No. 23-395

In the Supreme Court of the United States

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, ET AL.

ON CONDITIONAL CROSS-PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FIFTH CIRCUIT

BRIEF FOR THE FEDERAL CROSS-RESPONDENTS IN OPPOSITION

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QUESTIONS PRESENTED

In 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone as safe and effective for terminating early pregnancies. FDA's approval followed a four-year process involving review of clinical trial data and other scientific evidence. In 2022, cross-petitioners filed a lawsuit challenging FDA's approval of mifepristone and various subsequent FDA actions with respect to the drug. The questions presented are:

1. Whether the court of appeals erred in finding that cross-petitioners' challenge to FDA's approval of mifepristone in 2000 was untimely.

2. Whether, if cross-petitioners' challenge is timely, FDA's approval of mifepristone was arbitrary and capricious or otherwise unlawful.

3. Whether the court of appeals erred in holding that cross-petitioners lack standing to challenge FDA's 2019 approval of a generic version of mifepristone.

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OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-110a) is reported at 78 F.4th 210.[1] The opinion and order of the district court (Pet. App. 111a-195a) is not yet reported but is available at 2023 WL 2825871. This Court's order granting a stay (Pet. App. 245a-248a) is reported at 143 S. Ct. 1075. The court of appeals' order granting a stay in part (Pet. App. 196a-244a) is not reported but is available at 2023 WL 2913725.

[1] This brief uses "Pet." and "Pet. App." to refer to the petition for a writ of certiorari and appendix in No. 23-235, and "Cross-Pet." to refer to the conditional cross-petition for a writ of certiorari in No. 23-395.

JURISDICTION

The judgment of the court of appeals was entered on August 16, 2023. The petitions in Nos. 23-235 and 23-236 were filed on September 8, 2023, and placed on the docket on September 12, 2023. The conditional cross-petition for a writ of certiorari was filed on October 12, 2023. The jurisdiction of this Court is invoked under 28 U.S.C. 1254(1).

STATEMENT

The background of this case is described in the petition for a writ of certiorari in No. 23-235. See Pet. 2-11. This statement summarizes the aspects of that background that relate to the questions presented in the conditional cross-petition for a writ of certiorari.

A. Legal Background

Congress has entrusted the Food and Drug Administration (FDA) with the authority and responsibility to determine whether a "new drug" is safe and effective before it is distributed. 21 U.S.C. 321(p), 355; see 21 U.S.C. 393(b)(2)(B). The Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 *et seq.*, directs FDA to approve a new drug if, among other things, FDA finds that the sponsor's application contains substantial evidence demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. 355(d); see 21 C.F.R. 314.50, 314.105(c).

In 1992, FDA issued regulations providing for the imposition of conditions "needed to assure safe use" of certain new drugs that satisfy the other requirements for approval under the FDCA. 57 Fed. Reg. 58,942, 58,958 (Dec. 11, 1992). Those "Subpart H" regulations apply to certain new drugs that are used to treat "serious or life-threatening illnesses" and that provide

"meaningful therapeutic benefit to patients over existing treatments." 21 C.F.R. 314.500.

In 2007, Congress codified and expanded FDA's prior regulatory regime by authorizing the agency to require a "risk evaluation and mitigation strategy" (REMS) when it determines that such a strategy is necessary to ensure that the benefits of a drug outweigh the risks. 21 U.S.C. 355-1(a)(1); see Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, Tit. IX, § 901, 121 Stat. 922. The statutory REMS framework is not limited to drugs that treat illnesses. See 21 U.S.C. 355-1(a)(1)(B) and (C) (referring to the "disease or condition" treated by the drug). It also does not require a showing that a drug offers a benefit over existing treatments.

Under the statutory REMS framework, FDA's approval of a drug may require inclusion in the REMS of "elements to assure safe use," such as a requirement that a drug's prescribers have particular training or that a drug be dispensed only in certain settings. 21 U.S.C. 355-1(f)(3). After a drug is approved, FDA may require submission of a proposed modification to an approved REMS if it determines that the modification should be made to "ensure the benefits of the drug outweigh the risks of the drug" or to "minimize the burden on the health care delivery system of complying with the strategy." 21 U.S.C. 355-1(g)(4)(B)(i) and (ii).

B. FDA's Actions Addressing Mifepristone

1. In 2000, after a four-year review of the original sponsor's application, FDA approved mifepristone un-

der the brand name Mifeprex. C.A. Add. 181-191.[2] Mifepristone was and is approved for use with another drug, misoprostol, to end an early pregnancy. A patient who follows the two-drug regimen experiences cramping and bleeding similar to that associated with a miscarriage. *Id.* at 727-729. In approving mifepristone, FDA invoked its Subpart H regulations to impose requirements to assure the drug's safe use, including a requirement that it be dispensed by or under the supervision of a doctor with specified qualifications. *Id.* at 186. Based on a review of clinical trials and other scientific evidence, FDA concluded that when used under those conditions mifepristone was safe and effective to terminate pregnancy through seven weeks of gestation. *Id.* at 181-188.

