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 & DRUG ADMINISTRATION, *et al.*,
Defendants-Appellants.

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

BRIEF OF AMICUS CURIAE PUBLIC CITIZEN IN SUPPORT OF DEFENDANTS-APPELLANTS AND REVERSAL

Nicolas A. Sansone
Allison M. Zieve
Public Citizen Litigation Group
1600 20th Street NW
Washington, DC 20009
(202) 588-1000

Attorneys for Amicus Curiae
Public Citizen

May 1, 2023

SUPPLEMENTAL CERTIFICATE OF INTERESTED PERSONS

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Pursuant to this Court's Rule 29.2 and Federal Rule of Appellate Procedure 26.1, amicus curiae Public Citizen submits this supplemental certificate of interested persons to fully disclose all those with an interest in this brief and provide the required information as to their corporate statuses and affiliations.

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, in addition to those listed in

the briefs of the parties. These representations are made in order that the judges of this Court may evaluate possible disqualification or recusal.

A. Amicus curiae **Public Citizen** is a non-profit, non-stock corporation. It has no parent corporation, and no publicly traded corporation has an ownership interest in it of any kind.

B. The above-listed amicus curiae is represented by **Nicolas A. Sansone** and **Allison M. Zieve** of **Public Citizen Litigation Group**.

/s/ Nicolas A. Sansone
Nicolas A. Sansone

Attorney for Amicus Curiae Public Citizen

May 1, 2023

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INTEREST OF AMICUS CURIAE[1]

Public Citizen is a non-profit consumer advocacy organization with members in all fifty states. Among other things, Public Citizen works to advance access to health care and to ensure strong protections for public health. Since 1971, the physicians in Public Citizen's Health Research Group have studied the work of the U.S. Food and Drug Administration (FDA) and have filed dozens of citizen petitions challenging FDA approvals or labeling decisions, including more than forty petitions asking the FDA to ban an approved drug because of safety risks. *See, e.g.*, Public Citizen, *Petition to the FDA to Ban the Drug Hydroxyprogesterone Caproate (Makena), Approved for Prevention of Preterm Birth* (Oct. 8, 2019), https://tinyurl.com/3bk9xkkr; Public Citizen, *Petition to the FDA to Require a Black-Box Warning for the Osteoporosis Drug Prolia* (Apr. 16, 2019), https://tinyurl.com/bdhy4tj9. These citizen petitions generally ask the FDA to act based on new peer-reviewed studies or new adverse event reports that draw into question the FDA's earlier decision.

[1] This brief was not authored in whole or part by counsel for a party, and no one other than amicus curiae or its counsel made a monetary contribution to the preparation or submission of the brief. Public Citizen has moved for leave to file this brief with the consent of all parties.

As a consumer advocacy organization, Public Citizen has a strong interest in the safety and effectiveness of drugs marketed to patients in the United States. And as an FDA watchdog, Public Citizen has a strong interest in ensuring that citizen petitions are used appropriately to bring compelling new drug-safety evidence to the FDA's attention—not as a mechanism for disrupting the regulatory regime by attempting to reopen FDA determinations based on simple disagreement with the FDA's expert assessment of the scientific evidence undergirding its findings, without new evidence showing lack of safety or effectiveness.

SUMMARY OF ARGUMENT

Through the Food, Drug, and Cosmetic Act (FDCA), Congress entrusted the FDA with responsibility for assessing the safety and effectiveness of new drugs before they can be marketed, for determining the uses for which such drugs can lawfully be marketed, and for monitoring the safety of drugs after marketing approval. In carrying out these duties, the FDA brings together teams of medical doctors, chemists, microbiologists, statisticians, pharmacologists, and other experts to review a vast amount of information about a medication's safety and effectiveness, including peer-reviewed scientific literature and the

results of clinical trials conducted with oversight from disinterested institutional review boards.

Congress anticipated that this rigorous, science-based process would produce reliable outcomes that protect and advance Americans' health, and it does. Consequently, courts have appropriately recognized that the bar for second-guessing the FDA's determinations with respect to drugs' safety and effectiveness should be nearly insurmountable, absent either evidence of a meaningful procedural breakdown or new information that comes to light after approval and that reasonably should alter the FDA's considered analysis.

