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INTEREST OF *AMICI CURIAE*[1]

The Leukemia & Lymphoma Society, the ALS Association, American Cancer Society, American Cancer Society Cancer Action Network, The Academy of Managed Care Pharmacy, American Society of Clinical Oncology, American Society of Hematology, The Arc of the United States, Arthritis Foundation, Association for Clinical Oncology, Cancer*Care*, Council of Medical Specialty Societies, Crohn's & Colitis Foundation, Cystic Fibrosis Foundation, Epilepsy Foundation, Friends of Cancer Research, HealthyWomen, Hemophilia Federation of America, Lupus Foundation of America, Muscular Dystrophy Association, National Alliance on Mental Illness, National Multiple Sclerosis Society, National Organization for Rare Disorders, National Patient Advocate Foundation, and RESOLVE: The National Infertility Association represent millions of patients across the United States who have serious health conditions and depend on drugs approved by the U.S. Food and Drug Administration ("FDA") for treatment. For many of these patients, their lives depend on the reliability of FDA's approvals of those medications and their approved conditions of use. The Fifth Circuit's opinion partially affirming the district court's decision jeopardizes patients' and providers' ability to rely on FDA's expert process to deem drugs and their

[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 of use 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,

the drug's labeling and Risk Evaluation and Mitigation Strategy)—which patients and providers have relied upon for years—despite no evidence that the drug's risks now outweigh its benefits. *Amici* are particularly concerned that the decision improperly dismissed, and fundamentally miu

102-571, 106 Stat. 4491 (1992); The Food and Drug Administration Modernization Act of 1997, Pub. L. 105-115, 111 Stat. 2296; Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823; Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012); 21st Century Cures Act, Pub. L. No. 114-255, § 3022, 130 Stat. 1033, 1096 (2016); FDA Reauthorization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005.

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.

Beginning at the clinical trial stage, FDA evaluates 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 condition(s) for which the drug may be prescribed, specifically the indication(s), 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

Once a drug is on the market, FDA's oversight continues to ensure 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. A sponsor must 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]

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 compares the data presented in support of a supplemental application to the data presented with the application for the initial approval

[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).

of the drug and assesses 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.

Some of these changes are required by the agency. Labeling, for example, "must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading." 21 C.F.R. § 201.56(a)(2). The FDCA 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]

FDA approves drugs with a Risk Evaluation and Mitigation Strategy ("REMS") when safety concerns warrant stricter controls to ensure the benefits of the

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[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.

drug outweigh the risks. FDA is statutorily required to assess potential modifications to a REMS 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; in such cases, the agency has the authority to require the drug sponsor to submit a proposal for the necessary modification. *Id*. § 355-1(g). Changes to a REMS are categorized as REMS revisions, minor REMS modifications, or major REMS modifications, according to "the degree of their potential effect on (1) the information provided in the REMS related to the serious risk(s) associated with the drug; (2) the safe use of the drug; and/or (3) the actions that the application holder, patients, health care providers, and other stakeholders must take to comply with the REMS." FDA, *Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry* (June 2020).[5]

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

After FDA approves a drug, the terms of its approval typically evolve over time in accordance with real world evidence or clinical trial data. Approved indications frequently expand to encompass treatment of new conditions or new patient populations. In addition, a drug's labeling may be updated with a new dosage regimen or safety-related warnings. A drug's

[5] Available at https://www.fda.gov/media/128651/download.

