley Whyte, *FDA Increasingly Halting Human Trials as Companies Pursue Risky, Cutting-Edge Drugs*, Wall Street J. (Jan. 10, 2023), https://www.wsj.com/articles/fda-increasingly-halting-human-trials-as-companies-pursue-risky-cutting-edge-drugs-11673322324 ("[FDA] halted clinical trials for experimental drugs an average of 664 times each year from 2017 to 2021, up from 557 each of the previous five years, according to the review of agency data. Through mid-December last year, the FDA had placed 747 of the holds.").

[37] *See, e.g.*, 21 U.S.C. §§ 355(a), (e), (j)(5)(B)(iv), (j)(5)(B)(iv); 21 C.F.R. §§ 314.108, 316.31, 316.34.

[38] *See e.g.*, FDA, *Breakthrough Therapy* (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

for priority review) for companies researching treatments for particular diseases or conditions.[39]

Congress has also created tax credits to ease some of the expenses of research activities. *See, e.g.*, 26 U.S.C. §§ 21, 174. It has mandated waivers or reductions of drug application fees in situations where the fees might represent a barrier to innovation. *See* 21 U.S.C. § 379h(d)(1). Congress also provides direct funding for research through several programs.[40]

With the benefit of these initiatives, flexibilities, and financial incentives, FDA has shepherded thousands of life-saving drugs through the approval process. Were the lower court's approach to be upheld and adopted by other courts, the delicate balance that the agency and Congress have established to encourage investment in R&D, particularly into treatments that are challenging for

[39] *See* Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) (establishing priority review vouchers for tropical diseases); Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012) (establishing priority review vouchers for rare pediatric disease); Adding Ebola to the FDA Priority Review Voucher Program Act, Pub. L. No. 113-233, 128 Stat. 2127 (2014) (establishing priority review vouchers for Ebola); 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016) (establishing priority review vouchers for material threat medical countermeasures).

[40] For example, the Congressionally Directed Medical Research Program ("CDMRP") receives congressional appropriations for biomedical research in congressionally-identified diseases of concern and provides grants to researchers working on related treatments. Similarly, the Biomedical Advanced Research and Development Authority ("BARDA") funds areas of interest to the agency, such as antimicrobials and chemical threat medical countermeasures. 42 U.S.C. § 247d–7e(c)(4)(B).

technological or economic reasons, would be upended by researchers' inability to rely on FDA's science-based approval and market removal process as definitive.

C. Future Suits Challenging FDA Approvals Would Create Uncertainty Among Patients, Providers, and Drug Developers

The district court's opinion, including its improperly expansive theory of standing, has the potential to generate a flood of litigation challenging FDA drug approvals.[41] Emboldened advocacy groups can be expected to target the approvals of drugs they disfavor based on their lay understandings of scientific studies, cherry-picked data regarding rare side effects, or other grounds. For example, physicians who believe that the availability of a weight loss drug incentivizes "unhealthy" patient behavior in terms of nutrition and exercise could bring a challenge to the drug's underlying approval. Groups that believe certain drugs are priced too high could challenge their underlying approval. Indeed, groups motivated by a wide range of moral, ideological, or economic considerations would have wide latitude to bring suits. If drug approvals were reviewed under the lax standard of review that the district court applied here, the overturning of FDA approvals could become the norm.

It bears emphasis that courts are not suited to undertake the resource-intensive, scientifically rigorous analysis of the clinical impact of removing a drug

[41] Importantly, the court's approach would not be limited to drugs (and biologics); it might also be extended to approvals and clearances of medical devices.

from the market, or to balance the harm to patients of removing a drug from the market against other considerations such as safety risks. Congress entrusted FDA with that responsibility, subject to the agency's reasonable exercise of its scientific judgment. To fulfill that directive, FDA employs experts in science and medicine who are properly trained and equipped to undertake the rigorous analyses necessary for determinations about drug safety and efficacy and to evaluate input from patients and clinicians. Consistent with the FDCA, it is those experts' judgment about drug safety and efficacy, and the judgment of a patient's clinician, that should primarily influence the health and well-being of patients.