Plaintiffs' 2019 citizen petition, while asking the FDA to unwind its 2016 decision to alter certain restrictions on the use of mifepristone, suggested no flaw in the FDA's 2016 decisional process and relied on no significant new evidence.[2] Instead, the petition did exactly what courts have cautioned against: It disagreed with the FDA's decision by offering a competing assessment of the body of scientific data that the FDA had already evaluated in depth. If anything, the petition's fleeting references

[2] This brief uses the general term "mifepristone" to refer both to the branded product Mifeprex, which the FDA approved in 2000, and to the bioequivalent generic that the FDA subsequently approved.

to post-2016 studies served only to confirm that the evidentiary backdrop against which the FDA took its 2016 actions remained essentially unchanged. Should the Court reach this case's merits, then, it should hold that the FDA did not act arbitrarily or capriciously in rejecting the citizen petition's request that the FDA reverse its 2016 decision.

ARGUMENT

I. The FDA engages in rigorous and ongoing expert study of detailed scientific evidence when considering whether and under what conditions a drug is safe and effective for use.

A. Congress established the FDA to "protect the public health by ensuring," among other things, that "human and veterinary drugs are safe and effective." 21 U.S.C. § 393(b)(2)(B). Originally, the FDA's role was limited to policing the marketing of adulterated or misleadingly advertised drugs, with "no power to demand, prior to marketing, any evidence that a drug was safe or would perform as the seller claimed." Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1758 (1996). But in 1938, after an adulterated drug that had not undergone safety testing poisoned over one hundred people, Congress empowered the FDA to assess the safety of new drugs before they could be sold. *Id.* at 1761. Since then, Congress has

strengthened the FDA's premarket role by requiring it to consider a drug's effectiveness as well as its safety, *id.* at 1764–68, and "FDA concurrence" is now "a prerequisite for all critical steps in the development of a new drug," *id.* at 1798.

The FDA's role in evaluating a new drug—defined in relevant part as a drug that has not yet been "generally recognized[ ] among experts qualified by scientific training and experience … as safe and effective for use," 21 U.S.C. § 321(p)(1)—begins as soon as "the drug's sponsor (usually the manufacturer or potential marketer), having screened the new [drug] for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans." FDA, *Investigational New Drug (IND) Application* (July 20, 2022), https://tinyurl.com/hwwryzzr. If early preclinical animal and toxicology trials establish that the drug is "reasonably safe for initial testing in humans," the sponsor submits an Investigational New Drug application to the FDA with data from the preclinical studies, information about the drug's composition and manufacture, and details about the proposed clinical trials and the qualifications of the investigators who will be conducting them. *Id.* The FDA then has thirty days to review the

application and to "provide[ ] comments intended to improve the quality" of the proposed trials and ensure that they meet federal standards. FDA, *Step 3: Clinical Research* (Jan. 4, 2018), https://tinyurl.com/yttstres. Once the FDA gives its approval, the proposed trials may move forward. *Id.*

The ensuing clinical trials generally proceed in three phases. *See* 21 C.F.R. § 312.21. First, investigators conduct "closely monitored" studies of the drug's effect in roughly 20–80 subjects, with the aim of "determin[ing] the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, … gain[ing] early evidence on effectiveness." *Id.* § 312.21(a)(1). Second, investigators conduct "well controlled, closely monitored" studies on "usually … no more than several hundred subjects" to "evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug." *Id.* § 312.21(b). Finally, if the initial phases produce "preliminary evidence suggesting effectiveness of the drug," investigators conduct "expanded" studies involving "several hundred to several thousand subjects" to "gather the additional information about effectiveness and safety that is

needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling." *Id.* § 312.21(c). Throughout the trials, the sponsor has an ongoing obligation to review "all information relevant to the safety of the drug," including information from clinical investigations, animal studies, scientific literature, and unpublished scientific reports, *id.* § 312.32(b), and to report to the FDA on the progress of the trials and on evidence of potential safety risks, *id.* §§ 312.32(c), 312.33.

