Nos. 22A902 & 22A901

IN THE

Supreme Court of the United States

U.S. FOOD & DRUG ADMINISTRATION, ET AL.,
Applicants

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.
Respondents.

DANCO LABORATORIES, LLC,
Applicant

v.

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.
Respondents.

ON APPLICATION FOR STAY OF PRELIMINARY INJUNCTION PENDING APPEAL

BRIEF FOR FOOD AND DRUG LAW SCHOLARS AS *AMICI CURIAE* IN SUPPORT OF APPLICANTS

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April 14, 2023

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INTEREST OF THE *AMICI CURIAE*[1]

Amici curiae are U.S. food and drug law scholars from academic institutions across the United States.[2] *Amici* are well known in their field, and many have deep expertise in the drug approval process. *Amici* submit this brief to address errors the courts below made with respect to the U.S. Food & Drug Administration's authority to regulate prescription drugs. A full list of *amici* is included as an Appendix to this brief.

SUMMARY OF ARGUMENT

In the Federal Food, Drug, and Cosmetic Act (FDCA), Congress enacted a comprehensive statutory process under which the Food and Drug Administration (FDA or the Agency) must review and approve new drugs before they may be lawfully introduced into interstate commerce. Before approving a drug, FDA is required to make a determination, based on the full record before the Agency, that a product is safe and effective for the proposed conditions of use. That determination requires the review of extensive scientific evidence that sponsors submit in support of drug marketing applications.

Pursuant to that statutory process, FDA approved mifepristone in 2000 after reviewing data on mifepristone's safety and effectiveness. As part of its approval,

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[1] No party or counsel for a party authored this brief in whole or in part, and no person other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

[2] The views expressed herein are those of the *amici* in their individual capacities and do not necessarily represent the views of their respective institutions.

FDA imposed certain restrictions on mifepristone's use and distribution to address potential safety risks. After over a decade of approved use, FDA concluded—again based on the scientific data—that the restrictions initially imposed on mifepristone's use and distribution should be modified. Those actions were consistent with the FDCA as well as FDA's rules and policies.

In this case, the court of appeals and the district court second-guessed FDA's approval and subsequent decisions to modify mifepristone's use and distribution restrictions. Their orders rest on critical misunderstandings of federal food and drug law and the underlying regulatory history for mifepristone. The orders of the courts below replace FDA's scientific and medical expertise with the courts' own interpretations of the scientific evidence. In doing so, they upend the drug regulatory scheme established by Congress and implemented by FDA through regulations, guidance, and practice. The Court should grant the stay Applications.

ARGUMENT

I. Congress Has Vested FDA with the Authority to Approve and Regulate New Drugs.

Congress has established a comprehensive statutory process under which new drugs must be reviewed and approved by FDA before they may be lawfully introduced into interstate commerce. *See* 21 U.S.C. §§ 331(d), 355(a). Since 1962, the general contours of the drug approval process have remained consistent. Prior to marketing a new drug, a sponsor must file a New Drug Application (NDA) pursuant to section 505(b) of the FDCA, *see id.* § 355(b), and must demonstrate that the drug is safe and

effective for the proposed indication, *see id.* § 355(d). FDA's rigorous review and approval process encompasses not only a clinical assessment of the drug itself but also, among other things, the "labeling proposed to be used for such drug." *Id.* U.S.C. § 355(b)(1)(vi). FDA must refuse to approve an NDA if the Agency determines that there is "insufficient information to determine whether such drug is safe for use" under the proposed conditions of use, or a "lack of substantial evidence that the drug will have the effect it purports or is represented to have" under the conditions of use in the proposed labeling. *Id.* §§ 355(d)(4), (5); *see also* 21 C.F.R. § 314.125(b).[3]

In the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress granted FDA express authority to impose use and distribution restrictions to address safety risks associated with drug products, i.e., risk evaluation and mitigation strategies (REMS). *See* Pub. L. No. 110-85, § 901(b), 121 Stat. 823, 926-49 (2007) (codified at 21 U.S.C. § 355-1). FDA had previously established a regulatory mechanism to impose restrictions on the use and distribution of certain drugs under 21 C.F.R. Part 314, Subpart H. FDAAA codified and built on Subpart' H's restricted distribution provision.