When Congress adopted the REMS framework in 2007, it deemed each drug with existing Subpart H restrictions—including mifepristone—to have an approved REMS imposing the same restrictions. FDAAA § 909(b)(1) and (2), 121 Stat. 950-951 (21 U.S.C. 331 note). Congress further required the sponsor of such a drug to submit a proposed REMS to FDA for approval. Mifepristone's sponsor, cross-respondent Danco Laboratories, submitted such a proposal, which FDA approved on June 8, 2011. C.A. Add. 747, 769. As a result, the requirements to assure mifepristone's safe use are now governed by the statutory REMS framework, not by Subpart H.

2. In 2016, FDA approved a supplemental new drug application from Danco to modify the drug's conditions of use (including the REMS). C.A. Add. 768-775.

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[2] Like the petition in No. 23-235, this brief cites materials from the record below by referring to the addendum to the government's motion for a stay pending appeal in the Fifth Circuit.

Among other things, the modifications increased the gestational age limit from seven to ten weeks; reduced the required number of in-person visits from three to one; and changed the REMS to allow certain non-physician healthcare providers to prescribe and dispense mifepristone. *Id.* at 791-793. FDA's approval of those changes was based on a comprehensive review of the safety and efficacy of the proposed changes that considered "20 years of experience with [mifepristone], guidelines from professional organizations here and abroad, and clinical trials that have been published in the peer-reviewed medical literature." *Id.* at 677; see *id.* at 661-760.

3. In 2019, FDA approved an application from another sponsor, GenBioPro, to market a generic version of mifepristone. D. Ct. Doc. 1-37 (Nov. 18, 2022); see 21 U.S.C. 355(j). The same REMS covers both versions of the drug. D. Ct. Doc. 1-37, at 2-3.

4. In April 2021, FDA announced that, in light of the possible COVID-19-related risks associated with the in-person dispensing requirement, FDA intended to exercise enforcement discretion with respect to that requirement during the public health emergency, provided that all other requirements under the REMS were met. C.A. Add. 841.

C. Cross-Petitioners' Citizen Petitions

Before challenging FDA's decision to take or refrain from taking action with respect to a drug, a party must file a citizen petition with the agency. 21 C.F.R. 10.45(b). Cross-petitioners—doctors and associations of doctors who oppose abortion—filed two citizen petitions relevant here.

First, in 2002, two cross-petitioners filed a petition asking FDA to withdraw its 2000 approval of mifepris-

tone. C.A. Add. 804. FDA denied the petition in March 2016, on the same day it approved the changes to mifepristone's conditions of use described above. *Id.* at 804-836. In denying the petition, FDA explained that "well-controlled clinical trials" had "supported the safety" of mifepristone at the time of approval, and that "over 15 years of postmarketing data and many comparative clinical trials in the United States and elsewhere continue to support [its] safety." *Id.* at 820. FDA also explained that it had properly approved mifepristone under its Subpart H regulations, noting that "[p]regnancy can be a serious medical condition in some women," *id.* at 807, and that mifepristone can provide a "meaningful therapeutic benefit" over existing treatments as demonstrated by the fact that 92% of women in the U.S. phase 3 clinical trial of Mifeprex "avoided an invasive surgical procedure and anesthesia," *id.* at 807-808.

Second, in 2019, two cross-petitioners filed a petition challenging FDA's 2016 approval of changes to mifepristone's conditions of use. C.A. Add. 192-217. That petition did not ask FDA to revisit the 2000 approval; instead, it asked FDA to "restore" the 2000 conditions and "retain" the existing REMS, including the in-person dispensing requirement. *Id.* at 192. In December 2021, FDA denied that petition in relevant part. *Id.* at 837-876. FDA determined that none of the studies cited in the petition undermined FDA's findings from 2016. *Id.* at 843-857. FDA further determined that "the in-person dispensing requirement"—which was already subject to enforcement discretion beginning in April 2021 due to the COVID-19 pandemic, and which had been enjoined during much of 2020—"is no longer necessary to assure the safe use of mifepristone." *Id.* at 842. FDA accordingly directed Danco and GenBioPro to initiate the process of modifying the REMS to re-

move the in-person dispensing requirement. *Id.* at 842-843; see 21 U.S.C. 355-1(g)(4)(B)

D. Proceedings Below

1. In November 2022, cross-petitioners filed this suit challenging various FDA actions involving mifepristone, including the 2000 approval of Mifeprex; the 2016 changes to the drug's conditions of use; the 2019 approval of generic mifepristone; and FDA's 2021 actions regarding in-person dispensing. C.A. Add. 161-177. Cross-petitioners sought a preliminary injunction ordering FDA to suspend those actions. Pet. App. 117a.

2. The district court granted cross-petitioners' motion. Pet. App. 111a-195a. The court rejected the government's arguments that cross-petitioners lack standing, *id.* at 118a-133a, and that their challenge to the 2000 approval was untimely, *id.* at 134a-141a. On the merits, the court held that FDA violated its Subpart H regulations when approving mifepristone. *Id.* at 160a-172a. The court further held that FDA's challenged actions were arbitrary and capricious under the Administrative Procedure Act (APA), 5 U.S.C. 701 *et seq*. Pet. App. 172a-187a. The court then invoked 5 U.S.C. 705 to "stay" the effective date of "FDA's September 28, 2000, Approval of mifepristone and all subsequent challenged actions." Pet. App. 194a; see *id.* at 193a-195a.