Following these trials, a sponsor seeking FDA approval to sell and market the new drug must submit a New Drug Application (NDA), which is "supposed to tell the drug's whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged." FDA, *New Drug Application (NDA)* (Jan. 21, 2022), https://tinyurl.com/bdh9pmbx. The FDCA and FDA regulations require that the NDA include extensive "data and information," reported "in sufficient detail to permit the [FDA] to make a knowledgeable judgment about whether to approve the NDA or whether grounds exist … to refuse to approve the NDA." 21 C.F.R. § 314.50(d); *see*

21 U.S.C. § 355(b). The NDA must also include a summary that is "written at approximately the level of detail required for publication in, and [that] meet[s] the editorial standards generally applied by, refereed scientific and medical journals." 21 C.F.R. § 314.50(c)(1).

Upon receiving an NDA, an FDA review team made up of "medical officers, chemists, statisticians, microbiologists, pharmacologists, and other experts" evaluates the materials. U.S. Gov't Accountability Off., GAO-08-751, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex* 9 (2008), https://tinyurl.com/4ccdvv5y [GAO, *Approval & Oversight*]. Meanwhile, inspectors travel to clinical study sites to "look[ ] for evidence of fabrication, manipulation, or withholding of data." FDA, *Step 4: FDA Drug Review* (Jan. 4, 2018), https://tinyurl.com/bdcub9sj. Ultimately, the review team compiles a recommendation that "analyze[s] the condition or illness for which the drug is intended and evaluate[s] the current treatment landscape," considers "clinical benefit and risk information submitted by the drug maker, taking into account any uncertainties that may result from imperfect or incomplete data," and assesses potential "[r]isk management strategies." FDA, *Development & Approval Process: Drugs* (Aug. 8, 2022), https://

tinyurl.com/vajsn94c. These detailed recommendations typically span hundreds of pages of expert analysis. For example, an FDA integrated assessment of an NDA approved this year was 374 pages, supplemented by a 22-page clinical outcome assessment consult review and a 44-page statistical review of carcinogenicity studies. *See* FDA, Ctr. for Drug Eval. & Res., *Integrated Review: Jesduvroq* (July 20, 2022), https://tinyurl.com/cxev6pxc.

After completion of the scientific reviews, FDA managers conduct an independent analysis of the review team's recommendation on whether to approve the NDA. GAO, *Approval & Oversight* at 9. Congress has directed that the NDA must be rejected if the FDA has "insufficient information to determine whether [the] drug is safe for use" under the intended conditions or if the FDA lacks "substantial evidence"—defined to include "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience"—that the drug will "have the effect it purports or is represented to have." 21 U.S.C. § 355(d). If the drug clears those hurdles, the FDA must approve it, allowing the drug to enter the market. *See id.* § 355(a). The approval includes specification of the exact labeling for the

drug, requires manufacturers to comply with good manufacturing practice regulations, and may also impose additional requirements. *See* 21 C.F.R. §§ 201.1–201.328, 210.1–210.3, 314.520.

Following approval of its NDA, the sponsor remains under an obligation to "review all adverse drug experience information" it obtains "from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers." *Id.* § 314.80(b). The sponsor must report "serious and unexpected" adverse experiences to the FDA within fifteen days of learning about them, *id.* § 314.80(c)(1)(i), and it must report all other adverse experience data at quarterly intervals for three years following approval and at annual intervals thereafter, *id.* § 314.80(c)(2)(i). Separately, the sponsor must file an annual report with the FDA containing detailed information about any new developments that cast light on the drug's safety or effectiveness or on the appropriateness of the drug's labeling. *Id.* § 314.81(b)(2).

B. In approving an NDA, the FDA may elect to place restrictions on the drug's distribution to ensure that the drug is used in a manner that

the FDA can be confident is safe. *See* GAO, *Approval & Oversight* at 10. Under regulations promulgated in 1992 and collectively known as "Subpart H," the FDA can impose "such postmarketing restrictions as are needed to assure safe use" of a drug that "ha[s] been studied for [its] safety and effectiveness in treating serious or life-threatening illnesses and that provide[s] meaningful therapeutic benefit to patients over existing treatments." 21 C.F.R. §§ 314.500, 314.520. And in amendments to the FDCA enacted in 2007, Congress made clear that the FDA has authority to condition the approval of *any* new drug on the adoption of "a risk evaluation and mitigation strategy" (REMS) if such a strategy "is necessary to ensure that the benefits of the drug outweigh the risks." 21 U.S.C. § 355-1(a)(1). Congress also specified that any drug that was subject to Subpart H restrictions at the time of the 2007 amendments was "deemed to have in effect an approved [REMS] under" the FDCA until the sponsor submitted, and the FDA approved, a REMS pursuant to the statute. *Id.* § 331 note; *see* FDA, *Supplement Approval: Mifeprex* (June 8, 2011), https://tinyurl.com/2p8hkz2z [2011 Approval] (approving a REMS for mifepristone). Any drug subject to a REMS must undergo ongoing assessment until the FDA "determines that serious risks of the

