No. 23-10362

IN THE

United States Court of Appeals for the Fifth Circuit

ALLIANCE FOR HIPPOCRATIC MEDICINE, *et al.*,
Plaintiffs-Appellees,

v.

U.S. FOOD AND DRUG ADMINISTRATION,
Defendants-Appellants.

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

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BRIEF OF THE UNITED STATES MEDICAL ASSOCIATION AS *AMICUS CURIAE* SUPPORTING PLAINTIFFS-APPELLEES AND AFFIRMANCE

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CERTIFICATE OF INTERESTED PERSONS

The undersigned counsel of record certifies that the following listed persons and entities as described in the fourth sentence of Rule 28.2.1 have an interest in the outcome of this case. These representations are made in order that the judges of this Court may evaluate possible disqualification or recusal.

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INTEREST OF AMICUS CURIAE

Amicus curiae United States Medical Association (USMA)[1] is a medical society representing physicians within the United States. The central mission of the USMA is to serve as a network for physicians that will help maintain the integrity, dignity, and quality of the medical profession while helping to achieve the highest standards of care for patients. *Amicus* submits this brief to share its concerns with the Court regarding the U.S. Food and Drug Administration's ("FDA") methods of considering the use of mifepristone and the potentially deleterious impacts improprieties may have on patient safety and public health.

Further, any disregard of procedural safeguards by the FDA has significant practical and professional impacts upon *amicus'* members, including the possibility of having to respond to emergencies to treat the foreseeable complications of the use of mifepristone, and the professional and personal responsibility of having to participate in the completion of abortions that they ethically object to performing. Thus, *amicus* have a strong interest in ensuring that their viewpoint is shared with

[1] This brief is submitted under Federal Rule of Appellate Procedure 29(a) with the consent of all parties. No counsel for a party authored this brief, in whole or in part, and no counsel for a party, nor any person other than the *amicus curiae*, its members, or its counsel, contributed money that was intended to fund the preparation or submission of this brief.

the Court and that any shortcomings of the haphazard consideration of mifepristone's safety, efficacy, and potential deleterious effects be rectified.

PRELIMINARY STATEMENT

On behalf of its members and the patients which they serve, *amicus* urges the Court to require the FDA to comply with all applicable regulatory and statutory requirements when considering whether mifepristone may be safely and efficaciously be used in the United States and the conditions under which its use would be indicated.

Mifepristone in combination with misoprostol is the most common method for inducing a chemical (medical) abortion, accounting for 53.4% (291,890) of all abortions in the United States in 2020. When a woman chooses to undergo a medical abortion, she needs to know that the medication employed to induce that abortion has been found to be safe and effective by the appropriate national regulatory agencies, and she must possess a valid comparison between the risks and benefits of medical and surgical abortion methods. Similarly, a physician, when prescribing or administering such a medication, must have the confidence of knowing that a full vetting of the product has taken place by the FDA, including serious and measured consideration of objections and concerns raised by his or her colleagues. When it comes to mifepristone, the FDA has not conducted the full complement of regulatory oversight as required by Congress. Therefore, *amicus* urges this Court to uphold science and the rule of law by requiring the FDA to comply with basic principles of regulatory oversight.

Some suggest that the full regulatory vetting of mifepristone need not be required because a) the medication has already been demonstrated to be completely safe; and b) the medication has been a staple in the market for a sufficient time. These positions cannot withstand scrutiny. Neither a medication's popularity nor its *perceived* safety—based on anecdotal evidence—absolves an overseeing agency from fulfilling its duty to conduct a rigorous analysis of safety and efficacy.

Moreover, despite the claim of mifepristone's safety and efficacy as an abortifacient, there are substantial issues regarding the use of this medication, particularly in the manner authorized by the FDA. Proper consideration of these safety risks, which the FDA has not completed, could lead a reasonable overseeing agency to modify the recommended modes of usage.

Based on the above, the court ought to rescind the improperly issued new drug authorization ("NDA") of mifepristone, including its 2016, 2019, and 2021 modifications, and require that the drug undergo a thorough review of the medication's indications, contraindications, and associated potential complications as required by law.

