Nos. 25A1207, 25A1208

In The
Supreme Court of the United States

DANCO LABORATORIES, L.L.C.,
Applicant,
v.
LOUISIANA, ET AL.
Respondents.

GENBIOPRO, INC.,
Applicant,
v.
LOUISIANA, ET AL.
Respondents.

ON APPLICATIONS TO VACATE STAY OF THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

BRIEF OF BLOOD CANCER UNITED AND NINE OTHER ADVOCACY GROUPS AS *AMICI CURIAE* IN SUPPORT OF APPLICATIONS BY DANCO AND GENBIOPRO TO STAY OR VACATE THE FIFTH CIRCUIT'S STAY PENDING APPEAL

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INTEREST OF *AMICI CURIAE*[1]

Blood Cancer United, The Academy of Managed Care Pharmacy, American Society of Clinical Oncology, American Society of Hematology, Association for Clinical Oncology, Cancer*Care*, Friends of Cancer Research, Muscular Dystrophy Association, National Alliance on Mental Illness, and National Patient Advocate Foundation represent millions of patients and the medical professionals who take care of them 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 lives depend on the reliability of FDA approvals of medications and their approved conditions of use. The Fifth Circuit's opinion staying the 2023 REMS for mifepristone jeopardizes patients' and providers' ability to rely on FDA's congressionally mandated process for determining conditions of use under which a drug is safe and effective, and therefore available for treatment.

INTRODUCTION AND SUMMARY OF ARGUMENT

Congress established a regulatory regime for drugs that encourages research and development while also providing ongoing scrutiny of how drugs can be used safely and effectively without unduly burdening patient access. As a result, drugs must not only obtain approval by FDA prior to being marketed for specific uses or

[1] Pursuant to Supreme Court Rule 37.6, *amici curiae* states that no counsel for any party authored this brief in whole or in part and no entity or person, aside from *amici curiae*, its members, or its counsel, made any monetary contribution intended to fund the preparation or submission of this brief.

conditions, permissible uses and conditions are subject to update based on new data and evolving clinical practices. That includes through FDA's Risk Evaluation and Mitigation Strategies ("REMS")—the protocol by which FDA approves drugs when safety concerns warrant stricter controls to ensure the benefits of the drug outweigh the risks. Modifying a REMS could result in an expansion of a drug's permissible uses, but it also could result in a new restriction on those uses. Critically, the decision to modify a drug's previously approved conditions of use is subject to the *same* rigorous safety and effectiveness standard as the decision to approve particular conditions of use in the first instance. Approval ultimately is based on a scientific conclusion that the benefits of the intended use of the drug outweigh the risks.

In staying FDA's 2023 REMS modification to mifepristone's conditions of use, the Fifth Circuit impermissibly displaced FDA's evidence-based scientific judgment with its own, disregarding Congress's express vesting of authority in FDA's science-based determinations, and giving insufficient weight to the fact that FDA is currently reviewing the mifepristone REMS for potential modifications. The Fifth Circuit crafted its own understanding of how evidence supporting the safety and effectiveness of mifepristone's conditions of use should be interpreted—without any evidence that the risks of those conditions now outweigh their benefits.

Amici are particularly concerned that in so doing, the decision improperly dismissed, and fundamentally misunderstood, the significant reliance interests that patients and providers have on the statutorily mandated process by which FDA must

direct or approve updates to a drug's conditions of use. Providers rely on these decisions in making treatment plans, and patients depend on being able to take the drugs as prescribed by their providers. Because the 2023 REMS formalized a policy that had been in place since 2021, patients and providers have relied on mifepristone's conditions of use for five years. Yet in less than two pages addressing the merits, the Fifth Circuit effectively rewrote those conditions of use overnight.

The Fifth Circuit's ruling broadly jeopardizes the reliability of FDA's modifications to the conditions of a drug's use. And it provides a troubling roadmap for other litigants to challenge and dismantle conditions of use they disfavor—no matter the drug, no matter whether those changes expand or restrict how the drug can be used, and no matter whether their motivation is patient safety, profit, or something else. If current conditions of use can be so readily stayed, and effectively altered, despite FDA's previous and ongoing scientific assessments, the resulting uncertainty will jeopardize patient access to drugs, particularly in cases where FDA has expanded the approved uses of a drug to cover new diseases or conditions. It could also threaten patient safety, as FDA approves modifications to conditions of use where it determines they are needed to protect patients from risks of harm. Finally, the Fifth Circuit's decision would impair the development of new treatments, as uncertainty disincentivizes pharmaceutical manufacturers, clinicians, and patients from undertaking time- and resource-intensive clinical trials to study new drugs and new indications for approved drugs.