drug have been adequately identified and assessed and are being adequately managed." 21 U.S.C. § 355-1(d)(4)(C).

Separately, Subpart H provides a pathway for accelerated approval of certain new drugs when direct clinical benefit will not be observable in the short term but when "adequate and well-controlled clinical trials establish[ ] that the drug product has an effect on a surrogate endpoint that is reasonably likely … to predict clinical benefit." 21 C.F.R. § 314.510; *see also* 21 U.S.C. § 356(a)(1) (codifying an accelerated approval mechanism for certain drugs intended to "treat a serious or life-threatening disease or condition"); FDA, *Accelerated Approval* (Feb. 24, 2023), https://tinyurl.com/mrycz8mk. Drugs approved on an accelerated basis "must meet the same statutory standards for safety and effectiveness as those granted traditional approval" but are allowed to "rely on a particular kind of evidence, such as a drug's effect on a surrogate endpoint," to demonstrate effectiveness. FDA, *Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics* 19 (May 2014), https://tinyurl.com/3p9fjpzd. After accelerated approval, the drug must undergo "additional postapproval studies or trials" to resolve "any remaining doubts" about its clinical benefit. *Id.*

That accelerated approval pathway is not at issue in this case. *See* FDA, *Accelerated and Restricted Approvals Under Subpart H (Drugs) and Subpart E (Biologics)* (Aug. 26, 2014), https://tinyurl.com/2kdvr66a (listing mifepristone's "Approval Basis" as Subpart H's restricted approval provision ("R"), not its accelerated approval provision ("S")).

C. The FDA approved Mifeprex, the branded version of mifepristone, in September 2000, under the restricted distribution provision of Subpart H. GAO, *Approval & Oversight* at 5. The FDA's detailed review included three review cycles—the first two of which confirmed the drug's safety and effectiveness and the third of which focused on restrictions for use. *Id*. at 5–6. The FDA's approval process for mifepristone in 2000 "was generally consistent with the approval processes for … other … Subpart H restricted drugs," although the details of the process for each "depended on the drug's unique risks and benefits." *Id*. at 6. Today, mifepristone is one of the drugs that was initially approved with Subpart H restrictions but that is now subject to a REMS pursuant to the 2007 FDCA amendments. *See* 2011 Approval.

II. The FDA's robust processes ensure that it will rarely, if ever, be arbitrary or capricious for the FDA to deny a citizen petition that seeks withdrawal of approval or REMS decisions without presenting new evidence.

Resolving issues that "require[ ] a high level of technical expertise … is properly left to the informed discretion of the responsible federal agenc[y]." *Kleppe v. Sierra Club*, 427 U.S. 390, 412 (1976); *see Rempfer v. Sharfstein*, 583 F.3d 860, 868 (D.C. Cir. 2009) (recognizing that courts "owe considerable deference" to "a scientific judgment by the FDA"); *cf. Baltimore Gas & Elec. Co. v. Nat. Resources Def. Council, Inc.*, 462 U.S. 87, 103 (1983) (observing that "a reviewing court must generally be at its most deferential" when examining an agency's "predictions, within its area of special expertise, at the frontiers of science"). Accordingly, courts routinely recognize that "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise." *Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995); *see Atchafalaya Basinkeeper v. U.S. Army Corps of Engineers*, 894 F.3d 692, 701 (5th Cir. 2018) (noting the "particular judicial deference" owed to agencies on scientific matters). As then-Judge Kavanaugh wrote for a unanimous panel of the D.C. Circuit, "[a] court is ill-equipped to second-guess" the FDA's "scientific judgment" about medical technology under

the "arbitrary and capricious standard" of the Administrative Procedure Act. *Cytori Therapeutics, Inc. v. FDA*, 715 F.3d 922, 927 (D.C. Cir. 2013).