ARGUMENT

I. The FDA's Approval of Mifepristone Included Grave Irregularities.

Mifepristone is a synthetic steroid designed to induce the abortion of an unborn human when used in conjunction with misoprostol, a prostaglandin medication that causes uterine contractions.[2] The NDA for mifepristone was originally filed before the FDA in 1996 by the Population Council. *Alliance for Hippocratic Medicine*, 2:22-CV-223-Z, Slip op. at 2 (N.D. Tex. Apr. 7, 2023) [hereinafter "*Alliance for Hippocratic Medicine*"]. Despite observing that "adequate information ha[d] not been presented to demonstrate that the drug, when marketed in accordance with the terms of distribution proposed, is safe and effective for the use as recommended," *id.* at 2; the FDA subsequently approved the medication under Subpart H,[3] subsequently codified as Risk Evaluation and Mitigation Strategy ("REMS"). 21 U.S.C. § 355-1(a)(1)–(2). Concerned about the legality of the approval, plaintiffs challenged the NDA as early as 2002, *id.* at 3, but their repeated petitions were "stonewalled" and "ignored over sixteen years." *Alliance for Hippocratic Medicine*, at 1. Additionally, in 2006, an investigation by the congressional subcommittee on something or other noted multiple "approval

[2] The term "unborn human" is used here to describe a developing human who has not yet left the mother's womb. *See Alliance for Hippocratic Medicine*, at 2. n.1.
[3] Subpart H is a provision in federal law that allows for the accelerated approval of a medication designed for the treatment of a "life threatening illness." 21 C.F.R. § 314.500.

irregularities including a) the approval was unlawfully based solely on data from uncontrolled trials," *id.* at 15; b) the "FDA's abuse of Subpart H," *id*. at 19; and c) the "highly unusual placement of Misoprostol on the Mifeprex Label." H.R. Subcom. Crim. J., Drug. Pol., and Hum. Resources Rpt., *The FDA and RU-486: Lowering the Standard for Women's Health; Prepared for the Hon. Mark Souder Chairman, Subcommittee on Criminal Justice, Drug Policy and Human Resources*, at 23 (Oct. 2006) (hereinafter Crim. J. Subcom. Rpt.).

Despite these repeatedly raised concerns, on March 29, 2016, the FDA increased the maximum estimated gestational age at which mifepristone could be administered to induce abortion from seven weeks to ten weeks; reduced the number of required in-person office visits to one; allowed non-physicians to prescribe and administer the medication; and eliminated the reporting requirements for non-fatal adverse events. *Alliance for Hippocratic Medicine*, at 4. Additionally, on April 11, 2019, the FDA approved a generic version of mifepristone without requiring or reviewing new data. *Id.* at 5. On April 12, 2021, the FDA allowed the dispensing of mifepristone through the mail during the COVID pandemic in violation of the restrictions imposed by the Comstock Act, and then announced that it would permanently allow such dispensing by mail. *Id.*

This brief concentrates on the health and safety concerns associated with mifepristone and the perceived shortcomings in oversight repeatedly displayed by

the FDA in considering the abortifacient. It also evaluates the medical research and arguments presented to the court through the amicus brief of the self-described "leading medical and public health societies" upon whose medical and scientific expertise, according to the *amici*, "courts frequently rely." Brief for the American College of Obstetrics and Gynecology, *et al.*, *Alliance for Hippocratic Medicine v. U.S. Food and Drug Administration*, No. 23-10362 (5th Circ. May 1, 2023), at 1 [hereinafter ACOG Br.].