FDA may impose a REMS if it determines that a REMS is "necessary to ensure that the benefits of the drug outweigh the risks of the drug," taking into account, among other things, (1) "[t]he seriousness of the disease or condition that is to be

[3] Sponsors of generic drugs may file an Abbreviated New Drug Application (ANDA) that relies on the safety and effectiveness data of an already-approved drug. 21 U.S.C. § 355(j).

treated with the drug," (2) "[t]he expected benefit of the drug with respect to such disease or condition," and (3) "[t]he seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug." 21 U.S.C. § 355-1(a)(1). The components of a REMS may include, among other things, elements to assure safe use (ETASU). ETASU are used if the drug has been shown effective, but FDA determines that the drug is associated with a specific serious risk, and "can be approved only if . . . such elements are required as part of such strategy to mitigate a specific serious risk listed in the labeling of the drug." *Id.* § 355-1(f)(1)(A). In determining whether to require ETASU for a drug and, if so, what the ETASU should include, FDA is required to conduct a balancing exercise, weighing the drug's specific risks against the burdens on patient access to the drug and on the health care delivery system. *Id.* § 355-1(f)(2).

While all prescription drugs are required to have labeling that informs health care professionals about drug risks, FDA has required a REMS for only a tiny percentage of approved drugs. *See* FDA, *Risk Evaluation and Mitigation Strategies/ REMS*, https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems (last updated Dec. 17, 2021). Currently, out of the thousands of FDA-approved prescription drugs, only 61 are subject to REMS, of which 57 have ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/

risk-evaluation-and-mitigation-strategy-rems-public-dashboard (last updated Mar. 23, 2023).

II. FDA's Approval and Continued Regulation of Mifepristone Are Consistent with Federal Food and Drug Law.

A. In 2000, FDA Adhered to Its New Drug Approval Standards.

In 2000, FDA approved mifepristone under section 505 of the FDCA (21 U.S.C. § 355) based on a U.S. clinical trial and two French clinical trials that demonstrated mifepristone's safety and effectiveness.

1. Mifepristone's Approval Was Not Expedited.

The court of appeals and district court incorrectly describe the 2000 approval as an "accelerated approval" under Subpart H. As a threshold matter, FDA's authority to approve mifepristone stems from section 505 of the FDCA (21 U.S.C. § 355), not from Subpart H. In 1992, FDA promulgated regulations governing the approval, use, and distribution of certain drugs "studied for their safety and effectiveness in treating serious or life-threatening illnesses" that "provide meaningful therapeutic benefit to patients over existing treatments." 57 Fed. Reg. 58942, 58958 (Dec. 11, 1992) (creating 21 C.F.R. Part 314, Subpart H). Subpart H established specific regulatory mechanisms to facilitate approval of such drugs. As relevant here, Subpart H provides for the imposition of conditions "needed to assure safe use" for certain drugs. 21 C.F.R. § 314.520(a). In 2000, FDA invoked this mechanism when approving mifepristone under section 505 of the FDCA, requiring the drug to be provided by or

under the supervision of physicians meeting certain qualifications and imposing specific distribution requirements.[4]

Although the lower courts characterize the approval of mifepristone as an "accelerated approval," FDA uses that term to refer to a separate provision of Subpart H (21 C.F.R. § 314.510), which provides for the accelerated approval of a drug product based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. FDA did not invoke that provision in connection with the approval of mifepristone.