3. The government and Danco appealed and sought a stay pending appeal. The Fifth Circuit granted a stay as to FDA's 2000 approval of mifepristone, but otherwise denied relief. Pet. App. 196a-244a. The government and Danco then applied to this Court for a stay of the district court's order in its entirety. The Court granted the applications and stayed the district court's order pending appeal and, if necessary, the Court's con-

sideration and disposition of petitions for a writ of certiorari. *Id.* at 245a.

4. After further briefing and argument, the Fifth Circuit issued a decision affirming in part and vacating in part. Pet. App. 1a-110a.

a. The Fifth Circuit first held that cross-petitioners have Article III standing to challenge FDA's actions with respect to Danco's branded mifepristone product on the theory that those actions made it more likely that some of cross-petitioners' member-doctors may be called upon to treat a woman who had taken mifepristone. Pet. App. 14a-42a. But the court held that cross-petitioners lack standing to challenge FDA's approval of generic mifepristone because there was "nothing in the record * * * to show" that the approval of an additional version of the same drug "contributes to [cross-petitioners'] risk of harm." *Id.* at 43a. The court therefore vacated the portion of the district court's order suspending FDA's approval of the generic version of the drug. *Ibid.*

b. The Fifth Circuit next held that cross-petitioners' challenge to FDA's original approval of mifepristone was barred by the six-year statute of limitations in 28 U.S.C. 2401(a). Pet. App. 45a-51a. The court explained that cross-petitioners "admit[ted]" that they had failed to sue within six years after FDA's 2016 decision denying their citizen petition challenging the approval decision. *Id.* at 45a. And the court rejected their attempt to rely on a "judge-made exception to the statute of limitations called the 'reopening doctrine.'" *Id.* at 46a. The court noted that although the D.C. Circuit has applied that exception in some cases, this Court "has cast some doubt on whether the reopening doctrine is a legitimate exception to a statute of limitations." *Id.* at 46a n.6 (citing *Biden* v. *Texas*, 142 S. Ct. 2528, 2545 n.8 (2022)). But

the Fifth Circuit did not "address that threshold question" because it concluded that even if the reopening doctrine is valid, it "does not apply here." *Ibid.*

Cross-petitioners' principal theory was that FDA actually or constructively reopened the 2000 approval when it made changes to mifepristone's conditions of use in 2016, and that their suit was therefore timely because it was brought within six years of FDA's 2021 denial of their citizen petition challenging those changes. Cross-petitioners also argued that FDA's petition denial and other actions in 2021 actually or constructively reopened the original approval. The Fifth Circuit rejected each of those theories.

The Fifth Circuit first concluded that FDA's 2016 approval of changes to mifepristone's conditions of use did not actually reopen the 2000 approval. Pet. App. 46a-47a. The court explained that "[n]othing in FDA's approval of the [2016] amendments shows that it undertook a 'serious, substantive reconsideration' of the 2000 Approval." *Id.* at 47a (citation omitted). "Actually," the court continued, "the opposite is true," because FDA took the original approval "as a given" and "considered only whether the REMS amendments were safe and effective." *Ibid.*

The Fifth Circuit next held that FDA's 2016 action did not satisfy the D.C. Circuit's requirements for a so-called "constructive" reopening, which occurs only when a subsequent agency action "fundamentally alter[s] the nature of the regulation" such that the change "'could not reasonably have been anticipated'" and "'significantly alters the stakes of judicial review.'" Pet. App. 48a (citations omitted). The court explained that although the 2016 amendments made significant changes, they "d[id] not alter FDA's basic assumption

that mifepristone is safe and effective, subject to certain conditions for use." *Ibid.*

The Fifth Circuit similarly rejected cross-petitioners' assertion that FDA reopened the 2000 approval in denying their second citizen petition in 2021. Pet. App. 49a-50a. The court noted that the petition "did not actually ask FDA to reconsider its approval of mifepristone," but rather asked FDA to "restore" restrictions approved in 2000 and to "retain" restrictions contained in the existing REMS. *Id.* at 49a. FDA therefore "had no reason to reevaluate mifepristone from the ground up." *Ibid.* And the court concluded that FDA did not in fact "reexamine its prior approval." *Ibid.* The court further held that, "[a]s with the 2016 Amendments," exercising enforcement discretion with respect to the in-person dispensing requirement did not qualify as a constructive reopening. *Ibid.*

c. The Fifth Circuit went on to hold that cross-petitioners are likely to succeed on their claims that FDA's 2016 and 2021 actions were arbitrary and capricious. Pet. App. 51a-63a. The Fifth Circuit thus affirmed the district court's order as to FDA's 2016 and 2021 actions. *Id.* at 69a-74a. Those rulings are the subject of the petitions for writs of certiorari in Nos. 23-235 and 23-236.

d. Judge Ho concurred in part and dissented in part. Pet. App. 76a-110a. He agreed with the majority's analysis of the 2016 and 2021 actions, but would have affirmed the district court's suspension of FDA's 2000 approval of mifepristone as well. *Id.* at 83a-97a.

ARGUMENT

FDA approved mifepristone as safe and effective in 2000. The agency has maintained that scientific judgment across five presidential administrations, while up-

dating the drug's approved conditions of use based on additional evidence and experience. More than five million Americans have relied on mifepristone to terminate their pregnancies, and public health authorities around the world have likewise approved the drug.