II. The Safety of Mifepristone Has Not Been Definitively Established.

Concerns regarding the safety of mifepristone have been raised for decades. In January 2000, the FDA's Medical Officer's Review of the Mifepristone NDA ("MOR") noted, "[t]his method of pregnancy termination is of limited value because of the relatively short window of opportunity in which it can be employed. Its safety and effectiveness is based on its use during the seven weeks following the first day of the last menstrual period. . . [leaving] only a three week period for . . . women to secure this method of abortion." *FDA Medical Officer's Review of Amendments 024 and 033*, *Final Reports for the U.S. Clinical Trials Inducing Abortion up to 63 Days Gestational Age and Complete Responses Regarding Distribution System and Phase 4 Commitments*, at 18 (Nov. 22, 1999), *available at* http://www.fda.gov/cder/foi/nda/2000/20687_Mifepristone_medr_P1.pdf (accessed May 5, 2023) (hereinafter MOR). Further, the MOR found that comparative clinical

trials of medical abortions with surgical abortions demonstrated that the medical regimen "had more adverse events, particularly bleeding, than did surgical abortion … with an average duration of bleeding of 16 days …." *Id*. at 18. The MOR also found that medical abortions were less effective for pregnancies that had reached 50-63 days (7-9 weeks) estimated gestational age. *Id.* at 18-19. Even then, pro-medical-abortion organizations professed the often-repeated claim of the drug's safety very aggressively, causing questions regarding safety and efficacy to be "brushed aside." Crim. J. Subcom. Rpt., 6. Further, a 2006 Congressional hearing summarized the nation's experience since mifepristone's entry into the American market including "the deaths of six women, associated with the drug, nine life-threatening incidents, 232 hospitalizations, 116 blood transfusions, and 88 case infections. These and others cases have added up to a total of 1070 adverse reports (AERs) as of April 2006." *Id*. at 25.

Following the FDA's 2000 authorization, studies continued to raise concerns regarding the safety of mifepristone. In one study, researchers in Finland directly compared the immediate complication rates between medical and surgical abortions in all Finnish women who underwent an induced abortion with a gestational age of 63 days (9 weeks) or less between the years 2000 and 2006. Maarit Niinimaki, *et al*., *Immediate Complications After Medical Compared With Surgical Termination of Pregnancy*, 114 OBST. & GYNEC. 795, 797 (2009). There were 22,385 medical

and 20,251 surgical abortions in the study. *Id.* The incidence of adverse events was "fourfold higher" amongst medical abortions (20 percent) relative to surgical abortions (5.6 percent). *Id.* Although there was a total of 6 deaths within the cohort (two in the surgical group and four in the medical group), the differences did not reach statistical significance. *Id.* tbl. 2.

Another study summarizes the experience of Skaraborg Hospital, Sweden, in treating 4,945 patients who underwent abortions between the years of 2008 and 2015. Isabelle Carlsson, Karin Breding, and P.G. Larsson, *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-Up Study*. 18 BMC WOMEN'S HEALTH 158, 158 (2018) (hereinafter *Complications Related to Induced Abortion*). Here, the complication rate for chemical abortion performed with an estimated gestational age of less than 12 weeks was 7.3 percent, *id*. at 4, and the most common complication was incomplete abortion (57% of complications in this group). *Id.* at 161 tbl. 2. By comparison, the complication rate for surgical abortion was 5.7%, with the most common complication being infection. *Id* at 161 tbl. 2. Despite ACOG *et al.*'s reassurances that there was no increase in adverse events since the decision lifting mailing restrictions, ACOG Br. at 4, the researchers found that the complication rates from medical abortions in Sweden actually increased over time (4.2% in 2008 to 8.2% in 2015). *Complications Related to Induced Abortion* at 161 tbl. 2. The researches posited that this increased

complication rate was due to the increased use of mifepristone at home that Sweden experienced during the study period. *Id*. at 7.

The first reported study in the United States to address abortions using mifepristone without an in-person visit to an abortion provider likewise suggests that the use of mifepristone without close physician supervision is fraught with increased risks of complications. Elizabeth G. Raymond et al, *TelAbortion: Evaluation of a Direct to Patient Telemedicine Abortion Service in the United States*, 100 CONTRACEPTION 173, 176 (May 24, 2009) https://doi.org/10.1016/j.contraception.2019.05.013. In this study, mifepristone was dispensed to the patient by mail after completion of a remote work-up of eligibility was that included a screening pelvic ultrasound. *Id.* at 175. Despite the authors' conclusion that telehealth was a "safe, effective, efficient, and satisfactory" alternative through which to receive medical abortive care, *id.* at 173, 7 percent of the 177 patients receiving mifepristone in the study suffered incomplete abortions, with two hospitalizations—one "because of a seizure after an aspiration performed for bleeding," and the other due to severe anemia hemorrhage. *Id.* at 176. Even more disconcerting was the admission by the researchers of their inability to ascertain the outcomes of 58 package recipients. *Id.* Thus, even though the authors claimed that the rate of "serious adverse effects" was 1 percent, *id*. at 176; they were, in fact, unable to make such a determination due to a 23% loss-to-follow-up rate. *Id.*