In fact, FDA took far longer than average to approve mifepristone. The mifepristone approval process took more than 54 months following submission of the application. U.S. Gov't Accountability Off. (GAO), GAO-08-751, *Approval and Oversight of the Drug Mifeprex* 27 (Aug. 2008), https://www.gao.gov/assets/gao-08-751.pdf. By comparison, on average, FDA took approximately 18 months to approve NDAs for drugs submitted from 1996 through 2002. *Id.*

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[4] Even, assuming *arguendo*, that FDA improperly invoked Subpart H when approving mifepristone in 2000, any such procedural defect was cured by the subsequent transition of mifepristone's restrictions to a REMS. As part of its 2007 amendments to the FDCA, Congress determined that drugs previously approved with elements to assure safe use under Subpart H were "deemed to have in effect" an approved REMS and required sponsors of such drugs to submit proposed REMS for approval by September 21, 2008. Pub. L. No. 110-85, § 909(b), 121 Stat. 823, 950-51 (2007), reprinted at 21 U.S.C. § 331 note. When FDA reviewed its records to identify medications approved before the effective date of FDAAA that were deemed to have REMS in effect under section 909 of FDAAA, it identified 16 drugs—including mifepristone. *See* 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008). Pursuant to FDAAA and FDA's procedures to implement its REMS authority, Danco submitted a supplemental NDA (sNDA) with a proposed REMS for mifepristone in 2008, and FDA approved the mifepristone REMS, as amended, with ETASU in 2011. *See* FDA, *Supplement Approval Letter for NDA 020687* at 1 (June 8, 2011), Supplement Approval Letter for NDA 020687, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/020687s014ltr.pdf.

2. Other Purported Deficiencies in FDA's Approval Decision Are Unfounded.

The district court also erred in its assessment of other aspects of FDA's review, approval, and labeling standards as applied to mifepristone.

First, the district court erroneously concluded that mifepristone's approved labeling was required to include the transvaginal ultrasound that was included as part of the U.S. clinical trial protocol. District Court Order Granting Preliminary Relief 51 (N.D. Tex. Apr. 7, 2023) (hereinafter District Court Order). There is no basis for this requirement in the FDCA or FDA's regulations. Many clinical trials are conducted under conditions that are more restrictive than those set forth in the approved labeling, which is designed for post-approval clinical use. This approach helps protect clinical study subjects who, in many cases, use the study drug before FDA has made a determination that the drug is safe and effective. *See* FDA, Letter to Am. Ass'n of Pro-Life Obstetricians and Gynecologists, Christian Medical & Dental Associations, and Concerned Women for America Denying 2002 Citizen Petition 28, Docket No. FDA-2002-P-0364 (Mar. 29, 2016) (citing, as an example, requirements in clinical studies of hormonal therapies used to treat symptoms of menopause that were not recommended in the approved product labeling or are routinely performed by doctors when treating patients). In other instances, clinical trials may employ stringent selection criteria to improve the power and practicality of a clinical trial. FDA, *Good Review Practice: Clinical Review of Investigational New Drug Applications* 43 (Dec. 2013), https://www.fda.gov/media/87621/download. FDA recognizes that traditional

clinical trials are "largely separate from routine clinical practice" and are "designed to control variability and maximize data quality." FDA, *Framework for FDA's Real-World Evidence Program* 5 (Dec. 2018), https://www.fda.gov/media/120060/download.

Second, the district court incorrectly stated that FDA "entirely failed" to evaluate the "psychological effects" of mifepristone. District Court Order 51. The safety record for mifepristone that was before FDA as it considered whether to approve the drug included data about reported anxiety and depression in U.S. patients who were administered mifepristone. *See* FDA, *Medical Review for Application No. 20-687* at 12 (Nov. 22, 1999), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf (reporting that 2% of U.S. study participants reported anxiety); FDA, *Medical Officer's Summary of Safety Update for Application No. 20-687* 2 (June 20, 1996), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P2.pdf (stating that of 28 U.S. patient reports of adverse experiences, one reported depression). Neither anxiety nor depression was a commonly reported adverse event.