Cross-petitioners seek to upset that long-established status quo by challenging FDA's decades-old approval of mifepristone. As explained in the government's certiorari petition (Pet. 13-21), cross-petitioners lack Article III standing to challenge FDA's actions with respect to mifepristone, including the original approval. But even if cross-petitioners had standing, the Fifth Circuit correctly held that their challenge to the 2000 approval is plainly untimely. That holding neither conflicts with any decision of another court of appeals nor otherwise satisfies this Court's traditional certiorari standards.

Cross-petitioners also ask this Court to take up their underlying challenges to FDA's 2000 approval of mifepristone. But those issues do not warrant this Court's review because the Fifth Circuit did not consider them. Even setting aside that fatal problem, cross-petitioners do not and could not argue that their challenges satisfy this Court's certiorari standards. To the contrary, cross-petitioners ask this Court to parse a decades-old administrative record and to review FDA's compliance with a regulation whose application to mifepristone has long since been superseded by statute. Those stale, case-specific claims also lack merit.

Finally, cross-petitioners ask this Court to review the Fifth Circuit's holding that they lack standing to challenge FDA's approval of generic mifepristone. But they offer no good reason for this Court to review that factbound holding, which rested on cross-petitioners' failure to introduce *any* evidence of injury from the

availability of the generic version of the drug. This Court should deny the conditional cross-petition.

A. The Fifth Circuit Correctly Held That Cross-Petitioners' Challenge To FDA's 2000 Approval Of Mifepristone Is Barred By The Statute Of Limitations

Cross-petitioners' claims are subject to 28 U.S.C. 2401(a), which specifies that "every civil action commenced against the United States shall be barred unless the complaint is filed within six years after the right of action first accrues." FDA approved mifepristone in 2000. C.A. Add. 181-191. In 2002, cross-petitioners filed a citizen petition challenging that approval. *Id.* at 804-836. FDA denied that petition in March 2016, more than six years before cross-petitioners filed this suit in November 2022. *Ibid.* Cross-petitioners' claims challenging the 2000 approval are thus plainly time-barred.

Cross-petitioners seek to avoid that straightforward conclusion by asserting that FDA "reopened" its 2000 approval in a separate 2016 decision approving changes to mifepristone's conditions of use, and that their challenge is timely because they sued within six years of the FDA's 2021 denial of their citizen petition challenging the 2016 changes. But there is no basis for an atextual "reopening" exception to Section 2401(a)'s express time bar. And even if there were, cross-petitioners' challenge would not fit within even the most expansive understanding of the exception.

1. This Court has "never adopted" the D.C. Circuit's "reopening doctrine," *Biden* v. *Texas*, 142 S. Ct. 2528, 2545 n.8 (2022), and the Fifth Circuit questioned whether that doctrine is "a valid exception to the statute of limitations," Pet. App. 49a; see *id.* at 46a n.6. There is good reason for the Fifth Circuit's skepticism.

The traditional version of the D.C. Circuit's reopening doctrine applies in "situations where an agency conducts a rulemaking or adopts a policy on an issue at one time, and then in a later rulemaking * * * addresses the issue again without altering the original decision." *National Ass'n of Reversionary Prop. Owners* v. *Surface Transp. Bd.*, 158 F.3d 135, 141 (1998). In the D.C. Circuit's view, if "the agency actually reconsidered the rule, the matter has been reopened" and the limitations period "begins anew." *Ibid.*

The D.C. Circuit is correct that, in such a situation, a new limitations period would begin to run from the agency's final decision in the later rulemaking, and a person with a cognizable stake in the matter could thus challenge the agency's new decision, including its "renewed adherence" to the reconsidered policy. *Reversionary Property Owners*, 158 F.3d at 141 (citation omitted). But the D.C. Circuit has erred in describing such a suit as relying on "an exception to statutory limits on the time for seeking review" of the *original* decision. *Ibid.* Instead, such a suit is properly understood as a *timely* challenge to the *new* decision, which must be reviewed on the new record and based on the agency's new explanation.

In *Sierra Club* v. *EPA*, 551 F.3d 1019 (2008), cert. denied, 559 U.S. 991 (2010), the D.C. Circuit held that even absent an actual reconsideration, an agency can "constructively reopen" a prior decision if it "significantly alters the stakes of judicial review" by making changes that "could have not been reasonably anticipated" at the time of the original action. *Id.* at 1025 (brackets and citations omitted). In *Sierra Club*, for example, the court allowed a belated challenge to a regulation that "may not have been worth challenging" on its own, but that took on vastly greater significance when

the agency "*completely* changed the regulatory context." *Id.* at 1025-1026 (citations omitted).

Unlike the D.C. Circuit's traditional reopening doctrine, *Sierra Club*'s "constructive reopening" theory cannot be justified on the understanding that the plaintiff seeks review of the agency's "renewed adherence" to a prior policy in a new decision that is within the statute of limitations. *Reversionary Property Owners*, 158 F.3d at 141 (citation omitted). By definition, there is no renewed adherence to review because the agency has not actually reconsidered the original policy. Instead, the "constructive reopening" theory can only be understood as an atextual exception to the statute of limitations for challenging the agency's *original* action.