ACOG *et al.* dismiss Plaintiff's safety concerns regarding mifepristone as "disrupt[ing] the sound, evidence-based practice of medicine that is at the very core of *amici*'s missions." ACOG Br. at 8. Yet studies published in *Obstetrics & Gynecology*—which is "the official journal of the American College of Obstetrics and Gynecology," *see* Obstetrics & Gynecology: *About the Journal*, https://journals.lww.com/greenjournal/Pages/AbouttheJournal.aspx (visited May 3, 2023)—raise flags regarding the safety of this medication and its use. One such study, "performed with the cooperation of Planned Parenthood of Los Angeles," reviewed the experience of 30,146 women seeking abortions with estimated gestational ages of 9 weeks or less. Luu Doan Ireland, Mary Gatter, & Angela Y. Chen, *Medical Compare with Surgical Abortion for Effective Pregnancy Termination in the First Trimester*, 126 OBSTET & GYNECOL. 22, 22 (2015). As noted above, the authors claim that medical abortions are "highly effective and with low complication rates." *Id*. However, the claim is unsubstantiated since over 15.9% of women receiving a medical abortion in this report were lost to follow up. *Id.* at 24. Moreover, and in a breach of scientific impartiality, the authors considered *all* these women lost to follow-up (~2,102) "to have undergone uncomplicated, complete abortions" in their statistical analyses. *Id*. Partly due to this unfounded statistical manipulation, the authors allowed themselves to claim that medical abortions were 99.6% effective in successfully inducing abortion. *Id*. at 22.

Additionally, even with the authors' artificial skewing of the data, the immediate complication rate from medical abortions was over three times higher than in surgical abortions. *Id.* tbl. 3. Here, medical abortions had a lower rate of major complications than surgical abortions, which did not reach statistical significance. *Id.* Nevertheless, the odds ratio of complications was 6.6 times higher in the medical group than in the surgical abortion group. *Id.* at 25.

In the Appendix to the amicus brief of ACOG *et al.*, the authors provide a "sampling of the hundreds of studies prove . . . [that mifepristone] . . . is safe and effective, with exceptionally low rates of major adverse effects." ACOG Br., at 8. They cite a study appearing in *Obstetrics and Gynecology*, ACOG's official publication, to support the contention that major adverse events are exceedingly rare. *Id.* at 12 n.20. Specifically, they claim that the serious infection rate for medical abortions is approximately 0.3%. *Id*. at 12. However, they do not mention that the serious complication rate in that study was 1.94 times higher in the medical abortion group than in the surgical group during the first trimester (0.31% versus 0.16%). Ushma D. Upadhyay et al., *Incidence of Emergency Department Visits and Complications After Abortion*, 125 OBSTET. & GYNECOL. 175, 181 tbl.3 (2015). Interestingly, the major complication rate for surgical abortion after the first trimester was 0.41%, surpassing the medical abortion complication rate. *Id.* tbl. 3. Disturbingly, the overall complication rate for medical abortions in this study was

5.19 percent, four times higher than that for surgical abortions performed during the first trimester and 3.5 times higher than in surgical abortions performed in the second trimester or greater. *Id.* at 181.