(Jan. 2024).[7] FDA expanded the indications based on the results of several clinical trials,[8] and, for esophageal cancer, based on the results of two clinical trials.[9] Recently, FDA approved a further expanded use of Keytruda to treat an additional type of advanced

(Reference ID: 3395788) (Nov. 2013).[11] Since then, FDA has approved Imbruvica for additional indications, including treatment of chronic lymphocytic leukemia and small lymphocytic leukemia, as well as for the treatment of chronic graft versus host disease (a serious complication of certain stem cell and bone marrow transplants), based on FDA's evaluations of clinical trial results.[12on]

review of the results of 14 studies. FDA, *Approval Package for BLA 125104/33* (Jan. 14, 2008).[14]

Indication expansions are also common in drugs used to treat rare diseases, referred to as "orphan

update labeling to account for newly discovered side effects or newly recommended doses for specific patient populations. These determinations, just like an initial approval, are based on conclusions of benefit

Where FDA's continuous review of a drug's safety and effectiveness reveals that the risks of the drug's use outweigh the benefits (or where the drug's efficacy has been disproven), FDA initiates a process to remove indications from drug labeling, or to revoke the drug's approval altogether. 21 C.F.R. §§ 314.150, 314.151.

FDA also makes changes to protect patient safety by updating REMS for approved drugs that have a REMS. The REMS program developed, in part, out of a "restricted distribution program" FDA implemented in 1989 when approving Clozaril (clozapine). *See* FDA, *FDA's Role in Managing Medication Risks*.[27] 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).[28] The program required all patients to receive white blood count monitoring to reduce the risk of agranulocytosis, a life-threatening condition.[29] *See* FDA, *FDA's Role in Managing Medication Risks*.[30] Over the years, FDA has continued to make changes to Clozaril's labeling. Some of these changes have increased access to Clozaril, including through reducing the frequency of white blood count monitoring in 2005. *See* FDA,

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

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

[29] *Id*.

[30] *Supra* note 27.

Supplemental NDA Approval Letter for Clozaril, NDA 19-758 / S-054 (May 12, 2005).[31] But FDA has also taken action to mitigate newly identified risks, including requiring safety labeling changes to address the risk of serious cardiovascular adverse events upon reinitiating Clozaril after an interruption in treatment. *See* FDA, *Labeling Order for Clozaril, NDA 19-758* (Apr. 28, 2023).[32]

FDA has updated REMS for drugs, adding or removing restrictions, based on its evaluation of relevant clinical data. 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).[33] FDA removed the REMS in 2017 after determining that it was no longer necessary given that "prescribers demonstrated

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).[34]

It is important to note that 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).[35] FDA decided on the REMS based on weighing the benefits of the drug against the risk of that serious side effect. *Id.*

III. THE FIFTH CIRCUIT'S DECISION WOULD HARM PATIENTS AND PROVIDERS BY UNDERMINING THE RELIABILITY OF DRUG APPROVALS AND SUBSEQUENT CHANGES TO DRUG LABELING

The Fifth Circuit gave short shrift to patient and provider interests in a drug's availability according to FDA's approved conditions of use, dismissing these interests as "apply[ing] primarily (if not wholly) to the challenge to the 2000 Approval." Pet. Appx. 68a. But those interests *do* apply to the court's affirmance of the ruling on FDA's modifications of mifepristone's

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[34] 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.

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

conditions of use, and they are substantial. 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 decision to apply updates to the conditions of that drug's use. For all patients, access to safe and effective drugs that treat their conditions is a matter of utmost importance. But

providers benefit from access to labeling and conditions of use that transparently reflect FDA's latest expert judgment about how a drug may be used safely and effectively.[37]

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

Without FDA's informed judgment determining these supplemental changes, patients and providers would not be able to reliably access necessary medications. First, FDA would not be able to make changes to labeling that enable patients to gain better access to needed therapies. For example, prescription to over-the-counter switches have allowed more convenient access to a variety of treatments.[38] For instance, in 2023, FDA facilitated over-the-counter access to a naloxone hydrochloride nasal spray, a

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[37] *See, e.g.*, FDA, Frequently Asked Questions about Labeling for Prescription Medicines For Healthcare Professionals and Patients, available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/frequently-asked-questions-about-labeling-prescription-medicines (explaining that drug labeling is FDA's "primary tool for communicating drug information to healthcare professionals, and patients and their caregivers") (last visited Jan. 29, 2024).