In light of the above considerations, this Court should grant the applications for a stay or vacatur.

I. CONGRESS ENTRUSTED FDA TO DETERMINE WHETHER DRUGS ARE SAFE AND EFFECTIVE AND TO MAKE SCIENCE-BASED CHANGES TO HOW DRUGS MAY BE USED

FDA is the expert agency entrusted by Congress to ensure the safety of pharmaceuticals in the United States. *See* Food, Drug, and Cosmetic Act ("FDCA"), Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 301 *et seq*.); Drug Amendments of 1962, Pub. L. No. 87-781, § 102, 76 Stat. 780, 781–82 (codified as amended at 21 U.S.C. §§ 321, 331, 332, 348, 351–53, 355, 357–60, 372, 374, 376, 381).

Study of the safety and effectiveness of drugs, both investigational and approved, is the cornerstone of FDA's oversight at each stage of a drug's life cycle. The agency—staffed with experts in multiple scientific disciplines including medicine, biochemistry, chemical engineering, manufacturing, biostatistics, toxicology, epidemiology, pharmacology, social and behavioral science, and biology—possesses the depth and breadth of knowledge necessary to assess the evidence of the relative benefits and risks of drugs and to make scientific, evidence-based determinations as to whether or not to approve or modify the conditions of approval for a drug.

A. FDA Employs a Rigorous Process for Approving New Drugs

FDA may approve a new drug only if the sponsor's application presents "substantial evidence" of safety and effectiveness, 21 U.S.C. § 355(c)(1)(A) and (d), meaning "adequate and well-controlled investigations, … by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved," *id*. §§ 321(p), 331(d), 355(a). FDA is required to evaluate a new drug through an intensive assessment of its benefits and risks and the conditions under which it may be used. *Id*. § 355(d). Specialists conduct a full review of the application, including clinical data and animal studies. In cases where further consideration of the safety and effectiveness data is required, reviewers may utilize one of the agency's Advisory Committees for an additional level of review. Because FDA focuses on the drug's risk-benefit profile, a drug sponsor need not demonstrate that a drug has no potential adverse effects; rather, the sponsor must show that the drug's benefits outweigh any risks. *See Mutual Pharm. Co. v. Bartlett*, 570 U.S. 472, 476 (2013) ("In order for the FDA to consider a drug safe, the drug's probable therapeutic benefits must outweigh its risk of harm." (internal quotation marks and citation omitted)).

All prescription drugs approved by FDA are accompanied by official prescribing information ("PI") that reflects FDA's findings as to safety and effectiveness. *See generally* 21 C.F.R. pt. 201. The PI must include, among other things, a summary of essential scientific information needed for safe and effective use of the drug, the approved populations and conditions for which the drug may be prescribed,

specifically the indications, details regarding approved dosage and methods of administration, a statement of warnings, precautions and drug interactions, and any other conditions required for the drug to be administered safely and effectively. *Id.* §§ 201.56(a)(1), 201.57.

B. FDA's Process for Evaluating Changes to Permissible Uses Is Subject to the Same Rigorous Standard as Initial Approval

There are a number of instances where modifications to a drug's conditions of use are required. In the case of a REMS, FDA is statutorily required to assess potential modifications proposed by the drug sponsor. 21 U.S.C. § 355-1(h). The agency may also determine, independently of the drug sponsor, that modification of a REMS is necessary, for example to ensure that the benefits of a drug continue to outweigh its risks, *id.* § 355-1(g), and to ensure that the elements of the REMS are not "unduly burdensome on patient access" in light of the drug's risks, *id.* § 355-1(f)(2)(C). REMS aside, a sponsor must also obtain FDA approval for any change that "may relate to the safety or effectiveness of the drug product." 21 C.F.R. § 314.70. For example, drug sponsors must apply for supplemental approval to add a new indication (like marketing a drug to treat a different patient population or a different disease or condition), change the drug itself or its manufacturing process, or amend quality controls. *Id.* § 314.70(b).[2]

[2] Changes that do not bear on the safety or effectiveness of a drug, including editorial label changes and the like, are not required to go through this process and may, in some cases, instead be included in an annual report to the agency. 21 C.F.R. § 314.70(d).