ACOG *et al*. also criticize the District Court for ascertaining that medication abortions have the potential to cause emotional harm, claiming that the Court's conclusion is unsupported by scientific evidence. ACOG Br. at 15. The criticism goes so far as to claim that the District Court relied on "pseudoscience" in reaching its conclusions. *Id.* at 16. Yet the leading medical and public health societies fail to cite a single article to discredit the District Court's analysis, because *all* the articles they cite on this point fail to distinguish medication from surgical abortion in analyzing the mental-health effects of abortion, thus conflating two different experiences. *See* Brenda Major et al., *Abortion and Mental Health: Evaluating the Evidence*, 64 AM. PSYCH. 863 (2009); M. Antonia Biggs et al., *Mental Health Diagnoses 3 Years After Receiving or Being Denied an Abortion in the United States*, 105 AM. J. OF PUB. HEALTH 2557 (2015); M. Antonia Biggs et al., *Women's Mental Health and Well-Being 5 Years After Receiving or Being Denied an Abortion: A Prospective, Longitudinal Cohort Study*, 74 JAMA PSYCHIATRY 169 (2017); Vignetta E. Charles et al., *Abortion and Long-Term Mental Health Outcomes: A Systematic Review of the Evidence*, 78 CONTRACEPTION 436 (2008); Corrine H. Rocca et al., *Decision Rightness and Emotional Responses to Abortion in the United*

States: A Longitudinal Study, 10 PLOS ONE 1, 7 (2015). Indeed, ACOG *et al.* complain that the articles presented to the District Court are "authored by an anti-abortion research group that was based on blog posts made on anti-abortion research group website, and on studies that have been widely critiqued by researchers and scholars for their serious methodological flaws." ACOG Br. at 16. However, even the authors of that study acknowledge what ACOG *et al*. fail to recognize, namely "the dearth of research, particularly in the U.S., that examines women's personal experience with having this type of abortion procedure." Katherine A. Rafferty & Tessa Longbons, *#AbortionChangesYou: A Case Study to Understand the Communicative Tensions in Women's Medication Abortion Narratives*, 36 HEALTH COMM. 1485, 1485 (2021). In fact, those authors affirmatively recognize that their study "is one of the first to analyze women's narratives after having had a medical abortion." *Id.* Moreover, in their own research, they were able to find only one study out of Sweden that dealt specifically with the issue of women's personal experiences with medical abortions and their tendencies to feel misinformed about the procedure. *Id.* at 1485-1486; *see* Maria Hedqvist, Lina Brolin, Tanja Tydén, & Margareta Larsson, *Women's Experiences of Having an Early Medical Abortion at Home*, 9 SEXUAL & REPRODUCTIVE HEALTHCARE 1877 (2016). Moreover, a diligent literature search on this point confirms the conclusions of those researchers. A PubMed literature search using the combination of keywords "medical abortion,"

"chemical abortion," "mifepristone," and "mental health" identifies only one study dealing directly with the mental health or societal-support issues related to medical abortions.[4] Constant D, de Tolly K, Harries J, Myer L. *Mobile Phone Messages to Provide Support to Women During the Home Phase of Medical Abortion in South Africa: A Randomised Controlled Trial*, 3 CONTRACEPTION 226 (Sept. 2014). This South African study merely evaluated the potential role of text messages in assisting women with the home phase of medical abortion.

Finally, ACOG *et al*. attempt to reassure the court that the death rate "from medication abortion is near zero." ACOG Br. at 13. One should hope so, but as discussed below, a low death rate does not exempt an agency from conducting

[4] NLM, Pubmed search "'medical abortion' & 'mental health,'" performed on May 7, 2023 *at* https://pubmed.ncbi.nlm.nih.gov/?term=%22medical+abortion%22+%26+%22mental+health%22&filter=pubt.clinicaltrial&filter=pubt.meta-analysis&filter=pubt.randomizedcontrolledtrial&filter=pubt.review&filter=pubt.systematicreview&filter=dates.2000%2F1%2F1-2015%2F1%2F1&sort=date&size=200; NLM, Pubmed search "'chemical abortion' & 'mental health,'" performed on May 7, 2023, *at* https://pubmed.ncbi.nlm.nih.gov/?term=%22chemical+abortion%22+%26+%22mental+health%22&filter=pubt.clinicaltrial&filter=pubt.meta-analysis&filter=pubt.randomizedcontrolledtrial&filter=pubt.review&filter=pubt.systematicreview&filter=dates.2000%2F1%2F1-2015%2F1%2F1&sort=date&size=200; NLM, Pubmed search "'mifepristone & 'mental health,'" performed on May 7, 2023 *at* https://pubmed.ncbi.nlm.nih.gov/?term=%22chemical+abortion%22+%26+%22mental+health%22&filter=pubt.clinicaltrial&filter=pubt.meta-analysis&filter=pubt.randomizedcontrolledtrial&filter=pubt.review&filter=pubt.systematicreview&filter=dates.2000%2F1%2F1-2015%2F1%2F1&sort=date&size=200.