Furthermore, to the extent the district court's analysis implies that FDA's approval decision was flawed because FDA failed to consider the potential for a patient to regret her decision to choose mifepristone over procedural abortion—or over proceeding with a pregnancy—this misunderstands FDA's role. Whether a particular drug product is well-suited for a particular patient is generally a practice of medicine

question that is outside FDA's purview. What FDA can do, as it did with mifepristone, is tell prescribers that "[p]atients should be fully advised of the treatment procedures and its effects," *Mifeprex (Mifepristone) Tablets* (Sept. 28, 2000), https://www.accessdata.fda.gov/drugsatfda_docs/label/2000/20687lbl.pdf, and advise patients that they should discuss the risks and benefits of using mifepristone with their providers, *Mifepristone Medication Guide* (Sept. 28, 2000), https://web.archive.org/web/20001110011300/http:/www.fda.gov/cder/drug/infopage/mifepristone/medguide.htm.

B. FDA Had Adequate Basis to Modify the Mifepristone REMS.

In 2011, FDA approved a REMS for mifepristone pursuant to its express statutory authority in section 505-1 of the FDCA (21 U.S.C. § 355-1). Since that time, the Agency has approved multiple supplemental NDAs (sNDAs) containing REMS modifications.

In approving both the 2016 sNDA and the 2023 sNDA, FDA assembled a team of experts to conduct a thorough review. These experts conducted medical, chemistry, pharmacology, statistical, and clinical pharmacology and biopharmaceutics reviews of all the data submitted, including both the data submitted as part of the original application package and new data submitted as part of the sNDA application. *See Mifeprex (Mifepristone) Tablets* (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020TOC.cfm; *Mifeprex (Mifepristone) Tablets* (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf.

The lower courts concluded that FDA's 2016 sNDA approval decision with REMS modifications and all subsequent REMS-related decisions were arbitrary and capricious because: (1) FDA never reviewed a head-to-head clinical trial comparing the safety of the changes against the then-current regimen and (2) the elimination of the requirement for prescribers to report non-fatal adverse events left FDA with an incomplete picture of mifepristone's safety that compromised future Agency decisions.

The lower courts' analyses are flawed. First, the lower courts fundamentally misunderstand the statutory standards for modifying a REMS. Second, the lower courts ignore the robust postmarketing adverse event reporting requirements applicable to *all* approved drugs (including mifepristone), as well as the unique, heightened adverse event reporting requirements still applicable to mifepristone.

1. The Lower Courts' Orders Misstate What is Required to Modify a REMS.

The district court concluded that FDA arbitrarily and capriciously amended the REMS without directly "comp[aring] the safety of the changes against the then-current regimen, nor under the labeled conditions of use." District Court Order at 59. The Fifth Circuit agreed that the 2016 REMS modifications could have been justified only by data from studies evaluating the consequences of people taking mifepristone under the entire proposed, loosened set of restrictions. Court of Appeals Order Denying in Part Stay Pending Appeal 34-35 (5th Cir. Apr. 12, 2023) (hereinafter Fifth Circuit Order). The text of the FDCA does not support this reading. The

Act does not require FDA, when modifying or revoking a REMS, to assess data from such comparison studies or, for that matter, any particular type of data.

Under the FDCA, FDA may modify a REMS either on the NDA holder's initiative or on its own initiative. 21 U.S.C. § 355-1(g)(4). In the former situation, the NDA holder submits a proposed REMS modification to the agency containing "an adequate rationale" for the modification. *Id.* § 355-1(g)(4)(A). In the latter situation, FDA may require the NDA holder to submit a proposed REMS if it makes certain determinations including that a modification is necessary to ensure the benefits of the drug outweigh the risks of the drug or to minimize the burden on the health care delivery system. *Id.* § 355-1(g)(4)(B).

The text of the statute clearly does not require any additional controlled clinical studies to support a REMS modification. The statute provides that FDA may order the NDA holder to perform an "assessment . . . to evaluate whether the approved strategy should be modified." *Id.* § 355-1(g)(2)(C). "Assessment" simply means "the action or instance of making a judgment about something." *Assessment*, Merriam-Webster Dictionary, https://www.merriam-webster.com/dictionary/assessment. It does not imply any particular method of analysis or degree of rigor. By contrast, when Congress requires an FDA decision (such as the approval of a drug) to be based on clinical investigations, it is explicit on the point. *See* 21 U.S.C. § 355(d)

(requiring "adequate and well-controlled investigations, including clinical investigations" to demonstrate a drug's effectiveness); *see also id.* § 355a(a) (defining "pediatric studies" to mean "at least one clinical investigation").