FDA oversight ensures that the conditions of a drug's approval continue to be met and any significant changes proposed to a drug's formulation, manufacture, or intended uses are assessed for safety and efficacy. As is required for new drug approvals, FDA requires data to support supplemental approval applications, according to the degree of risk presented by the change. Major changes, such as to the drug substance, production, quality controls, or a new indication, require data derived from studies that assess the effects of the change. 21 C.F.R. § 314.70(b)(3). FDA reviews a supplemental application to assess the safety and effectiveness of the proposed change—the same standard by which the initial application was judged. *Id.* §§314.70, 314.71. The agency also considers how a change in indication would impact clinical practice and patient care.

FDA may also require certain changes. The FDCA, for example, requires safety labeling changes to communicate "new safety information" about an approved prescription drug.[3] *See* 21 U.S.C. § 355(o)(4); *see also* FDA, *Guidance for Industry Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* 1 (Jul. 2013).[4] Labeling thus "must be updated when new information becomes

[3] New safety information consists of "information derived from a clinical trial, an adverse event report, a postapproval study. . . , peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system; . . . or other scientific data deemed appropriate by [FDA]" regarding "a serious risk or an unexpected serious risk associated with use of the drug that [FDA] has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the [REMS] was required, or since the last assessment of the approved [REMS] for the drug" or "the effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS]." 21 U.S.C. § 355-1(b)(3).

[4] Available at https://www.fda.gov/media/116594/download.

available that causes the labeling to become inaccurate, false, or misleading." 21 C.F.R. § 201.56(a)(2).

II. FDA UPDATES THE PERMISSIBLE USES AND LABELING OF APPROVED DRUGS AS SCIENTIFIC KNOWLEDGE EVOLVES

FDA oversight may result in a variety of modifications to the terms of a drug's approval. For instance, FDA review frequently leads to the expansion of indications to encompass treatment of new conditions or new patient populations. FDA review may additionally result in updates to a drug's labeling, with a new dosage regimen or safety-related warnings. It may also cause a drug's formulation or manufacturing to change, to improve its risk-benefit profile. Or it may result in an alteration to a drug's delivery methods. While "off-label" use of medications occurs in some instances, supplemental changes to a drug's labeling provide "adequate directions for use" that equip health care practitioners to treat patients based on scientific information extrapolated from evolving real world evidence about a drug's safety and effectiveness. Such supplemental changes are all placed at risk of easy challenge and quick dismantlement by the Fifth Circuit's decision below.

A. FDA Expands Indications for Drugs Based on Clinical Data

The indications for innovative drugs, such as certain cancer medications, are often expanded as new clinical data demonstrate safety and effectiveness in treating additional conditions, like other forms of cancer. Newly available treatment options thus often derive not from approvals of new molecular entities, but from

supplemental approvals of existing drugs. For example, FDA originally approved Keytruda (pembrolizumab), a cancer immunotherapy, in 2014 to treat melanoma in certain patients. FDA, *Keytruda Label (Reference ID: 3621876)* (Sept. 2014).[5] Over the last decade, FDA has approved dozens of supplemental applications for Keytruda, expanding the indications for the medication to over twenty types of cancer, including certain types of non-small cell lung cancer, classical Hodgkin lymphoma, urothelial cancer, esophageal cancer, gastric cancer, cervical cancer, and triple-negative breast cancer, among others. FDA, *Keytruda Label (Reference ID: 5775987)* (Apr. 2026).[6] Recently, FDA approved a further expanded use of Keytruda to treat an additional type of advanced cervical cancer based on a clinical trial that "demonstrated a statistically significant improvement in [progression-free survival] in the overall population." FDA, *FDA approves pembrolizumab with chemoradiotherapy for FIGO 2014 Stage III-IVA cervical cancer* (Jan. 12, 2024).[7]

FDA has similarly expanded the indications for certain drugs to allow their use for a completely different disease. For example, FDA originally approved Tysabri (natalizumab) in 2004 to treat patients with relapsing forms of multiple sclerosis (MS). FDA, *Tysabri Label* (Nov. 2004).[8] In 2008, FDA approved a supplemental

[5] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf.

