Nos. 23-235, 23-236

In The Supreme Court of the United States

FOOD AND DRUG ADMINISTRATION, ET AL.,
Petitioners,
v.
ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.
Respondents,

DANCO LABORATORIES, L.L.C.,
Petitioner,
v.
ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.
Respondents,

ON WRITS OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

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

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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, once allowed on the market, can be used safely and effectively. This scrutiny manifests both in the requirement to obtain approval by the Food and Drug Administration prior to marketing a drug for a specific use or condition, and in FDA regulating updates to a drug's conditions of use, including its labeling, to reflect new data and evolving clinical practices, including to expand the permissible uses of a drug or to add restrictions. FDA's decision whether to approve a drug in the first instance, and whether to approve modifications to a drug's previously approved conditions of use, are subject to the same rigorous standard of safety and effectiveness. Approval ultimately is based on a scientific conclusion that the benefits of the contemplated terms of use of the drug outweigh the risks.

In affirming the district court's ruling on FDA's 2016 and 2020 modifications to mifepristone's conditions of use, the Fifth Circuit substituted its own assessment of scientific evidence for FDA's, contrary to explicit authority given to FDA by Congress. The court below crafted its own requirements for how FDA must consider the effect of changes in a drug's conditions of use. The decision would alter established conditions of use for this drug (in this case, including

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 misunderstood, the significant reliance interests that patients and providers have on the agency's decisions to approve updates to a drug's labeling and other conditions of use.

The Fifth Circuit's substituting its evaluation of drug safety and effectiveness for FDA's expert determinations affects far more than the modifications to the conditions of use for the single drug at issue here. Patients and their providers depend on FDA's determinations about safety and effectiveness and expect drugs to be available according to the terms of the FDA approval, including supplemental approval. Providers rely on FDA's expertise-based approval of drug uses in making treatment plans, and patients depend on being able to take the drugs as prescribed by their providers.

The Fifth Circuit's ruling broadly jeopardizes the reliability of FDA's original approvals of drugs, and the agency's approvals of modifications to the conditions of their use. It is effectively a roadmap for other litigants seeking to overturn drug approvals or conditions of use they disfavor—whether those changes expand (as was the case here) or restrict how the drug can be used. If approved drugs or modifications to conditions of use can be so readily enjoined despite FDA's scientific assessments, the resulting uncertainty would 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.

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). In recent decades, Congress has repeatedly expanded FDA's oversight authority, providing the agency with new enforcement and review tools, reauthorizing and expanding the agency's authority to collect user fees from pharmaceutical industry participants, and establishing new pathways for agency review and approval of specialized drugs. *See, e.g.*, Prescription Drug User Fee Act of 1992, Pub. L.

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. 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 expert, scientific 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).

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.

formulation and manufacturing may change to improve its risk-benefit profile. Permissible delivery methods for a drug may also change. These supplemental changes to the terms of the drug's approval allow health care practitioners to treat patients based on scientific information extrapolated from real world evidence about a drug's safety and effectiveness.

A. FDA Expands Indications for Drugs Based on Clinical Data

Often, newly available treatment options derive not from approvals of new molecular entities, but from supplemental approvals of existing drugs. 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. 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).[6] 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 5309748)*

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

(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 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).[10] As another example, FDA initially approved Imbruvica (ibrutinib) in 2013 to treat mantle cell lymphoma. FDA, *Imbruvica Label*

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[7] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s147lbl.pdf.

[8] *See, e.g.*, FDA, *FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer* (Jul. 27, 2021), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-high-risk-early-stage-triple-negative-breast-cancer; FDA, *FDA approves pembrolizumab combination for the first-line treatment of cervical cancer* (Oct. 13, 2021), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-combination-first-line-treatment-cervical-cancer; FDA, *FDA extends approval of pembrolizumab for classical Hodgkin lymphoma* (Oct. 15, 2020), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-extends-approval-pembrolizumab-classical-hodgkin-lymphoma.

[9] FDA, *FDA approves pembrolizumab for advanced esophageal squamous cell cancer* (Jul. 31, 2019), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-advanced-esophageal-squamous-cell-cancer.

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

(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.[12]

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).[13] In 2008, FDA approved a supplemental 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

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[11] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205552s000lbl.pdf.

[12] *See* FDA, *FDA approves ibrutinib plus rituximab for chronic lymphocytic leukemia*, (Apr. 21, 2020); https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ibrutinib-plus-rituximab-chronic-lymphocytic-leukemia; FDA, *FDA approves ibrutinib for pediatric patients with chronic graft versus host disease, including a new oral suspension* (Aug. 24, 2022), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ibrutinib-pediatric-patients-chronic-graft-versus-host-disease-including-new-oral.