Neither the D.C. Circuit nor cross-petitioners have explained how that exception could be reconciled with Section 2401(a)'s unambiguous direction that a suit "shall be barred" unless it is filed within six years. Courts have no authority to create exceptions to statutes enacted by Congress. And unlike equitable tolling, a novel "constructive reopening" exception is not a "traditional feature of American jurisprudence" and cannot be justified as "a background principle against which Congress drafts limitations periods." *Boechler, P.C.* v. *Commissioner*, 596 U.S. 199, 208-209 (2022).

2. In any event, even if a "reopening" exception to the statutory time bar were valid, cross-petitioners' challenge to FDA's decision to approve mifepristone in 2000 would not fall within it.

a. As an initial matter, FDA plainly did not "expressly reopen[]" its approval of mifepristone when it approved changes to certain conditions for the drug's use in 2016. Cross-Pet. 18 (emphasis omitted). FDA had already found that mifepristone was safe and effective *with* those conditions in 2000. Thus, the only ques-

tion in considering the 2016 changes was whether mifepristone would remain safe and effective *without* those conditions. During its review in 2016, FDA evaluated new evidence bearing on whether those conditions continued to be necessary, found that mifepristone would remain safe under the proposed conditions, and accordingly relaxed the REMS requirements. FDA did not reconsider its decision to approve mifepristone in the first place; rather, as the Fifth Circuit explained, FDA took mifepristone's approval under "the restrictions imposed in 2000 as a given, and considered only whether the REMS amendments were safe and effective." Pet. App. 47a.

FDA's decision approving the 2016 changes thus did not reconsider the agency's reliance on Subpart H in approving mifepristone or its conclusion that the studies on which it relied in 2000 supported its original determination that the drug was safe and effective. Instead, FDA issued a separate decision addressing those issues in denying cross-petitioners' citizen petition challenging the 2000 approval on the same day it approved the 2016 changes. C.A. Add. 804-836. Cross-petitioners "likely could have challenged the 2000 Approval if they had timely filed suit in response to the petition denial." Pet. App. 47a. "But they did not." *Ibid.* And cross-petitioners' effort to conflate the changes made in 2016 with the denial of their citizen petition challenging mifepristone's original approval "is really just an end-run around the fact that [cross-petitioners] were too late to challenge FDA's denial of their citizen petition." *Ibid.*

b. FDA also did not actually reopen its 2000 approval of mifepristone when it denied cross-petitioners' second citizen petition in 2021. As the Fifth Circuit observed (Pet. App. 49a), that petition asked FDA to "restore" the 2000 conditions and "retain" the existing

REMS requirements. C.A. Add. 192. FDA did not "trigger the reopener doctrine" when, in the course of denying the second citizen petition, it merely "responded to assertions in the petition." *National Mining Ass'n* v. *United States Dep't of the Interior*, 70 F.3d 1345, 1352 (D.C. Cir. 1995). To the contrary, because FDA denied cross-petitioners' request to rescind the 2016 decision, judicial review is strictly "limited to the 'narrow issues as defined by the denial of the petition'" and does not otherwise reach "the agency's original action." *NLRB Union* v. *FLRA*, 834 F.2d 191, 196 (D.C. Cir. 1987) (citation and emphasis omitted); cf. *Public Emps. for Envt'l Responsibility* v. *EPA*, 77 F.4th 899, 913 (D.C. Cir. 2023) ("PEER cites no cases, and we are aware of none, in which an agency reopened an issue by merely responding to a petition for rulemaking submitted by a third party.").

Cross-petitioners emphasize FDA's statement that it conducted a "full review" of the mifepristone REMS in 2021. Cross-Pet. 20 (citation and emphasis omitted). But they do not identify any way in which that review revisited the drug's original approval. FDA did not, for example, reevaluate the strength of the clinical trials underlying that original approval or otherwise take steps that questioned "the basic concept of allowing women to use mifepristone." Pet. App. 49a. And neither the 2019 petition nor FDA's decision denying it revisited FDA's invocation of Subpart H at all. Instead, in its 2021 decision, FDA responded to cross-petitioners' specific arguments concerning the changes to the conditions of use in 2016. In responding to those arguments —which, again, presupposed the continued approval of the drug—FDA had "no reason to reevaluate mifepristone from the ground up." *Ibid.*

c. Cross-petitioners alternatively assert (Cross-Pet. 17, 21-23) that the 2016 changes "fundamentally alter[ed]" the regulatory landscape for mifepristone, and thus constituted a "constructive reopening" under *Sierra Club*. But this case is nothing like *Sierra Club*. There, the D.C. Circuit held that an agency constructively reopened a previous regulation because it made amendments that fundamentally changed the regulatory scheme and "significantly alter[ed] the stakes of judicial review" for an original rule that "may not have been worth challenging" on its own. *Sierra Club*, 551 F.3d at 1025-1026 (citation omitted). Here, in contrast, cross-petitioners—who vehemently oppose mifepristone and seek to completely preclude its use—cannot plausibly maintain that FDA's 2000 approval of the drug was a minor event that they did not regard as "worth challenging," *id.* at 1026 (citation omitted), until FDA's regulatory changes in 2016 and 2021. To the contrary, cross-petitioners *did* challenge FDA's original approval of mifepristone by submitting their first citizen petition—they simply failed to timely seek judicial review of FDA's denial of that petition.