rigorous scrutiny of safety and effectiveness and complying with regulatory requirements. And, of course, ACOG *et al.*'s observation ignores the effect of mifepristone on the other patient, the unborn human being, whose death rate from its use approaches 100 percent.

III. Irregularities Abounded in the FDA's Approval of Mifepristone.

There have been significant and recurrent irregularities in the FDA's consideration of mifepristone dating back to the original NDA proceedings in 2000. To begin with, Subcommittee on Criminal Justice, Drug Policy and Human Resources regarding Mifepristone found that the drug's approval was unlawful based on the FDA's failure to comply with the requirement in 21 CFR 314.126(e) that "uncontrolled studied or partially controlled studies are not acceptable as the sole as the sole basis for the approval of claims of effectiveness." Crim. J. Subcom. Rpt., at 15. In this case, the Subcommittee found that neither the French nor the American trials upon which the FDA relied to grant the NDA were randomized trials; nor were the subjects "concurrently controlled." *Id.* at 16. Instead, at the Subcommittee Hearing on the matter, the Deputy Commissioner for Operations of the FDA asserted that the agency's findings on drug effectiveness were based on a comparison "to a historical control of the expected rate of continued pregnancy." *Id.* at 17. The Subcommittee also learned from a Letter by the Assistant Commissioner for Legislation of the FDA to the Subcommittee's Chair that the "historical control

to which the Deputy Commissioner referred consisted of 'the well-established data and pool of medical knowledge concerning both the natural course of pregnancy itself, included the well-documented rate of spontaneous abortion on miscarriage (less than 20%) and surgical abortion.'" *Id.* Additionally, the Subcommittee appeared to agree with Plaintiffs' contention regarding the FDA's abuse of Subpart H due to its disregard for the restriction that the provision only apply for consideration of drugs "'that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses.'" *Id.* at 19. Finally, the Subcommittee found that the FDA's addition of misoprostol as an adjuvant to the Mifepristone treatment represented a highly irregular approval of an unapproved use, since misoprostol "was actually contraindicated at the time." *Id.* at 23.

The District Court also properly took note of a long series of additional irregularities in the FDA's approval process, all of which are well-supported:

1. The FDA did not ascertain that the trials upon which it relied when initially approving mifepristone required (1) that each woman receive an ultrasound to confirm gestational age and exclude ectopic pregnancy; (2) that physicians have experience at performing surgical abortions and admitting privileges at medical facilities providing emergency care; (3) that all patients were within one hour of the medical facilities and of the principal investigator; and (4) that women be monitored for four hours

following the administration of mifepristone. *Alliance for Hippocratic Medicine*, at 25;

2. The misapplication of subpart H for a condition (pregnancy) that is clearly not an illness, *id.* at 39-42;
3. The related misapplication of Subpart H relating due to the absence of any "meaningful therapeutic benefit," *id.* at 44-47;
4. The FDA ignored the federal legal prohibition on mailing abortifacients, *id*. at 25, 32-38;
5. The FDA's lack of reliance on appropriate studies when (1) eliminating the requirement for prescribers to report all nonfatal, serious, adverse effects; (2) extending the allowable maximum gestational age to 70 days; (3) eliminating the in-clinic administration of misoprostol; (d) discontinuing in-person follow-up requirements; and (e) allowing non-physicians to dispense chemical abortion drugs, *id.* at 58; and
6. The FDA's lack of reliance on studies of a generic formulation of mifepristone when providing its 2019 generic approval, *id*. at 60.