The judicial deference owed to the FDA's scientific determinations derives not only from the FDA's subject-matter expertise but also from the rigor of the process through which Congress directed the FDA to bring that expertise to bear in assessing a drug's safety and effectiveness. *See, e.g.*, *Rutherford v. United States*, 806 F.2d 1455, 1461 (10th Cir. 1986) (recognizing Congress's intent "to give the [FDA] the primary jurisdiction to determine evidentiary matters concerning drugs about which it has a special expertise"). As described above, the process by which the FDA approves a new drug and adopts or modifies its REMS requires close expert analysis of a vast body of scientific evidence at every turn. For this reason, Congress specified that, when the FDA disapproves an NDA or withdraws a previous approval, the FDA's factual findings, "if supported by substantial evidence, shall be conclusive." 21 U.S.C. § 355(h); *cf. Whitehead v. Colvin*, 820 F.3d 776, 779 (5th Cir. 2016) (per curiam) (explaining in a Social Security case that "[a] finding of no substantial evidence is appropriate only if no credible evidentiary choices … support the decision" (quoting *Boyd v. Apfel*, 239 F.3d 698, 704 (5th Cir. 2001)).

To be sure, the FDA is not infallible in its decision to approve or restrict a new drug. For example, in unusual instances, impermissible considerations, rather than scientific judgment, could drive its decisionmaking. *See, e.g.*, *Tummino v. Torti*, 603 F. Supp. 2d 519, 545–46 (E.D.N.Y. 2009) (vacating the denial of a citizen petition where the FDA Commissioner overrode the "strong[ ]" recommendations of an "Advisory Committee *and* FDA scientific review staff" and instead succumbed to "pressure[ ] by the White House" to restrict sale of a drug in a way that the "overwhelming evidence" showed to be unnecessary). Moreover, post-approval developments might reveal safety or effectiveness concerns that the initial approval process failed to identify. For this reason, Congress gave the FDA authority to withdraw approval of an NDA if, for example, "clinical or other experience, tests, or other scientific data show that [a] drug is unsafe for use," or if "new information" undermines the FDA's conclusion that there is "substantial evidence that the drug will have the effect it purports or is represented to have." 21 U.S.C. § 355(e). Indeed, the FDA has eventually withdrawn approval of more than twenty drugs that Public Citizen, through citizen petitions written by its medical experts, urged the FDA to remove,

primarily based on post-marketing evidence raising significant safety concerns. *See*, *e.g.*, FDA, *FDA Drug Safety Communication: FDA Recommends Against the Continued Use of Propoxyphene* (Nov. 19, 2010), https://tinyurl.com/57wz46cx (noting action in response to a Public Citizen petition).

As the above example illustrates, where post-approval information calls the FDA's original judgment into question, an "interested person" may file a citizen petition urging the FDA to revisit its prior decision. 21 C.F.R. § 10.25(a). When an interested party simply disagrees with the FDA's analysis of the scientific evidence, however, the FDA's denial of the petition will rarely, if ever, be arbitrary or capricious. "The scope of review under the 'arbitrary and capricious' standard is narrow[,] and a court is not to substitute its judgment for that of the agency." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). After all, in light of the high stakes, the careful, data-driven process for assessing new drugs and the restrictions to be placed on their use is designed to produce rational results capable of standing up under scrutiny.

III. The FDA's denial of plaintiffs' 2019 citizen petition challenging the 2016 REMS modifications was not arbitrary or capricious because the petition simply disagreed with the FDA's expert assessment of the evidence and offered virtually no new evidence of its own.