In providing examples of acceptable sources of data to include in a REMS assessment, FDA does not even *mention* data from additional clinical trials. FDA, *Draft Guidance for Industry, REMS Assessment: Planning and Reporting* 7-12 (Jan. 2019), https://www.fda.gov/media/119790/download. Instead, the agency expects such assessments—and thus the resulting REMS modifications—to be based on "a combination of qualitative and quantitative information about the REMS" derived from sources such as company databases, stakeholder surveys, drug utilization data, postmarketing adverse event data, observational data, epidemiological data, and "stakeholder outreach" to assess "the impact of the program on the healthcare delivery system and on patient access to the drug." *Id.* 7-12.

FDA thus typically modifies and removes ETASU—and even releases REMS altogether—without data from new clinical trials. For example, FDA fully released the REMS for Tikosyn® (dofetilide) after reviewing utilization and survey data contained in the sponsor's REMS assessments. *See Supplement Approval/Release REMS Requirement for Tikosyn (Dofetilide) Capsules* (Mar. 8, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020931Orig1s012,s013ltr.pdf. The Agency based its decision on the fact that "health care providers, including non-certified prescribers, demonstrated acceptable knowledge of the product's risks," and the

product's safe use conditions could "be conveyed appropriately via the current product labeling." *Id.*

Reading the REMS provisions of the FDCA to require FDA to obtain and review new clinical trial data before removing ETASU would frustrate Congress's purposes and goals in authorizing distribution and use restrictions. The FDCA does not encourage the liberal inclusion of ETASU in REMS; to the contrary, it cabins their use in various ways. The statute demands that ETASU be "necessary to assure safe use of the drug" such that the NDA would have to be denied or withdrawn without them. 21 U.S.C. § 355(f)(2)(A). It requires these elements to be "commensurate" with a "specific serious risk listed in the labeling." *Id.* § 355(f)(2)(A). It compels FDA to publicly explain the need for the ETASU. *Id.* § 355(f)(2)(B). It requires the elements to be designed "so as to minimize the burden on the health care system." *Id.* § 355(f)(2)(D). And critically, the Act mandates that ETASU "not be unduly burdensome on patient access to the drug, considering in particular . . . patients who have difficulty accessing health care (such as patients in rural or medically underserved areas) . . . and . . . patients with functional limitations." *Id.* § 355(f)(2)(C)(ii), (iii). The Fifth Circuit opinion does not even mention this statutory imperative.

Requiring the submission of new clinical trial data as a prerequisite to the modification or elimination of ETASU would keep stringent restrictions in place even after the agency has acquired information demonstrating they are no longer warranted in light of the statutory factors. Indeed, if the NDA holder were unable or

unwilling to fund such studies, the ETASU would likely become permanent. By deterring or thwarting the loosening or removal of ETASU, this reading of the statute would bring about troubling changes in the REMS system. FDA, with an eye toward reducing burdens and increasing access, typically loosens and releases REMS as they become less necessary due to the prescribing community's increasing knowledge about the drug and experience using it. Thus, FDA has released 206 REMS since the establishment of the procedure in 2007—including eight REMS with ETASU. *See* FDA, *Risk Evaluation & Mitigation Strategy (REMS) Public Dashboard*, https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/risk-evaluation-and-mitigation-strategy-rems-public-dashboard. In none of these eight instances was new clinical trial data used to support the agency's decision.

2. Mifepristone Continues to Be Subject to More Stringent Adverse Event Reporting Requirements than Almost Any Other Drug.

According to the lower courts, because FDA eliminated from the REMS certain adverse event reporting requirements for prescribers, the resulting "lax" reporting requirements rendered FDA's subsequent REMS-related decisions deficient. *See e.g.*, District Court Order at 58 (discussing FDA's "lax reporting requirements"); Fifth Circuit Order at 35 (criticizing FDA's so-called "ostrich's-head-in-the-sand approach").