[6] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/125514s195lbl.pdf.

[7] Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-chemoradiotherapy-figo-2014-stage-iii-iva-cervical-cancer.

[8] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/125104lbl.pdf.

application to extend Tysabri's indications to treat adult patients with moderately to severely active Crohn's disease (an inflammatory bowel disease), based on the agency's review of the results of 14 studies. FDA, *Approval Package for BLA 125104/33* (Jan. 14, 2008).[9]

Indication expansions are also common in drugs used to treat rare diseases, referred to as "orphan drugs." A recent study found that between 1990 and 2022, 14 percent of the 491 orphan drugs approved to treat an orphan indication were first approved for a common disease and later received approval to treat a rare disease. Kathleen L. Miller & Michael Lanthier, *Orphan Drug Label Expansions: Analysis of Subsequent Rare and Common Indication Approvals* 43 Health Affs. 18, 20 (Jan. 2024). Indeed, FDA has approved another form of mifepristone, the drug at issue here, to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance.[10] FDA's ability to expand labeling indications is thus critical to the treatment of rare diseases and disabilities.

FDA also updates indications of approved drugs, based on clinical data, to extend to additional patient populations. As an example, for cystic fibrosis (CF) patients, there are therapies known as CFTR modulators that are approved for people based

[9] Available at https://www.accessdata.fda.gov/drugsatfda_docs/bla/2008/125104Orig1s0033.pdf.

[10] *See* Orphan Drug Designation for Korlym®, *https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=239507* (approved by FDA in 2012).

on their specific genotype. Since their initial approvals, FDA has approved multiple label expansions to add more genetic variants to the indications for these therapies—expanding the number of people with CF who can benefit from these drugs.

These expansions are particularly important for pediatric patients. Most drugs are initially approved for specified adult populations, and not children. FDA recognizes that children may differ from adults in terms of drug safety, effectiveness, and dosing and, as a result, has emphasized the importance of pediatric-specific labeling.[11] For example, Gilenya was initially approved in 2010 for the adult population with relapsing forms of MS.[12] In 2017, FDA approved Gilenya for use in pediatric patients age 10 years and older.[13]

For drugs used to treat progressive, sometimes terminal, diseases with a typical onset in early childhood or adolescence, FDA's ability to expand labeling to include pediatric populations is essential. As an example, FDA originally approved Emflaza (deflazacort), a drug used to treat Duchenne muscular dystrophy, a progressive neuromuscular disease, for use in patients 5 years of age and older. FDA, *Approval Package for Emflaza* (Feb. 9, 2017).[14] In 2019, FDA approved a supplemental

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[11] *See* FDA, *Pediatric Labeling Changes* (June 4, 2025), https://www.fda.gov/science-research/pediatrics/pediatric-labeling-changes.

[12] Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022527s000ltr.pdf.

[13] Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/022527Orig1s024ltr.pdf.

[14] Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000Approv.pdf.

application to extend the indication of Emflaza for use in patients 2 years of age and older. FDA, *Supplemental Approval Letter for Emflaza*, NOA 208684/S-003 and NOA 208685/S-003 (Jun. 7, 2019).[15]

In all these scenarios, drug sponsors, providers, and patients have always been able to count on an FDA approval remaining in place absent compelling new evidence that requires that approval decision to be revisited. The Fifth Circuit's decision undermines those settled expectations.

B. FDA Modifies Safeguards According to New Evidence About Patient Safety

FDA may also modify a drug's approval to impose conditions, including by changing dosage or contraindications, or place warnings on an approved drug as a result of new clinical studies, real-world evidence, or other clinical input such as patient or provider complaints. Such conditions or warnings may also be driven by changes in clinical practice, such as the existence of a new therapy that may necessitate warning about new interactions with the use of an existing drug, or a need for a new warning about using the drug if a patient has a form of virus that did not exist when the drug was originally approved. In addition, FDA may update labeling to account for newly discovered side effects or newly recommended doses for

[15] Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2019/208684Orig1s003,208685Orig1s003ltr.pdf.

specific patient populations. These determinations, just like an initial approval, are based on an analysis of benefits versus risks.