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

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 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). The study also found that 15 percent of orphan drugs were approved for treatment of multiple rare diseases. *Id.* In all, among 491 orphan drugs studied, there were a total of 650 subsequent approvals, with a total of 312 new indications and 338 expansions of previously approved indications. 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.[15] 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

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

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

populations. As an example, for cystic fibrosis (CF) patients, there are therapies known as CFTR modulators that are approved for people based 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. Dosages cannot necessarily be adjusted based simply on weight and height.[16] In the words of FDA, "children aren't small adults" when it comes to prescription drugs, so it is beneficial to have pediatric-specific approved labeling.[17] For example, Gilenya was initially approved in 2010 for the adult population with relapsing forms of MS. FDA, *FDA expands approval of Gilenya to treat multiple sclerosis in pediatric patients* (May 1, 2018).[18] In 2017, FDA approved Gilenya for use in pediatric patients age 10 years and older. *Id.* Similarly, Imbruvica's labeling was updated in 2022 to include pediatric patients age

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[16] *See, e.g.*, C. Spadoni, *Pediatric Drug Development: Challenges and Opportunities*, 90 Current Therapeutic Rsch., Clinical & Experimental 119 (2019), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6677569/.

[17] *See* FDA, *Drug Research and Children* (May 4, 2016) (formatting omitted), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/drug-research-and-children.

[18] Available at https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gilenya-treat-multiple-sclerosis-pediatric-patients.

1 year and older with chronic graft versus host disease. FDA, *FDA approves ibrutinib for pediatric patients with chronic graft versus host disease, including a new oral suspension* (Aug. 24, 2022).[19]

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 critically important. 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).[20] In 2019, FDA approved a supplemental 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).[21]

Similarly, FDA originally approved CFTR modulators for people with CF with certain genotypes 12 years of age and older. Through multiple label expansions, supported by robust laboratory evidence on top of previous clinical trial data and the drug's established record of safety and efficacy, these

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[19] Available at https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ibrutinib-pediatric-patients-chronic-graft-versus-host-disease-including-new-oral.

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

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

therapies were approved for hundreds of additional mutations.[22]

B. FDA Narrows Access to and Imposes Safeguards on Approved Drugs when Necessary to Protect Patients

FDA may 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 can 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

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[22] Each of these "rare" or "ultra-rare" mutations affects so few people in the United States that approval based on clinical trials would not have been feasible. By using *in vitro* data derived from biological model systems known to predict clinical responses to CFTR modulators, FDA was able to make these life-changing therapies available to hundreds of people with CF who would not otherwise have access to them. FDA, *FDA expands approved use of Kalydeco to treat additional mutations of cystic fibrosis* (May 17, 2017), https://www.fda.gov/news-events/press-announcements/fda-expands-approved-use-kalydeco-treat-additional-mutations-cystic-fibrosis; Vertex, *Vertex Announces FDA Approvals of TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor), SYMDEKO® (tezacaftor/ivacaftor and ivacaftor) and KALYDECO® (ivacaftor) for Use in People With CF With Certain Rare Mutations* (Dec. 21, 2020) https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-approvals-trikaftar.

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 versus risk, and are often based on evolving information.

These kinds of labeling changes result from FDA's determination that a drug continues to offer a positive benefit-risk profile but requires new or additional safeguards. FDA or the drug sponsor can initiate them. If a drug sponsor seeks to add a significant warning or condition of use, it submits an application for supplemental approval of the change. 21 C.F.R. § 314.70.[23]

Advances in pharmacogenomics—the study of how an individual's genetics affects drug response[24]—have also led to drug labeling changes, sometimes decades after a drug's initial approval. For example, the labeling of warfarin, a commonly prescribed blood thinner originally approved by FDA in 1954, was updated in 2007 and again in 2010 to include

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[23] Major changes to labeling go into effect once a supplemental application is approved by FDA. 21 C.F.R. § 314.70(b). Moderate changes to labeling may go into effect 30 days after submission of a supplemental application to FDA, subject to FDA's subsequent approval of the supplement. *Id.* § 314.70(c).