As an initial matter, both opinions fail to acknowledge that FDA regulations impose robust postmarketing adverse event reporting requirements on *NDA holders*

for all drugs, including mifepristone. *See* 21 C.F.R. § 314.80.[5] For adverse drug experiences that are both serious and unexpected, FDA requires "the applicant" (NDA holder) to submit a report to the Agency "as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant." *Id.* § 314.80(c)(1)(i). The applicant must then "promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports" and must submit follow-up reports to the Agency. *See id.* § 314.80(c)(1)(ii). This reporting obligation also applies to any additional person who appears on the drug's label as a manufacturer, packer, or distributor, although such people can meet this obligation by submitting reports to the NDA-holder instead of directly to FDA.

In addition, the NDA holder must report all other (i.e., nonserious and/or expected) adverse drug experiences to FDA at regular intervals. *See id.* § 314.80(c)(2)(i). Failure by the NDA holder to submit any of these required adverse event reports can result in FDA withdrawal of the application. *Id.* § 314.80(k). Therefore, contrary to the lower courts' misunderstanding, the 2016 elimination of the mifepristone REMS requirement that prescribers report all adverse events did not deprive FDA of a comprehensive postmarketing safety data record for the drug.

Furthermore, the lower courts incorrectly discount the fact that even following the 2016 REMS revision, mifepristone remains subject to a more rigorous adverse event reporting regime than the vast majority of other drugs on the market. The

[5] Similar reporting requirements apply to drugs approved under an ANDA. *See* 21 C.F.R. § 314.98.

mifepristone REMS still requires *prescribers* to report any deaths of patients who received the drug to the manufacturer. Mifepristone is one of only 25 approved drugs (out of over 20,000 total[6]) for which FDA requires prescribers to report adverse drug experiences. The Agency mandates prescriber reporting of adverse drug experiences only as a part of REMS programs,[7] and only 25 of the 61 drugs approved with REMS require prescribers to report adverse events.

Moreover, the current mifepristone REMS is not unusual in limiting the types of adverse drug experiences that prescribers must report. Not a single currently effective REMS requires prescribers to report all adverse events, as the mifepristone REMS did prior to 2016. FDA decided the requirement for prescribers to report nonfatal adverse events was "no longer warranted," because FDA determined, following 15 years of receiving such reports, that "the safety profile of Mifeprex is well-characterized, that no new safety concerns have arisen in recent years, and that the known serious risks occur rarely." *Mifeprex (Mifepristone) Clinical Review* 8 (Mar. 29, 2016), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf.

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[6] *See* FDA, *Fact Sheet: FDA at a Glance* (Aug. 17, 2022), https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance.

[7] Nothing prohibits a prescriber or other treating healthcare professional from submitting reports of adverse events to FDA. In fact, healthcare professionals are encouraged to report adverse events. *See, e.g.*, FDA, *Reporting Serious Problems to FDA* (May 22, 2018), https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda.

III. The Remedies Adopted by the Lower Courts Are Statutorily Improper and Would Undermine Drug Development and the Public Health.

A. A Preliminary Injunction Invalidating an Approval or Supplemental Approval Based on a Disagreement with FDA's Scientific Judgment Would Be Inconsistent with Statutory Requirements.

The lower courts' orders also conflict with the process established by Congress in the FDCA to govern withdrawal of an approved application. *See* 21 U.S.C. § 355(e). Withdrawal requires a finding of one of the statutory criteria by FDA, as well as notice and opportunity for a hearing for the sponsor.

Under the FDCA, the Secretary of the U.S. Department of Health & Human Services shall withdraw approval of an application if "the Secretary finds" that the evidence demonstrates that the drug's benefit-risk balance merits withdrawal. The Secretary has delegated the responsibility for making such a finding to the Commissioner of Food and Drugs (Commissioner). *See* FDA, *Staff Manual Guides 1410.10, Delegations of Authority to the Commissioner of Food and Drugs* 1.A(1) (Nov. 29, 2022), https://www.fda.gov/media/81983/download (delegating all functions vested in the Secretary under the FDCA to the Commissioner).