As directed by statute, FDA makes changes to REMS to protect patient safety and to eliminate or modify restrictions that are not necessary to maintain the safety and effectiveness of the drug, including elimination or modification of REMS elements that are determined to be "unduly burdensome on patient access." 21 U.S.C. § 355-1(f)(2)(C). The REMS program developed, in part, out of a "restricted distribution program" that FDA implemented in 1989 when approving Clozaril (clozapine). *See* FDA, *FDA's Role in Managing Medication Risks*.[16] Clozapine is an important antipsychotic used for treatment-resistant schizophrenia as well as other psychiatric disorders. *See, e.g.,* Dara Gammon et al., *Clozapine: Why Is It So Uniquely Effective in the Treatment of a Range of Neuropsychiatric Disorders?*, 11 Biomolecules 1, 1 (2021).[17] The program required all patients to receive white blood count monitoring to reduce the risk of agranulocytosis, a life-threatening condition.[18] *See* FDA, *FDA's Role in Managing Medication Risks*.[19] Over the years, FDA has continued to make changes to Clozaril's labeling. Some of these changes have increased access to Clozaril, including by reducing the frequency of white blood count

[16] Available at https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks (last revised Jan. 26, 2018).

[17] Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8301879/.

[18] *Id.*

[19] *Supra* note 18.

monitoring in 2005. *See* FDA, *Supplemental NDA Approval Letter for Clozaril, NDA 19-758 / S-054* (May 12, 2005).[20] As of June 2025, FDA removed the REMS for clozapine, including Clozaril, finding that while there remains a "risk of severe neutropenia with clozapine use, clozapine labeling (including a new Medication Guide) is sufficient to mitigate this risk and maintain a positive benefit/risk profile." *See* FDA, *FDA removes risk evaluation and mitigation strategy (REMS) program for the antipsychotic drug Clozapine* (last revised Apr. 3, 2026).[21]

FDA has updated REMS for drugs, adding or removing restrictions, in other instances as well. For example, in 2010, FDA approved a REMS for Erythropoiesis-Stimulating Agent (ESA) use in patients with cancer. J. Bohlius et al., *Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update*, 3 J. Clinical Oncology 1197, 1197 (2019).[22] FDA removed the REMS in 2017 after determining that it was no longer necessary because "prescribers demonstrated acceptable knowledge of the risks of ESAs and the need to counsel patients about the risks, and utilization data suggested an increase in appropriate prescribing practices." *Id.* at 1199. FDA made this determination based on its "evaluation of the results of the REMS Assessments submitted by [the drug

[20] Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/019758s054ltr.pdf.

[21] Available at https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks.

[22] Available at https://ashpublications.org/bloodadvances/article/3/8/1197/260121/Management-of-cancer-associated-anemia-with.

manufacturer], and additional FDA analyses to understand the impact of the various regulatory and other actions on the use of ESAs." FDA, *Information on Erythropoiesis-Stimulating Agents (ESA)* (Mar. 31, 2017).[23]

FDA's addition of REMS has also, in some cases, increased access to critical medications. For example, in 2006, the inclusion of a REMS helped facilitate the return of Tysabri, the MS drug, to the market after its removal based on a "rare but life-threatening side effect." *Previously banned MS drug to return to market,* NBC News (Jun. 5, 2006).[24] In implementing the REMS, FDA weighed the benefits of the drug against the risk of that serious side effect. *Id.*

III. THE FIFTH CIRCUIT'S DECISION HARMS PATIENTS AND PROVIDERS BY UNDERMINING THE RELIABILITY OF DRUG APPROVALS AND SUBSEQUENT CHANGES TO CONDITIONS OF USE

The Fifth Circuit's decision to upend FDA's modification of a drug's conditions of use without consideration of the impact such a decision has on patients' and providers' reliance interests, patient safety, and future research and development is reason enough to grant the applications for a stay or vacatur. *See* Pet. Appx. 15a-16a. If the Fifth Circuit's approach is upheld, courts will frequently be invited to

[23] Available at https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin.

[24] Available at https://www.nbcnews.com/health/health-news/previously-banned-ms-drug-return-market-flna1c9467593.

upend FDA's approval process without any requirement that they consider such significant impacts.