In addition, as the D.C. Circuit has explained in subsequent decisions refusing to extend *Sierra Club*, that decision demands a truly unforeseeable "sea change" in the relevant regulatory regime. *National Biodiesel Bd.* v. *EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016) (citation omitted). Nothing like that happened here: Once mifepristone was approved, it was entirely foreseeable that FDA would continue to approve changes to its conditions of use as more experience and data regarding its use were accumulated. FDA's actions in 2016 and 2021 were in no sense a "sea change." Again, as the Fifth Circuit explained, those modifications "d[id] not alter FDA's basic assumption that mifepristone is safe and

effective, subject to certain conditions for use." Pet. App. 48a. FDA thus did not reopen the original 2000 approval even under the most expansive version of the constructive reopening theory.

Cross-petitioners assert (Cross-Pet. 21) that the government's stay application in this Court "effectively admit[ted]" that the 2016 and 2021 changes reopened the original approval because the government highlighted the serious practical consequences of an order blocking those changes. The government made no such concession. The stay application simply emphasized the "abrupt shift in the regulatory landscape" that would have followed if the stay panel's ruling had taken effect, thereby rendering "all extant doses of mifepristone misbranded" and causing the generic version of the drug to "cease to be approved altogether." Appl. to Stay at 4, *FDA* v. *Alliance for Hippocratic Medicine*, No. 22A902 (filed Apr. 14, 2023).

The fact that an abrupt court-ordered return to superseded conditions of use would cause profound disruption does not mean that the 2016 and 2021 changes "significantly alter[ed] the stakes of judicial review" within the meaning of *Sierra Club*, 551 F.3d at 1025 (citation omitted). That standard does not ask whether the agency's regulatory changes are significant in the abstract. Instead, it asks whether unforeseeable changes excuse the plaintiff's failure to bring a timely challenge to an earlier regulation because that regulation "may not have been worth challenging" on its own. *Id.* at 1026 (citation omitted). Cross-petitioners do not contend—and could not plausibly contend—that they lacked an incentive to challenge FDA's original approval of mifepristone. And their insistence that *any* significant regulatory change qualifies as a constructive reopening justifying noncompliance with the statute of

limitations underscores the startling breadth and indeterminacy of the atextual exception they seek.

B. FDA's Approval Of Mifepristone Was Not Arbitrary And Capricious Or Otherwise Unlawful

Because the Fifth Circuit correctly held that cross-petitioners' challenge to the 2000 approval of mifepristone is time-barred, it did not consider their objections to the 2000 approval. None of those objections has merit.

1. In approving mifepristone in 2000, FDA "reasonably considered the relevant issues" and "reasonably explained [its] decision." *FCC* v. *Prometheus Radio Project*, 141 S. Ct. 1150, 1158 (2021). FDA relied on three clinical trials that involved more than 2500 patients and that demonstrated the drug's safety. C.A. Add. 181. The agency thoroughly explained why those trials and other scientific evidence supported its approval. *Id.* at 181-188. And in 2016, FDA considered and refuted each of cross-petitioners' challenges to that decision. *Id.* at 804-836.

Evidence and experience from the last two decades confirm FDA's determination that mifepristone is safe. More than five million women have used mifepristone to terminate their pregnancies in the United States. And study after study has shown that when mifepristone is taken in accordance with its approved conditions of use, serious adverse events are "exceedingly rare." C.A. Add. 707. Unsurprisingly given its safety profile, mifepristone is approved in more than 90 other countries. See Gynuity Health Projects, *Mifepristone Approved List* (Mar. 2023), https://perma.cc/MHY4-KQNW. And the World Health Organization has declared it to be an "Essential Medicine[]." C.A. Add. 672.

2. Cross-petitioners do not point to any relevant evidence that FDA ignored when approving mifepristone. Instead, they assert (Cross-Pet. 12-13, 30-31) that, because the clinical trials underlying the 2000 approval included the use of ultrasound for dating a pregnancy and diagnosing ectopic pregnancy, as well as a period of post-administration observation, it was arbitrary and capricious for FDA to fail to include those requirements in the drug's approved conditions of use.

Cross-petitioners' "study match" requirement finds no support in the FDCA. Congress directed FDA to evaluate drug safety based on "the information submitted * * * as part of the application" and "any other information" before the agency. 21 U.S.C. 355(d). No provision requires FDA to limit conditions of approval to the precise protocols in clinical trials or existing studies. And such a requirement would make little sense because—as this case illustrates—clinical studies often include extra requirements "designed to control variability and maximize data quality" rather than to ensure safety and effectiveness. 23-235 Pharmaceutical Companies Amicus Br. 15-16 (citation omitted). In part for that reason, "[t]here are virtually always differences between clinical trial conditions and approved labeling." *Id.* at 15.

Rather than prescribing rigid limits on the studies FDA can consider, Congress granted the agency broad authority to "exercise [its] discretion or subjective judgment in determining whether a study is adequate and well controlled." *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 621 n.17 (1973). Agencies often operate without "perfect empirical or statistical data," and FDA's approval of mifepristone—like its approval of countless other drugs—reflected "a reasona-

ble predictive judgment based on the evidence it had." *Prometheus*, 141 S. Ct. at 1160.