IV. FDA Irregularities Are Not Unique to Mifepristone.

Unfortunately, the FDA's disregard for proper procedure in this case is not a unique or isolated event. The FDA has demonstrated suboptimal conduct in the past, sometimes with devastating effects. On May 21, 1999, the FDA granted

authorization to market rofecoxib (Vioxx), a novel nonsteroidal anti-inflammatory medication. Eric J. Topol, *Failing the Public Health–Rofecoxib, Merck, and the FDA*, 352 NEW ENG. J. MED. 351 (2004), *at* https://www.nejm.org/doi/full/10.1056/nejmp048286 [hereinafter *Failing the Public Health*]. By the year 2000, and perhaps even at from the outset, there was publicly available evidence of an association between the use of rofecoxib and myocardial infarction. Claire Bombardier, *et al.*, *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520 (2000). Despite these associations, the FDA's Arthritis Committee did not meet to consider this information until two years following its approval of rofecoxib. *Failing the Public Health, supra*. The elevation in cardiovascular events was unexpected, resulting in a "Special Communication" released in the *Journal of the American Medical Association*, which is an official publication of the American Medical Association ("AMA") (one of the *Amici* in ACOG *et al*.). In it, the AMA called for the FDA to undertake further evaluation on the association between rofecoxib and cardiac issues. Debabrata Muhkerjee, Steven E. Nissen, and Eric J. Topol, *Risk of Cardiovascular Events Associated With Selective Cox-2 Inhibitors*, 286 J. AM. MED. ASS'N 954 (2000), *at* https://jamanetwork.com/journals/jama/article-abstract/194132; *Failing the Public Health, supra.* The FDA, which had the authority to demand such a study, never

did. *Failing the Public Health, supra*. Instead, four years later, after over 80 million people were exposed to the medication, rofecoxib was removed from the market, not because of the FDA's actions, but because the manufacturer (Merck) voluntarily recalled it. *Id*. Although no specific death was ever proven to have been cause by rofecoxib, through statistical analyses, tens of thousands of patients were estimated to have experienced adverse events because of exposure to the medication. *Id.*

More recently, the FDA's handling of aducanumab (Aduhelm) has also been called into question. Aducanumab is a monoclonal antibody for the treatment of Alzheimer's disease. Inderbir S. Padda, Mayur Parmar, *Aducanumab*, https://www.ncbi.nlm.nih.gov/books/NBK573062/ (accessed May 7, 2023). It was approved by the FDA under the "accelerated approval process." FDA, *Aducanumab (Marked Aduhelm) Information*, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/aducanumab-marketed-aduhelm-information (accessed May 7, 2023). The drug's approval, which took place on June 7, 2021, FDA, *FDA Grants Accelerated Approval for Alzheimer's Drug*, https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-drug (accessed May 7, 2023), raised so many questions that an investigation was undertaken by two congressional committees. H.R. Comm. On Oversight and Reform & Comm. on Energy and Commerce, *The High Price of Aduhelm's Approval: An Investigation into the FDA's Atypical Review Process and*

Biogen's Aggressive Launch Plans (Dec. 2022). The committees found that the drug approval process "was rife with irregularities," *id.* at 15, including the presence of "atypical collaboration and interaction between [the] FDA and Biogen," *id.*; a failure on the part of the FDA to follow its own documentation procedure, *id*. at 17; inappropriate and inadequate joint misrepresentations of the differing views within the FDA by the agency and Biogen, *id.* at 19; the unusual manner in which the FDA "pivoted" to an accelerated approval process in considering the medication, *id*. at 21; and the unexpected issuance of a "brown label indication" regarding the medication, *id.* at 24. In sum, the Committees found that the "FDA's lapses in protocol" in the Aduhelm approval process "raise serious concerns" and bring to question the integrity of its review process. *Id.* at 43. So also with mifepristone.

V. Affirming the District Court's Decision Will Serve the Public Interest and Protect Patient Safety.

In upholding the decision of the District Court, the Court will serve the public interest and protect patient safety.