In such a landscape, patients and providers will struggle to determine appropriate courses of treatment for critical conditions, uncertain if approval of drugs and conditions of use might suddenly be enjoined through litigation brought by groups who object to a medical treatment on ideological grounds, or by companies seeking to remove competing products for commercial gain. And companies will be unwilling to invest in research and development of new indications for existing drugs, for fear such uses will be enjoined by a court in disregard of FDA's evidence-based determinations.

A. The Fifth Circuit's Approach Threatens Reliable Access to Necessary Medications

Patients and their providers have a critical interest in being able to rely not only on FDA's initial approval of a drug, but also on the agency's evidence-based decision to update the conditions of that drug's use. Patients and their providers reasonably expect that expanded access to drugs will be determined pursuant to FDA's congressionally authorized procedures and scientific and technical expertise, and will not be upended years later absent compelling new evidence that calls into question the drug's safety or effectiveness.

For patients, reliable and consistent access to safe and effective drugs that treat their conditions is a matter of utmost importance. For some, including cancer

patients and patients with other life-threatening illnesses whom *amici* represent, such access may be a matter of life and death. Those patients' lives depend on drugs that are available because of FDA's drug approval process, including FDA's approval of modifications to a drug's use. For instance, many medications with newly identified risks can remain on the market with labeling changes and/or carefully crafted REMS programs because REMS modifications serve to mitigate newly identified risks.[25] But if FDA cannot effectively administer REMS modifications with its expert scientific staff, in accordance with the congressionally mandated statutory factors, and without unwarranted judicial interference, beneficial therapies could be removed from the market or approved conditions of use could be narrowed.

FDA facilitates access to medications in other ways as well, including by removing unnecessary barriers that impose real costs on patients and impede their access to them. Most obviously, the FDA will periodically convert an approved prescription drug to over-the-counter status if it determines that a prescription is "not necessary for the protection of the public health" and "the drug is safe and effective for use in self-medication as directed in proposed labeling." 21 C.F.R. § 310.200(b). In 2023, FDA thus facilitated over-the-counter access to a naloxone hydrochloride

[25] "To date, FDA has not removed a drug with a REMS from the market due to new or serious issues that could not be mitigated by the REMS." *See* FDA, *Frequently Asked Questions (FAQs) about REMS*, (last revised Jan. 26, 2018), https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems.

nasal spray, a standard treatment for opioid overdose.[26]

Labeling changes can also be critical to expanding access to new and innovative drugs for additional patient populations, such as children.[27] That is particularly so because health insurance programs will not always cover an "off-label" use of a drug. Updated labeling may therefore be essential to a patient's ability to obtain the drug as a practical matter.[28]

The serious harm to patients from the loss of or serious impediments to access to medications is self-evident. Studies conducted in the context of drug shortages have found that sudden lack of availability of drugs causes serious harms, including significant rates of delayed and cancelled treatment and surgical intervention,[29]

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[26] FDA, *FDA Approves First Over-the-Counter Naloxone Nasal Spray* (Mar. 29, 2023), *available at* https://www.fda.gov/news-events/press-announcements/fda-approves-first-over-counter-naloxone-nasal-spray.

[27] FDA, *FDA expands pediatric indication for entrectinib and approves new pellet formulation* (Oct. 20, 2023), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-pediatric-indication-entrectinib-and-approves-new-pellet-formulation.

[28] *See, e.g.*, CMS, *Local Coverage Determination, Drugs and Biologicals, Coverage of, for Label and Off-Label Uses* (L33394) (eff. July, 13, 2025), *available at* https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33394 (describing that "off-label" uses may be, but are not necessarily, covered by Medicare).

[29] *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, *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6499468/; 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), *available at* https://ascopubs.org/doi/full/10.1200/OP.21.00883; Kenneth L. Kehl et al., *Oncologists' Experiences With Drug Shortages*, 11 J. Oncology Practice e154, e157 (2015), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4371121/; Keerthi Gogineni & Katherine L. Shuman, *Correspondence: Survey of Oncologists about Shortages of Cancer Drugs*, 369 New Eng. J. Med. 2463, 2464 (2013), *available at* https://www.nejm.org/doi/full/10.1056/nejmc1307379; 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), *available at* https://store.ons.org/cjon/17/5/drug-

increased medication errors,[30] and serious adverse patient outcomes—including death.[31] Uncertainty regarding 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);[32] *see also* 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?");[33]

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shortages-and-burden-access-care-critical-issue-affecting-patients-cancer; Milena McLaughlin et al., *Effects on Patient Care Caused by Drug Shortages: A Survey*, 19 J. Managed Care Pharmacy 783, 786 (2013), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10437927/; American Hospital Association, *AHA Survey on Drug Shortages* (July 12, 2011), https://www.aha.org/system/files/content/11/drugshortagesurvey.pdf.