[24] Pharmacogenomics is "the study of variations of DNA and RNA characteristics as related to drug response." *See* FDA, *Pharmacogenomic Data Submissions Guidance for Industry* 1 (Mar. 2023), https://www.fda.gov/media/166258/download (citing E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories (April 2008)).

pharmacogenomic information. Katarzyna Drozda et al., *Pharmacogenetic Labeling of FDA-Approved Drugs: A Regulatory Retrospective*, 3 J. Am. Coll. Cardiology 545, 546 (2018). Those changes included extensive updates to dosing recommendations for patients with certain gene variants to ensure these patients received the proper dose based on their genetic profile. *Id.*

More recently, Keytruda's labeling has been reviewed and updated since its initial approval in 2014, with labeling changes accounting for new safety and effectiveness data from use of the drug in practice. Dosage and Administration instructions were updated following FDA approval of additional indications. *Compare* FDA, *Keytruda Label (Reference ID: 3621876)* (Sept. 2014)[25] *with* FDA, *Keytruda Label (Reference ID 5309748)* (Jan. 2024).[26] The Warnings and Precautions as well as the Adverse Reactions sections of Keytruda's labeling have been updated as studies have demonstrated, for example, the possibility of additional side effects such as hypertension or peripheral neuropathy when Keytruda is prescribed in combination with other medications. *Id.* And information related to the risk associated with the drug's use in certain patient populations, including patients who are pregnant and nursing, has expanded significantly since the drug's initial approval. *Id.*

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

[26] Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/125514s147lbl.pdf.

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 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 manufacturer], and additional FDA analyses to

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

[32] Available at https://www.fda.gov/media/167933/download?attachment.

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

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 for some, including cancer patients and patients with other life-threatening illnesses whom amici represent, that access can be a matter of life or death. Some patients' lives depend on drugs that are available because of FDA's drug approval process, including the subsequent approval of changes to a drug's use. Patients, and their treating providers, reasonably expect that 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 new evidence calling into question the drug's safety or effectiveness.

The Fifth Circuit's willingness to undermine and disregard FDA's scientific judgment, years after the fact, threatens the reliability of the drug approval process on which patients and providers depend by inviting frequent challenges to the terms of a drug's approved use. If the Fifth Circuit's approach is upheld, courts would be invited to upend FDA's approval process, without consideration of impact on patients, the availability of alternative treatments, and other factors that comprise the statutorily based risk-benefit determination. Patients and providers in this landscape would struggle to determine appropriate courses of treatment for critical conditions, uncertain if approval of drugs and

conditions of use could be suddenly enjoined through litigation brought by groups who object to a medical treatment on moral grounds, or by companies seeking to remove competing products for commercial gain.

A. Patients and Providers Rely on FDA's Expert Oversight of Approved Drugs and Subsequent Modifications to Their Approved Uses

In dismissing the substantial reliance interests of patients and providers, the Fifth Circuit opined that patient and provider concerns are "lessened by the fact that mifepristone would remain available under the 2011 REMS . . . ." Pet. Appx. 68a. That reasoning is incorrect. A drug's initial approval and ongoing availability does not obviate a patient's interest in the *supplemental* approval of or updates to the drug, for several reasons. First, unnecessary barriers to access impose real costs on patients and providers. The Fifth Circuit's reasoning ignores that patients and providers have an interest in the lifting of unnecessary access restrictions so that an expanded population can benefit from treatment. Second, health insurance programs will not necessarily cover an "off-label" use of a drug—meaning that updated labeling of a drug approved for one indication may be essential to the patient being able to access the drug for other uses.[36] Finally, it is well-established that patients and

[36] *See, e.g.*, CMS, *Local Coverage Decision, Drugs and Biologicals, Coverage of, for Label and Off-Label Uses* (L33394) (eff. Nov. 1, 2022), *available at* https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33394&ver=47. (describing that "off-label" uses may be, but are not necessarily, covered by Medicare).

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 will 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 by reason of the drug's toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, and . . . the drug is safe and effective for use in self-medication as directed in proposed labeling." 21 C.F.R. § 310.200(b).

standard treatment for opioid overdose.[39] Notably, these switches are not necessarily supported by the drug sponsors and are vulnerable to challenge under the Fifth Circuit's decision.

Second, the agency's ability to update REMS, whether adding or removing restrictions, helps expand patient access to life-saving drugs while maintaining safe use. But the Fifth Circuit's approach threatens access to medications that could provide crucial health benefits when new information has demonstrated they can be safely administered. Worse still, and as discussed below, drug developers would be less incentivized to attempt to expand access to drugs.