Any potential withdrawal of an NDA or sNDA on safety or effectiveness grounds thus requires a finding by the Commissioner that the evidence demonstrates that the drug's benefit-risk balance merits withdrawal. As this Court has recognized, Congress has granted FDA primary jurisdiction over both the determination of a drug's safety and effectiveness under section 505(d) of the FDCA (21 U.S.C. § 355(d))

and the determination that there is a lack of such evidence meriting withdrawal under section 505(e) (21 U.S.C. § 355(e)). *See Weinberger v. Hynson, Wescott & Dunning, Inc.*, 412 U.S. 609, 630 (1973) ("The Act requires the Commissioner to disapprove any application when there is a lack of 'substantial evidence' that the applicant's drug is effective. Similarly, he may withdraw approval for any drug if he subsequently determines that there is a lack of such evidence."); *see also id.* at 633 ("The [FDCA] did not provide any mechanism other than the Commissioner's suspension authority under § 505(e), whereby an NDA once effective could cease to be effective."); *Weinberger v. Bentex Pharms., Inc.*, 412 U.S. 645, 652 (1973) (stating that "Congress desired that the administrative agency" make the determination under sections 505(d) and (e)).

Moreover, under section 505(e) of the FDCA, FDA must provide "due notice and opportunity for hearing to the applicant" prior to withdrawing an approved application. 21 U.S.C. § 355(e). FDA regulations provide a specific set of procedures under which the Agency must provide notice of the opportunity for a hearing to the applicant and allow the applicant to submit data and information. *See* 21 C.F.R. §§ 314.150, 314.200. Only after exhaustion of applicable administrative remedies can a party seek judicial review of the final decision regarding withdrawal. *Id.* § 10.45.

B. The Lower Courts' Rulings Would Be Harmful to the Drug Approval System and Have Far-Reaching Consequences.

If this Court allows either of the lower courts' rulings to stand, there will be far-reaching implications for the entire drug approval system. No drug is without

risk, and allowing a court to unilaterally overturn FDA's safety and effectiveness determinations could lead to challenges to the Agency's benefit-risk determinations for drugs it has approved to treat other diseases and conditions. Patients who rely on medications for their health and well-being could see their drugs removed from the market.

The potential for this outcome would also create widespread uncertainty in the pharmaceutical industry and chill research and development. FDA is the sole U.S. agency with which industry engages on issues related to drug review, approval, and labeling changes. Manufacturers are familiar with the FDCA and FDA's regulations and procedures, and they invest heavily in clinical research and costly clinical trials against the backdrop of that framework. Manufacturers would be forced to simultaneously navigate a patchwork of judicial decisions regarding what is required for drug approval. Congress created a system for drug approvals and regulation, and courts should not circumvent it.

IV. FDA's Authority to Approve and Regulate Mifepristone is Not Limited by the Comstock Act.

FDA's approval and regulation of mifepristone is not limited by the Comstock Act, 18 U.S.C. §§ 1461, 1462, and the Northern District of Texas and Fifth Circuit placed more weight on the Comstock Act than it can carry. When discussing FDA's actions, the courts below ignored the many instances in which Congress affirmed FDA's authority to approve new drugs for introduction into interstate commerce and regulate their distribution, irrespective of the prohibitions in the Comstock Act.

When Congress enacted the FDCA in 1938, it authorized FDA to approve "any new drug" for "introduc[tion] into interstate commerce" and made no exception to this authority for abortifacients. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052 (1938) (creating 21 U.S.C. § 355(a)) (emphasis added). Courts frequently explain that the word "any" means "all" or "every." *See, e.g.*, *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1353 (2018); *Sullivan v. Stroop*, 496 U.S. 478, 486 (1990) (Blackmun, J., dissenting); *Regions Bank v. Legal Outsource PA*, 936 F.3d 1184, 1194 (11th Cir. 2019) ("when Congress uses the word 'any' without 'language limiting the breadth of that word, "any" means all.'" (citation omitted)).[8]

Two prominent examples of drugs that FDA approved despite their inclusion in the Comstock Act at the time of approval are the oral contraceptive Enovid and mifepristone itself. In neither instance did Congress respond by limiting FDA's authority.