Here, the central agency action that took place within the six years before plaintiffs filed this lawsuit in November 2022 was the FDA's denial of the 2019 citizen petition,[3] in which plaintiffs, in relevant part, challenged aspects of the FDA's March 2016 decision to modify the REMS for mifepristone.[4] *See* 28 U.S.C. § 2401(a) (establishing six-year statute

[3] The FDA approved a generic version of mifepristone in 2019, but plaintiffs have not challenged that approval except to the extent that it derives from the FDA's initial approval of mifepristone in 2000. *See* Dkt. No. 183-2 at 32 (motions panel's recognition that plaintiffs' challenge to the 2019 generic approval is "entirely dependent on the underlying 2000 Approval"). As the FDA and Danco explain, Dkt. No. 222 at 35–38; Dkt. No. 229 at 32–40, and as the motions panel preliminarily concluded, Dkt. No. 183-2 at 23, plaintiffs' challenge to the 2000 approval is time-barred. In addition, although the FDA announced in 2021 that it would exercise enforcement discretion to permit mifepristone to be distributed by mail during the COVID-19 public health emergency, that announcement has been superseded by a 2023 REMS modification and, in any event, will not apply by its own terms after the end of the public health emergency on May 11, 2023. *See* Dkt. No. 222 at 61–62.

[4] The citizen petition also requested that the FDA, at a minimum, retain the requirements of the 2016 REMS and, in particular, the requirement that mifepristone be dispensed in person. The FDA partially granted and partially denied that request, but the partial denial has been superseded by later events. *See supra* n.3.

of limitations for claims against the United States). The FDA's denial of the petition was not arbitrary or capricious. The petition neither identified a breakdown in the 2016 REMS modification process that caused the FDA to overlook critical data nor presented substantial new evidence that was unavailable in 2016.

The FDA's process with respect to mifepristone has been extensive. Beginning with its evaluation of the NDA, the FDA subjected mifepristone to the same rigorous scrutiny it applies to every new drug. *See* FDA, *Drug Approval Package: Mifeprex (Mifepristone) Tablet* (Sept. 28, 2000), https://tinyurl.com/5ejsucmw (linking to nearly 200 pages of detailed medical, chemistry, environmental, pharmacology, statistical, and clinical pharmacology biopharmaceutics reviews). The FDA's 2016 decision to lift some of the restrictions it had previously imposed on mifepristone came only after a comparable level of scientific inquiry. A 108-page medical review considered extensive clinical evidence of safety and effectiveness, including evidence of mifepristone's observed effects following its entry into the market. *See* FDA, Ctr. for Drug Eval. & Res., *Medical Review(s): Mifeprex* (July 2015), https://tinyurl.com/fsw4fst6 [REMS Medical Review]. In addition, the proposed REMS changes

underwent further review by chemists, clinical pharmacologists, statisticians, and others. *See* FDA, *Mifeprex (Mifepristone) Tablets* (Mar. 29, 2016), https://tinyurl.com/4f3baukc (linking to 2016 approval documents). A cross-disciplinary team leader synthesized these studies into an 87-page review document and concurred in the recommended REMS changes. *See* FDA, Ctr. for Drug Eval. & Res., *Cross Discipline Team Leader Review: Mifeprex* (Apr. 6, 2016), https://tinyurl.com/3yztydfm.

Plaintiffs' 2019 citizen petition disagreed with the FDA's expert analysis of the medical literature available at the time of the 2016 REMS modifications but offered virtually no new information. Indeed, the citizen petition did not discuss the FDA's detailed analysis in adopting the 2016 REMS modifications *at all*, let alone identify any subsequent developments that called that analysis into question. Nearly all the evidence cited in the section of the petition opposing the modifications predates 2016 and, therefore, does nothing to suggest that the body of available scientific evidence had meaningfully changed since the FDA concluded that the REMS modifications would not compromise patient safety. Instead, the petition simply disagreed with the outcome of the

agency's extensive expert evaluation of the drug's safety and effectiveness, and the conditions needed to ensure safe and effective use.

The portion of the petition that challenged the 2016 modifications identified only a handful of new facts:

- The petition cited data showing that, as of the end of 2018, ninety-seven women in the United States with ectopic pregnancies had received mifepristone, although mifepristone's labeling is required to state that it is contraindicated for ectopic pregnancies, and two of these women had died because the ectopic pregnancy had gone undiagnosed. Am. Ass'n of Pro-Life Obstetricians & Gynecologists, et al., Citizen Petition, at 5 (Mar. 29, 2019), https://tinyurl.com/3xnpkyfw [Citizen Petition] (citing FDA, *Mifepristone U.S. Post-Marketing Adverse Events Summary Through 12/31/2018*, at 1, https://tinyurl.com/3utjk7ur). But eighty-nine of these ectopic pregnancies, and both of the fatalities, were reported and addressed by the FDA's experts *before* the FDA made the 2016 modifications. *See* REMS Medical Review at 82, 84. The FDA had thus already considered such risks in 2016.