Finally, patients would not be able to rely on access to beneficial drugs through supplemental FDA approvals. The agency's expansion of initial drug indications is essential to providing vital treatments. FDA's ability to expand access to drugs to additional patient populations, such as children, through labeling changes has proven crucial for access to new and innovative drugs.[40]

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

[40] *See, e.g.*, FDA, *FDA expands approval of Gilenya to treat multiple sclerosis in pediatric patients* (May 1, 2018), https://www.fda.gov/news-events/press-announcements/fda-expands-approval-gilenya-treat-multiple-sclerosis-pediatric-patients; FDA, *FDA approves ibrutinib for pediatric patients with chronic graft versus host disease, including a new oral suspension*, https://www.fda.gov/drugs/resources-information-

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 from risks identified after approval. 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.[41]

Safety information about a marketed drug is often dynamic and evolving; it is frequently based on real-world experience. Having up-to-date information in the label is crucial for time-sensitive and potentially life-altering treatment decisions. But under the Fifth Circuit's approach, upon discovering new safety information, FDA would confront the dilemma of waiting for a much higher level of evidence (such as a time-consuming clinical trial) while patients may be exposed to a risk, or facing legal challenges that would

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approved-drugs/fda-approves-ibrutinib-pediatric-patients-chronic-graft-versus-host-disease-including-new-oral, *supra* note 19.

[41] *See, e.g.*, FDA, *Supplemental NDA Approval Letter for Clozaril, NDA 19-758 / S-054* (May 12, 2005), *supra* note 31; FDA, *Labeling Order for Clozaril, NDA 19-758* (Apr. 28, 2023), *supra* note 32.

also threaten to delay, if not muzzle, the additional safety information.

Second, many medications with newly identified risks can remain on the market with labeling changes and/or carefully crafted REMS programs because they continue to provide benefits as long as the newly identified risks are mitigated.[42] But if FDA cannot effectively administer labeling changes and REMS changes with its expert scientific staff, and without judicial interference, beneficial therapies could be removed from the market or approved conditions of use could be changed—even in the absence of any evidence showing lack of safety or effectiveness. The serious harm to patients from the loss of 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,[43] increased

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[42] To date, FDA has not removed a drug with a REMS from the market. *See* FDA, *Frequently Asked Questions (FAQs) about REMS*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/frequently-asked-questions-faqs-about-rems (last revised Jan. 26, 2018).

[43] *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),

medication errors,[44] and serious adverse patient outcomes—including death.[45]

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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-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.

[44] *See, e.g.*, Phuong, *supra* note 43, 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 43, at e1291; McKeever, *supra* note 43, at 491; McLaughlin, *supra* note 43, at 785.

[45] *See, e.g.*, Phuong, *supra* note 43, at 5-10 (citing eight studies linking drug shortages to patient deaths); Kehl, *supra* note 43, at e157; McKeever, *supra* note 43, at 491 (citing studies linking patient deaths to delays or cancellations in oncology treatment or drug substitutions); McLaughlin, *supra* note 43, at 785 (noting 41.4% of directors of pharmacy reported possible or probable adverse events from drug shortages); AHA, *supra* note 43, 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).

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,

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

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

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

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 threatens to derail progress by destabilizing the regulatory system on which drug developers rely.

Pharmaceutical innovation requires drug developers to tolerate high risks and high costs.[52] Among the risks that drug developers must tolerate—and that drug developers have, over the years,

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[51] Available at https://www.nytimes.com/2023/06/23/magazine/golden-age-medicine-biomedical-innovation.html.

[52] *See, e.g.*, CBO Report, *supra* note 50, 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* http://web.hks.harvard.edu/publications/getFile.aspx?Id=267 (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"); Bernard H. Munos & William W. Chin, *How to Revive Breakthrough Innovation in the Pharmaceutical Industry*, Sci. Translational Med. (Jun. 2011), at 2, *available at* https://www.science.org/doi/full/10.1126/scitranslmed.3002273 ("The upshot is that there is no low-risk strategy in pharmaceutical R&D.").

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 entered phase III trials, and only about 12 gained FDA approval" but observing that one of the incentives for manufacturers to tolerate the high risk and costs associated with drug development stems from assessing its future value at the different stages of the FDA regulatory approval process, as "[d]evelopment of a drug that will eventually reach the market often entails a decade or more of R&D expenditures. Each successive phase of clinical trials requires increasing amounts of spending. Drug developers can reassess their commitment at each stage, and a drug's expected value may change as more is learned in clinical trials or as market conditions change—that is, there is an option value to continuing. Companies will not necessarily cancel a drug project even if its likely future costs exceed its likely value when that assessment is made, because the expected value might rise with additional information about the drug or its market.").

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 "cumulative effect" of the particular conditions of use. *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 "cumulative 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

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

[57] *See, e.g.*, CBO Report, *supra* note 50, at 2, 15.

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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