In 1960, FDA approved Enovid, the first oral contraceptive—despite the fact that contraceptives were Comstock-listed articles at the time, and despite the fact that the sale of contraceptives remained illegal in much of the nation.[9] *See* Martha Bailey, *"Momma's Got the Pill": How Anthony Comstock and Griswold v. Connecticut*

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[8] When Congress amended the Comstock Act in 1971 to remove contraceptives from coverage under that Act, the House report noted that the FDCA would "still" (*i.e.*, would continue to) regulate the "interstate *transportation* of drugs, medicines, and other articles for the prevention of conception." H.R. Rep. No. 91-1105, at 3 (1970) (emphasis added) (quoting the Department of Health, Education, and Welfare's conclusion); *id.* (quoting the Department of Labor's conclusion that the FDCA "would continue to apply to imports and shipments" of contraceptives). Congress thus confirmed its understanding that FDA regulates all drugs in interstate commerce, including Comstock-listed drugs.

[9] This Court had not yet decided *Griswold v. Connecticut*, 381 U.S. 479 (1965).

Shaped US Childbearing, 100 Am. Econ. R. 98, 105-06 (2010). Just two years after Enovid's approval, Congress enacted the Kefauver-Harris Amendments to the FDCA. *See* Pub. L. No. 87-781, 76 Stat. 780 (1962). Rather than curtail FDA's oversight and regulation of drug products, including with respect to contraceptives, the 1962 Kefauver-Harris Amendments strengthened FDA's authority to approve drugs for introduction into interstate commerce. And although a pending marketing application for an oral contraceptive was discussed during floor debate on the legislation, there was no suggestion that approval of the application would violate the Comstock Act or exceed FDA's authority. *See* 108 Cong. Rec. 21088 (Sept. 27, 1962). By December 1965—while contraceptives were still Comstock-listed articles—FDA had approved no fewer than seven oral contraceptives for introduction into interstate commerce. *See* FDA, *Fact Sheet: Oral Contraceptives* (Dec. 1965) (hereinafter FDA Contraceptive Fact Sheet).

Since FDA approved mifepristone in 2000, Congress has amended section 505 of the FDCA (21 U.S.C. § 355)—which sets forth FDA's authority to approve and regulate new drugs—no fewer than 18 times, including post-*Dobbs*. It has also enacted the section authorizing REMS (21 U.S.C. § 355-1) and amended it seven times during this period, including post-*Dobbs*. Yet Congress has never amended the FDCA to

curtail FDA's authority to approve abortifacients with whatever restrictions FDA determines are necessary.[10]

In sum, Congress has assigned FDA the task of ensuring that drugs submitted to it for approval are safe and effective for their intended use, including implementation of whatever restrictions FDA determines are necessary. The Comstock Act has no bearing on that decision. *See* 21 U.S.C. § 355(d) (listing grounds on which FDA may refuse to approve an application for a new drug); *see also* FDA Contraceptive Fact Sheet ("New drugs must be proved both safe and effective if used as directed, before clearance can be granted. But if the product is established as safe and effective, FDA *must* grant the clearance.") (emphasis in original)). By Congress's design, enforcement of the Comstock Act was not a factor in FDA's decision to approve or regulate mifepristone.

[10] *See, e.g.*, Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002); Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003); Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (2003); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007); Patient Protection and Affordable Care Act, Pub. L. No. 111-148, 124 Stat. 119 (2010); Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012); Consolidated Appropriations Act, Pub. L. No. 117-328, §§ 3001-3631 (2022) ("Food and Drug Omnibus Reform Act of 2022").

CONCLUSION

The Court should grant the Applications.

April 14, 2023

Respectfully submitted,

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