In particular, FDA reasonably declined to impose an ultrasound requirement. As FDA explained in 2000, "[t]he role of ultrasound was carefully considered," but "other clinical methods" are also effective for dating pregnancies and diagnosing an ectopic pregnancy. C.A. Add. 185. FDA reasonably left the determination of how best to accomplish those objectives to "the medical judgment of the physician." *Ibid.* When FDA denied plaintiffs' citizen petition in 2016, it again thoroughly explained why an ultrasound requirement was unnecessary. *Id.* at 820-822 (discussing alternative methods). Cross-petitioners ignore that detailed explanation.[3]

Similarly, FDA explained in 2000 that concerns over the possibility of post-administration complications "ha[d] been dealt with through the labeling, which makes clear that if there isn't adequate access to emergency services, the medication is contraindicated." C.A. Add. 185. Again, cross-petitioners do not address that explanation, much less demonstrate that it was arbitrary and capricious.

Unable to identify any flaws in the substance of FDA's decision, cross-petitioners resort to repeating (Cross-Pet. 11-12) the district court's assertion that FDA found mifepristone to be dangerous but later yielded to political pressure. That assertion badly misreads the record. FDA determined in February 2000

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[3] Cross-petitioners' ultrasound argument also rests on a mistaken premise about the French trials underlying FDA's approval. Those trials—which involved roughly 1800 women—"did not require an ultrasound examination" in all cases, but instead left the decision of whether ultrasound was needed "to the discretion of" medical professionals. C.A. Add. 821 n.47; see *id.* at 181.

that there was insufficient evidence to show that mifepristone would be safe and effective *without distribution restrictions*, which FDA concluded were needed to assure safe use of the product. C.A. Add. 184, 186. The sponsor thus proposed additional restrictions, and six months later FDA concluded that "adequate information has been presented to approve" mifepristone *with* those restrictions. *Id.* at 189.

3. Cross-petitioners further contend (Cross-Pet. 24-28) that FDA's approval of mifepristone in 2000 was invalid under Subpart H of its regulations. That argument fails for multiple reasons.

Most obviously, Subpart H is now entirely irrelevant to FDA's regulation of mifepristone. When FDA approved mifepristone in 2000, it relied on Subpart H to impose restrictions on the drug's distribution. But the approval itself rested on FDA's underlying statutory authority under 21 U.S.C. 355, not Subpart H. And in 2007, Congress created the new REMS framework and incorporated mifepristone's distribution restrictions into that framework. FDAAA, Tit. IX, 121 Stat. 922. FDA then approved a REMS for mifepristone in 2011. Ever since, mifepristone has been regulated under the REMS framework—not Subpart H. C.A. Add. 838. The FDAAA and FDA's subsequent actions thus supersede and render irrelevant any issues concerning FDA's prior reliance on Subpart H in 2000.

In any event, FDA properly invoked Subpart H. Cross-petitioners insist (Cross-Pet. 2, 12, 24-26) that Subpart H was inapplicable to mifepristone because it applied only to drugs that treat "serious or life-threatening illnesses," 21 C.F.R. 314.500, and pregnancy is not an "illness." But the preamble to FDA's final rule explained that Subpart H was available for drugs that treat serious or life-threatening conditions. 57 Fed.

Reg. at 58,945-58,948. Moreover, FDA reasonably found that pregnancy "can be a serious medical condition in some women." C.A. Add. 807.

FDA also correctly concluded that Subpart H applied to mifepristone because the drug provides "meaningful therapeutic benefit[s] to patients over existing treatments." 21 C.F.R. 314.500. FDA found that mifepristone avoided a surgical procedure for 92% of patients. C.A. Add. 807-808. Cross-petitioners assert (Cross-Pet. 27-28) that "avoidance of the current standard of care's delivery mechanism" can never be a meaningful benefit. But avoiding invasive surgery and the risks of the associated anesthesia are obvious benefits, and cross-petitioners point to nothing in law or logic supporting their contrary view.

C. The Fifth Circuit Correctly Held That Cross-Petitioners Had Failed To Establish Their Standing To Challenge FDA's Approval Of Generic Mifepristone

Cross-petitioners also argue (Cross-Pet. 31-35) that FDA erred in approving generic mifepristone in 2019. The Fifth Circuit correctly held that cross-petitioners lack standing to challenge that decision because they failed to provide any evidence that the approval of generic mifepristone caused their alleged harms. See Pet. App. 43a-44a. The Fifth Circuit emphasized that there is "no evidence that the number of women experiencing medical complications after taking mifepristone has risen as a result of the generic." *Id.* at 43a. In fact, the Fifth Circuit emphasized that "the preliminary-injunction exhibits do not mention generic mifepristone at all." *Ibid.*

Cross-petitioners do not dispute that they failed to offer evidence of injury specific to generic mifepristone. They note (Cross-Pet. 33-34) that the aggregate use of

mifepristone has increased since the approval of the generic version of the drug, and they infer that the increase is attributable to the availability of a generic alternative. But as the Fifth Circuit explained, cross-petitioners bore the burden to establish their standing, and they "cannot carry their burden of proof with legal argument." Pet. App. 43a.

Regardless, cross-petitioners' challenge to the approval of generic mifepristone is entirely derivative of their challenge to FDA's approval of Mifeprex. See Cross-Pet 31. Because cross-petitioners' challenge to that approval fails, either on timeliness or on the merits, their challenge to the generic approval fails as well.