[30] *See, e.g.*, Phuong, *supra* note 29, 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 29, at e1291; McKeever, *supra* note 29, at 491; McLaughlin, *supra* note 29, at 785.

[31] *See, e.g.*, Phuong, *supra* note 29, at 5-10 (citing eight studies linking drug shortages to patient deaths); Kehl, *supra* note 29, at e157; McKeever, *supra* note 29, at 491 (citing studies linking patient deaths to delays or cancellations in oncology treatment or drug substitutions); McLaughlin, *supra* note 29, at 785 (noting 41.4% of directors of pharmacy reported possible or probable adverse events from drug shortages); AHA, *supra* note 29, 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, *available at* https://www.bmj.com/content/371/bmj.m4087 (finding significant association between treatment delay and increased mortality).

[32] *Available at* https://abcnews.go.com/Health/shortagecriticalcancer-drug-forcingchildren/story?id=66411784.en/story?id=66411784.

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

Rob Stein, *How A Drug Shortage Hiked Relapse Risks For Lymphoma Patients*, NPR (Dec. 26, 2012) (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").[34]

B. Decreased Reliability of FDA's Processes Threaten Patient Safety

The ruling below threatens not only patients' access to treatments that have proven to be safe, effective, and essential, but also patient safety itself. Most significantly, the Fifth Circuit's reasoning threatens FDA's ability to make safety labeling changes, in accordance with its congressionally mandated process, to protect patients from risks identified after approval and to ensure patient access to essential medications. FDA requires safety labeling changes to communicate "new safety information" about an approved prescription drug, and its ability to update labeling appropriately has proven crucial to protecting patients from risk while still allowing them access to vital medications.[35]

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[34] Available at https://www.npr.org/sections/healthshots/2012/12/26/168038307/how-a-drug-shortage-hiked-relapserisks-for-lymphoma-patients.

[35] *See, e.g.*, FDA, *Supplemental NDA Approval Letter for Clozaril, NDA 19-758 / S-054* (May 12, 2005), *supra* note 20; FDA, Labeling Order for Clozaril, NDA 19-758 (Apr. 28, 2023), https://www.fda.gov/media/167933/download?attachment; FDA, FDA removes risk evaluation and mitigation strategy (REMS) program for the antipsychotic drug Clozapine (last revised Apr. 3, 2026), https://www.fda.gov/drugs/drug-safety-communications/fda-removes-risk-evaluation-and-mitigation-strategy-rems-program-antipsychotic-drug-clozapine?utm_medium=email.

Safety information about a marketed drug is often dynamic and evolving; it is frequently based on real-world experience. Having up-to-date information on the label is crucial for time-sensitive and potentially life-altering treatment decisions. But under the Fifth Circuit's approach, FDA's evidence-based determinations can be undone well after the fact, rather easily, without acknowledgment or consideration of the impact on patients.

C. Uncertainty About the Reliability of Drug Approvals Disincentivizes Research and Development that Benefits Patients

Finally, uncertainty as to the sustainability of regulatory approvals disincentivizes investment in new drug development and in researching *new indications* for existing drugs, at the expense of patients. Many important advances in treatment derive not from the discovery of a new molecular entity (or biologic), but from research into how, and under what conditions, an existing drug can be used to treat a new condition or new patient population.

To develop cutting-edge therapies that benefit patients around the United States and the world, drug developers invest significant time, effort, and money—for example, developers spent $83 billion on research and development (R&D) in 2019 alone. CBO Report, *Research and Development in the Pharmaceutical Industry* 1 (Apr. 8, 2021).[36] But the Fifth Circuit's approach threatens to derail progress by destabilizing the regulatory system on which drug developers rely.