CONCLUSION

For the foregoing reasons, this Court should reverse the district court's order granting Plaintiffs-Appellees' motion for preliminary injunction.

Respectfully submitted,

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May 1, 2023
Washington, D.C.

CERTIFICATE OF SERVICE

I hereby certify that I e-filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Fifth Circuit by using the appellate CM/ECF system on May 1, 2023.

Participants in the case who are registered CM/ECF users will be served by the appellate CM/ECF system.

May 1, 2023
Washington, D.C.

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CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limits of Rule 32(a) of the Federal Rules of Appellate Procedure because, according to the word count feature of Microsoft Word, it contains 5512 words. This brief also complies with the typeface requirements and type-style requirements of Federal Rules of Appellate Procedure 32(a) and 5th Cir. Rule 32.1 because it was prepared in Times New Roman, a proportionally spaced typeface, 14-point font, with footnotes in Times New Roman 12-point font.

/s/ Emily I. Gerry
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APPENDIX

LIST OF *AMICI CURIAE*

The Leukemia & Lymphoma Society
Rye Brook, NY
The Leukemia & Lymphoma Society ("LLS") is the world's largest voluntary health agency dedicated to fighting blood cancer and ensuring that the more than 1.3 million blood cancer patients and survivors in the United States have access to the care they need. LLS's mission is to cure leukemia, lymphoma, Hodgkin's disease, and myeloma, and to improve the quality of life of patients and their families. LLS advances that mission by advocating that blood cancer patients have sustainable access to quality, affordable, coordinated health care, regardless of the source of their coverage.

American Cancer Society
Atlanta, GA
The mission of the American Cancer Society ("the Society") is to improve the lives of people with cancer and their families through advocacy, research, and patient support, to ensure everyone has an opportunity to prevent, detect, treat, and survive cancer. Since 1946, the Society has funded over $5 billion in cancer research, including giving grants to 50 investigators who went on to win the Nobel Prize. The Society also provides extensive patient support, from housing patients in Hope Lodges across the nation to having a call center open 24-7.

American Cancer Society Cancer Action Network
Washington, DC
The American Cancer Society Cancer Action Network ("ACS CAN") is the nonprofit, nonpartisan advocacy affiliate of the Society, making cancer a top priority for public officials and candidates at the federal, state and local levels. ACS CAN empowers advocates across the country to make their voices heard and influence evidence-based public policy change as well as legislative and regulatory solutions that will reduce the cancer burden.

American Childhood Cancer Organization
Kensington, MD
The American Childhood Cancer Organization ("ACCO") was founded in 1970 by parents of children diagnosed with cancer. ACCO is dedicated to making childhood cancer a national health priority through shaping policy, expanding research, raising

awareness, and providing educational resources and innovative comfort programs for children with cancer, survivors, and their families.

American Society of Clinical Oncology
Alexandria, VA
The American Society of Clinical Oncology ("ASCO") is a national organization representing more than 45,000 physicians and other health care professionals specializing in cancer treatment, diagnosis, and prevention. ASCO is committed to ensuring that safe and effective treatments for cancer are available to all Americans with an equitable an evidence-based approach.

American Society of Hematology
Washington, DC
American Society of Hematology ("ASH") represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematologic (also known as non-malignant) conditions such as sickle cell disease ("SCD"), thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. ASH believes that all individuals should have access to evidence-based, high-quality, clinically appropriate care, and the Society is committed to fostering high-quality, equitable care, transformative research, and innovative education to improve the lives of patients with blood and bone marrow disorders.

American Urological Association
Linthicum, MD
The American Urological Association ("AUA") is a globally engaged membership organization with more than 22,000 members practicing in more than 100 countries. Our members represent the world's largest collection of expertise and insight into the treatment of urologic disease. Of the total AUA membership, more than 18,000 are based in the United States and provide invaluable support to the urologic community by fostering the highest standards of urologic care through education, research, and formulation of health policy.

Arthritis Foundation
Atlanta, GA
The Arthritis Foundation, the nation's largest nonprofit organization focusing on arthritis, is boldly pursuing a cure for America's #1 cause of disability championing the fight to conquer arthritis with life-changing science, resources, advocacy and community connections.