[38] FDA wi1.1(or)3(0).32 2668(d)3(co(-)-4.3.4(l)2vTJ ET .3(Jrt)-493.1(F.5 Tf3 Q q 4

C. Decreased Reliability of FDA's Processes Would Threaten Patient Safety

The ruling below threatens not only patients' access to treatments that have proven to be effective, but also patient safety in a variety of respects. First, the Fifth Circuit's reasoning threatens FDA's ability to make safety labeling changes to protect patients

also

medication errors,[44] and serious adverse patient

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);[46] *see also* Elizabeth Cohen & Amanda Musa, *Thousands of people can't get full treatments of a lifesaving cancer drug*, CNN (Feb. 17, 2023) (quoting patient with bladder cancer, in response to being told that due to a shortage he would not be able to receive his remaining doses of cancer drug Bacillus Calmette-Guérin, as stating, "It's a very, very frightening circumstance to realize that at that point, what they deem to be an aggressive cancer could in fact come right back");[47] 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?");[48] Rob Stein, *How A Drug Shortage Hiked Relapse Risks For Lymphoma Patients*, NPR (Dec. 26,

[46] *Available at* https://abcnews.go.com/Health/shortage criticalcancer-drug-forcingcStd

2022) (quoting mother, whose 10-year-old daughter with lymphoma lost access to cancer drug Mustargen due to a shortage, as expressing "When a doctor says, 'This is what you need to take.' And then all of a sudden somebody tells you, 'Well, that is what you need to take but this isn't available so we're going to try this instead,' it's very scary").[49]

D. Uncertainty About the Reliability of Drug Approvals would Disincentivize 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).[50] Increased innovation has brought us to a "golden age for new treatments."

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

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

David Wallace-Wells, *Suddenly, It Looks Like We're in a Golden Age for Medicine*, N.Y. Times Magazine (June 23, 2023).[51] But the Fifth Circuit's approach

designed strategies to address—is the risk that a drug will not pass FDA regulatory scrutiny.[53] But the uncertainty resulting from a system in which plaintiffs with varying motivations would be incentivized to invite courts to upend decisions made by FDA scientists in accordance with FDA's congressionally mandated drug approval process could easily prove too much for the pharmaceutical industry to bear.

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[53] *See, e.g.*, Scherer, *supra* note 52, 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 50, 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

The Fifth Circuit's reasoning 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 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).[54] 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.[55] The valuable information that post-approval studies can generate includes evidence that products are unsafe or ineffective for specific

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[54] 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).

[55] *See, e.g.*, CBO Report, *supra* note 50, at 2.

indications[56]—evidence that can lead to changes in labeling or approvals.

If upheld, the Fifth Circuit's reasoning would be a significant disincentive to conducting expansive research beyond the conditions of use for a particular drug, and particularly to conducting phase IV clinical trials after drug approval, which are not generally required but which drug developers often choose to conduct to show that their products are superior to others on the market.[57] The Fifth Circuit found that, while "the evidence does not show that mifepristone is unsafe in all applications," the changes in the 2016 Amendments *could* be unsafe when implemented together, *even if demonstrated by clinical studies to each be safe.* Pet. Appx. 69a. It criticized FDA for "stud[ying] the amendments individually" and "fail[ing] to seek data on the cumulative effect." *Id.* at 53a. In practice, this would mean that studies conducted in support of an approval must be conducted only according to the precise conditions of use for a particular drug—otherwise, the study could be tossed out by a court as not examining the correct

Id. Conducting expansive clinical trials that are not limited to the conditions of use to be included in labeling could lead a court to decide the sponsor did not consider the correct [()Edumulative effect" of the conditions of use and thus to overturn the approved conditions of use. Drug developers would be incentivized to structure their clinical studies to be as

[56] *See, e.g.*, Eisenberg, *supra* note 54, at 370.

[57]

narrow as possible and to avoid phase IV clinical trials, to the detriment of patients and providers.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted.

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January 30, 2024