[36] Available at https://www.cbo.gov/publication/57025.

Pharmaceutical innovation requires drug developers to tolerate high risks and high costs.[37] Among the risks that drug developers must tolerate—and that drug developers have, over the years, designed strategies to address—is the risk that a drug will not pass FDA regulatory scrutiny.[38] But the uncertainty resulting from a system in which plaintiffs with varying motivations would be incentivized to invite courts to upend evidence-based decisions made in accordance with FDA's congressionally mandated drug approval process could easily prove too much for the pharmaceutical industry to bear.

The Fifth Circuit's decision also strips away incentives for drug developers to *continue to* invest in rigorous clinical trials, including post-market surveillance. FDA "uses its powers as a market gatekeeper and as a censor of marketing claims not just

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[37] *See, e.g.*, *Id.* at 2 ("Developing new drugs is a costly and uncertain process, and many potential drugs never make it to market. Only about 12 percent of drugs entering clinical trials are ultimately approved for introduction by the FDA. In recent studies, estimates of the average R&D cost per new drug range from less than $1 billion to more than $2 billion per drug. . . . The development process often takes a decade or more, and during that time the company does not receive a financial return on its investment in developing that drug."); F. M. Scherer, *Markets and Uncertainty in Pharmaceutical Development* 10, 12, (Harvard Univ., Working Paper No. RWP07-039, Sept. 2007), *available at* https://www.hks.harvard.edu/publications/markets-and-uncertainty-pharmaceutical-development (asserting that "pharmaceutical R&D (along with biopharmaceutical R&D) is among the riskiest innovative activities, along with investment in new airliners, in the domain of product research and development," and noting that "[c]learly, at both the discovery stage and in clinical testing, success is much rarer than failure. And the costs are substantial").

[38] *See, e.g.*, Scherer, *supra* note 37, at 4, 10-15 (observing that "[m]odern drug discovery is driven by advances in science, but to bring a drug to market, the entity must be clinically tested to the satisfaction of national or supra-national drug regulators" and describing development strategies that drug developers employ to address "uncertainties in finding molecules that are interesting therapeutically, and in the end, those that can pass regulators' safety and efficacy hurdles"); CBO Report, *supra* note 36, at 13, 15 (noting that "[i]n one sample of drugs in clinical trials, researchers found that for every 100 drugs entering phase I trials, around 60 advanced to phase II trials, just over 20 entered phase III trials, and only about 12 gained FDA approval").

to protect patients from untoward risks of harm, but also to motivate drug sponsors to generate valuable information about their drugs." Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 Mich. Telecomm. Tech. L. Rev. 345, 370 (2007).[39] Conducting clinical trials and post-approval testing for safety-monitoring or marketing purposes makes up a large share of R&D spending for large pharmaceutical companies.[40] The valuable information that post-approval studies can generate includes evidence that products are unsafe or ineffective for specific indications[41]—evidence that can lead to changes through REMS or modifications of REMS. However, the Fifth Circuit's approach undermines the reliability of FDA's REMS determinations. Reduced reliability of REMS determinations disincentivizes manufacturers to conduct post-approval studies.

CONCLUSION

This Court should grant the applications for a stay or vacatur.

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[39] Available at https://heinonline.org/HOL/Page?handle=hein.journals/mttlr13&div=15&g_sent=1&casa_token=&collection=journals ("The clinical trials that are necessary to generate this information are costly, time-consuming, and risky. The information that they provide is valuable, but trial sponsors are unable to capture much of that value. In fact, trial sponsors stand to lose revenue if trials indicate that their products are unsafe or ineffective for certain indications. Indeed, from the perspective of the manufacturer, rigorous clinical trials of off-label uses may be as likely to diminish the value of a particular product as to enhance it. How to motivate firms to invest in generating this information in an honest, scientifically sound fashion is a major challenge for the law. By requiring that firms conduct rigorous clinical trials before bringing their products to market and before making promotional claims for their products, the FDA plays an important structural role in promoting a valuable form of biomedical R&D that private firms are undermotivated to perform on their own, while internalizing the costs of this R&D to the firms.") (footnote omitted).

[40] *See, e.g.*, CBO Report, *supra* note 36, at 2.

[41] *See, e.g.*, Eisenberg, *supra* note 39, at 370.

Respectfully submitted.

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