A. Affirming the District Court Will Serve the Public Interest.

The FDA is the most important pharmaceutical regulatory agency in the United States. More than any other, the FDA has been given the authority and ability to oversee the introduction of new medications into the marketplace. These medications must be deemed safe and efficacious prior to their release to the public. The nation's experience with rofecoxeb, and its potential threat to tens of thousands

of lives, vividly illustrates the consequences of allowing the integrity of the FDA's NDA process to falter. In that case, just four years were enough to result in over 80 million people being exposed to a medication for which data suggested ongoing dangers absent absent regulatory intervention.

Further, the FDA seems doomed to replicate its disastrous experience with rofecoxib. Here, the recent, unresolved controversy surrounding the rapid approval process for aducanumab raises compelling similarities between the dual-committee investigation in that case, the subcommittee findings regarding the mifepristone authorization processes, and those of the District Court. Clearly, mere congressional and public scrutiny of the FDA is insufficient at motivating the agency to correct its own unforced errors. Judicial scrutiny is required. Indeed, the mifepristone case represents an invaluable opportunity for judicial oversight to check the FDA's errant actions and spur improvement of the drug authorization process.

Moreover, agency actions that overtly disregard the plain meaning of the law must be invalidated. The FDA's action of approving the delivery by mail of mifepristone, in direct violation of the Comstock Act's plain language, is unacceptable. If advocates for change to the Comstock Act wish to have its restriction overturned, the proper venue is Congress, not the courts or agencies.

B. Affirming the District Court Will Protect Patient Safety.

The literature and evidence reviewed herein raises serious concerns about patient safety from mifepristone. First, mifepristone as an abortifacient poses greater overall risks of complications than surgical abortions. While it may often be more convenient than the surgical method, that convenience may be achieved by sacrificing patient safety. It is the FDA's role to conduct a rigorous analysis of these questions, and based on the record before the District Court, it is clear that the FDA has abdicated this role. In demanding that the FDA perform a thorough, unbiased evaluation of the safety, indications, conditions of use, and efficacy of this medication, the Court will help ensure that physicians and patients alike will be better equipped to address the issues of safety and optimal conditions of use of mifepristone for their patient.

CONCLUSION

For these reasons, *amicus curiae* respectfully requests that the Court affirm the decision of the District Court.

Dated: May 12, 2023 Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on May 12, 2023, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Fifth Circuit by using the appellate CM/ECF system. I further certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

/s/ D. John Sauer
Counsel for *Amicus Curiae*

CERTIFICATE OF COMPLIANCE

I hereby certify that this brief complies with the type-volume limitations of Federal Rule of Appellate Procedure 32(a)(7)(B) because it contains 4,963 words as counted by the word-count feature of Microsoft Word, excluding the parts of the brief exempted by Rule 32(f).

I hereby certify that this brief also complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5)(A) and the type-style requirements of Rule 32(a)(6). It is prepared in a proportionally spaced font using Microsoft Word Times New Roman font size 14.

/s/ D. John Sauer
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No. 23-10362 Alliance Hippocratic Medicine v. FDA
USDC No. 2:22-CV-223

Dear Mr. Sauer,

The following pertains to your brief electronically filed on May 13, 2023.

You must electronically file a "Form for Appearance of Counsel" within 5 days from this date. You must name each party you represent, see **FED. R. APP. P.** 12(b) and **5TH CIR. R.** 12 & 46.3. The form is available from the Fifth Circuit's website, www.ca5.uscourts.gov. If you fail to electronically file the form, the brief will be stricken and returned unfiled.

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No. 23-10362 Alliance Hippocratic Medicine v. FDA
USDC No. 2:22-CV-223

Dear Counsel,

You must submit the 7 paper copies of your brief required by 5th Cir. R. 31.1 **by Monday, May 15, 2023,** pursuant to 5th Cir. ECF Filing Standard E.1. Failure to timely provide the appropriate number of copies may result in the dismissal of your appeal pursuant to 5th Cir. R. 42.3. Exception: As of July 2, 2018, Anders briefs only require 2 paper copies.

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