- The petition cited a 2018 study for the proposition that complications from medication abortions are more frequent for people who undergo the procedure at home rather than in a healthcare facility. Citizen Petition at 8 (citing Isabelle Carlsson, et al., *Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-Up Study*, BMC Women's Health (Sept. 25, 2018), https://tinyurl.com/26t36cjz). The FDA, however, explained that the study found "no statistically significant difference" in complication rates for medication abortions that take place at home, as compared to those that take place in a hospital. Letter from Patrizia A. Cavazzoni, Director, Ctr. for Drug Eval. & Res., to Donna J. Harrison, Executive Director, Am. Ass'n of Pro-Life Obstetricians & Gynecologists, et al., at 15 (Dec. 16, 2021), *available at* https://tinyurl.com/5evavs6k [Response Letter]. And the FDA had already "assessed serious adverse events … as reported in [plaintiffs'] literature" when initially adopting the 2016 REMS modifications. *Id.*
- In arguing that the FDA should not have eliminated the requirement that a patient return to her healthcare provider for

a follow-up examination after taking mifepristone, the petition cited a 2017 study explaining the need to ensure that postpartum patients who are Rh-negative receive a particular medication. Citizen Petition at 9 (citing Am. Coll. of Obstetricians & Gynecologists, *Practice Bulletin No. 181: Prevention of Rh D Alloimmunization* (Aug. 2017), https://tinyurl.com/43urspd8 [ACOG, *Practice Bulletin*]). As the study noted, the importance of providing such care has been known since the 1970s, *see* ACOG, *Practice Bulletin*—before the challenged decision. *See also* Citizen Petition at 9 (citing a 2003 study for the same point). And the FDA's response to the petition—explaining why an in-person "follow-up clinic visit" is not necessary for a patient to obtain the necessary treatment, Response Letter at 18—cannot reasonably be described as arbitrary and capricious.

- Finally, the petition *critiqued* two 2018 studies that suggested that follow-up visits after a medication abortion might not be necessary. *See* Citizen Petition at 9–10. The FDA obviously did not rely on these post-2016 studies in crafting its 2016 REMS

modifications. Any flaws in the studies would not call into question the FDA's decisionmaking.

In short, the citizen petition's 14-page discussion of the 2016 REMS modifications did not present new information drawing into question the decision the FDA reached in making those modifications based on the expert evaluation of its medical officers, chemists, pharmacologists, statisticians, and clinical pharmacology biopharmaceutics experts. *See supra* at 19–20. Nonetheless, the FDA walked point by point through the petition's arguments in a 40-page, single-spaced response that addressed the cited material and reaffirmed the substantial evidentiary basis for the FDA's 2016 action. Although Public Citizen in its 50-year history has disagreed with FDA approval decisions dozens of times, the case law and Congress both correctly recognize that attempts to overturn an FDA decision with respect to a new drug's approval and the conditions thereof properly face a high bar. In this case, plaintiffs fall well short of that high bar for second-guessing the agency's decision.

CONCLUSION

This Court should reverse the district court's judgment.

Respectfully submitted,

/s/ Nicolas A. Sansone
Nicolas A. Sansone
Allison M. Zieve
Public Citizen Litigation Group
1600 20th Street NW
Washington, DC 20009
(202) 588-1000

Attorneys for Amicus Curiae Public Citizen

May 1, 2023

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rules of Appellate Procedure 29(a)(5) and 32(a)(7)(B)(i) because, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and the Rules of this Court, it contains 4,740 words.

This brief also complies with the typeface and type style requirements of Federal Rules of Appellate Procedure 29(a)(4), 32(a)(5), and 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point Century Schoolbook.

/s/ Nicolas A. Sansone
Nicolas A. Sansone
Attorney for Amicus Curiae
Public Citizen

CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing Brief of Amicus Curiae with the Clerk of the Court for the United States Court of Appeals for the Fifth Circuit on May 1, 2023, using the Appellate Electronic Filing system. I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the CM/ECF system.

/s/ Nicolas A. Sansone
Nicolas A. Sansone
Attorney for Amicus Curiae
Public Citizen