Cancer*Care*
New York, NY
Cancer*Care* is the leading national organization providing free, professional support services and information to help people manage the emotional, practical and financial challenges of cancer.

Cancer Support Community
Washington, DC
As the largest professionally led nonprofit network of cancer support worldwide, the Cancer Support Community ("CSC") is dedicated to ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community. CSC delivers more than $50 million in free support and navigation services to cancer patients and their families. CSC also conducts cutting-edge research on the emotional, psychologic, and financial journey of cancer patients and advocates at all levels of government for policies to help individuals whose lives have been disrupted by cancer.

Council of Medical Specialty Societies
Chicago, IL
The Council of Medical Specialty Societies ("CMSS") is a coalition of 50 specialty societies representing more than 800,000 physicians across the house of medicine. CMSS works to catalyze improvement through convening, collaborating, and collective action. Together, CMSS addresses critical issues across specialties that influence the future of healthcare and the patients they serve.

Epilepsy Foundation
Bowie, MD
The Epilepsy Foundation is the leading national, voluntary health organization representing over 3.4 million Americans with epilepsy and seizures. Timely access to quality, affordable, physician-directed care including access to anti-seizure medications is vital for people with epilepsy. Uncontrolled seizures can lead to disability, injury, and death. Epilepsy medications are the most common, cost-effective treatment for controlling and/or reducing seizures.

Friends of Cancer Research
Washington, DC
Friends of Cancer Research is working to accelerate policy change, support groundbreaking science, and deliver new therapies to patients quickly and safely. Friends of Cancer Research unites scientists, pharmaceutical companies, and policy makers with shared trust and guides them toward meaningful cooperation. This collaboration among partners from every healthcare sector ultimately drives advances in science, policy, and regulation that speed life-saving treatments to patients.

Hemophilia Federation of America
Washington, DC
Hemophilia Federation of America ("HFA") is a community-based, grassroots advocacy organization that assists, educates, and advocates for people with hemophilia, von Willebrand disease, and other rare bleeding disorders. Bleeding disorders are serious, life-long, and expensive. HFA seeks to ensure that individuals affected by bleeding disorders have timely access to quality medical care, therapies and services, regardless of financial circumstances or place of residence.

Muscular Dystrophy Association
Chicago, IL
The Muscular Dystrophy Association ("MDA") is the number one voluntary health organization in the United States for people living with muscular dystrophy, ALS, and related neuromuscular diseases. For over 70 years, MDA has led the way in accelerating research, advancing care, and advocating for the support of their families. MDA's mission is to empower the people they serve to live longer, more independent lives.

National Patient Advocate Foundation
Washington, DC
National Patient Advocate Foundation ("NPAF") is dedicated to amplifying the voices of patients and advocating for better access to affordable, equitable, quality care. As the advocacy affiliate of the Patient Advocate Foundation, NPAF provides educational resources to help patients advocate for themselves and make informed, personalized health care decisions.

National Multiple Sclerosis Society
New York, NY
The National Multiple Sclerosis Society mobilizes people and resources so that the nearly one million people affected by multiple sclerosis ("MS") can live their best

lives while the Society works to stop MS in its tracks, restore what has been lost and end MS forever.

National Organization for Rare Disorders
Quincy, MA
National Organization for Rare Disorders ("NORD") is a unique federation of voluntary health organizations dedicated to helping people with rare diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services. NORD believes that all individuals with a rare disease should have access to quality and affordable health care that is best suited to meet their medical needs.

RESOLVE: The National Infertility Association
McLean, VA
RESOLVE: The National Infertility Association, established in 1974, is dedicated to ensuring that all people challenged in their family building journey reach resolution through being empowered by knowledge, supported by community, united by advocacy, and inspired to act. RESOLVE is the oldest and largest patient advocacy non-profit for infertility and family building in the United States.

WomenHeart: The National Coalition for Women with Heart Disease
Alexandria, VA
WomenHeart: The National Coalition for Women with Heart Disease is the nation's only patient-centered organization focused solely on providing support, education and advocacy to women living with or at risk for heart disease.