D. The Questions Presented In The Cross-Petition Do Not Warrant Further Review

1. Cross-petitioners do not contend that the challenged aspects of the decision below conflict with any decision of this Court or implicate any circuit conflict warranting this Court's review. And none of the issues that cross-petitioners seek to raise otherwise satisfies this Court's traditional certiorari standards.

First, cross-petitioners' challenge to the Fifth Circuit's timeliness holding presumes the existence of a "reopening doctrine" that this Court has never recognized. Pet. App. 46a & n.6, 49a; see *Texas*, 142 S. Ct. at 2545 n.8. To find cross-petitioners' claim timely, therefore, the Court would have to first decide to recognize the reopening doctrine. But this case would not be an appropriate vehicle in which to consider the antecedent question of whether the reopening doctrine is a valid exception to the statute of limitations because the Fifth Circuit specifically declined to address it. See *Cutter* v. *Wilkinson*, 544 U.S. 709, 718 n.7 (2005) ("[This Court is] a court of review, not of first view."). Even setting aside

that problem, this case would be a very poor vehicle in which to consider the reopening doctrine. It involves a complicated and unusual procedural history that is far removed from the circumstances where the reopening doctrine has been applied. Cf. *Public Emps. for Envt'l Responsibility*, 77 F.4th at 914 (collecting cases where the D.C. Circuit has "found a reopening of the administrative process"). Indeed, cross-petitioners themselves acknowledge that their argument rests on what they deem (Cross-Pet. 20) the "unique circumstances" of this case. And as already explained, cross-petitioners seek to extend the reopening doctrine well beyond the limits established by *Sierra Club* and the D.C. Circuit's subsequent decisions. See pp. 17-19, *supra*; see also Pet. App. 48a (distinguishing *Sierra Club*, *supra*). Cross-petitioners thus err to the extent they seek to imply (Cross-Pet. 22) that the Fifth Circuit's rejection of their effort to avoid the statute of limitations on a "reopening" rationale is in tension with *Sierra Club*.

Second, even aside from the threshold bar of the statute of limitations, cross-petitioners' substantive challenges to the approval of mifepristone would not warrant consideration by this Court. Cross-petitioners identify no sound reason for the Court to depart from its ordinary practice by considering their contentions regarding the merits of the 2000 approval decision when the Fifth Circuit did not do so. Nor do cross-petitioners offer any sound reason for this Court to take up their challenges to FDA's compliance with a regulatory provision whose application to mifepristone has long since been superseded by statute.

Finally, the Fifth Circuit's conclusion that cross-petitioners lack standing to challenge the approval of generic mifepristone was based on the court's conclusion that they had failed to offer any evidence of harm

attributable to the generic version of the drug. That factbound assessment of the preliminary-injunction record does not warrant further review.

2. Rather than attempting to satisfy this Court's ordinary certiorari standards, cross-petitioners assert (Cross-Pet. 11, 16) that the Court should consider the questions they present regarding FDA's 2000 approval of mifepristone because those questions are "inextricably intertwined" with, and might "provide[] the background for," the issues raised in the petitions filed by FDA and Danco. In so doing, cross-petitioners purport to invoke the federal policy "against piecemeal appeals." *Id.* at 16 (quoting *Switzerland Cheese Ass'n* v. *E. Horne's Mkt., Inc.*, 385 U.S. 23, 24 (1966)). But that policy concerns review in the courts of appeals, not this Court's discretionary certiorari docket. And this Court has never applied a presumption in favor of taking up every issue in a case merely because some issues warrant review.

To the contrary, this Court "has made it plain that, as a matter of its discretion, it will 'decline to entertain' questions presented by a respondent 'in the absence of * * * an indication that the issues are of sufficient general importance to justify the grant of certiorari.' " Stephen M. Shapiro et al., *Supreme Court Practice* 6.35, at 493 (10th ed. 2013) (quoting *United States* v. *Nobles*, 422 U.S. 225, 242 n.16 (1975)). Indeed, the Court has recently and repeatedly denied cross-petitions raising additional questions that did not independently warrant this Court's review. See, *e.g.*, *NetChoice* v. *Moody*, No. 22-393 (Oct. 2, 2023); *Community Fin. Servs. Ass'n of Am.* v. *CFPB*, 143 S. Ct. 981 (2023) (No. 22-663); *Jarkesy* v. *SEC*, 143 S. Ct. 2690 (2023) (No. 22-991). It should do the same here.

In arguing otherwise, cross-petitioners greatly overstate the degree of "overlap," Cross-Pet. 15, between the cross-petition and the petitions filed by FDA and Danco. Those petitions concern decisions FDA made in 2016 and 2021. Those decisions were based on different records and raise different legal questions than cross-petitioners' claims about FDA's original approval of Mifeprex in 2000 and its generic version in 2019. Indeed, the cross-petition principally concerns a distinct timeliness issue and a factbound challenge to that earlier decision. As the Fifth Circuit's decision makes clear, the outcome of cross-petitioners' challenge to the 2000 approval has no bearing on the resolution of the important questions raised by FDA and Danco. Granting the cross-petition would thus serve only to complicate this Court's consideration of those questions by injecting numerous additional issues that do not independently warrant review.

Nor do the strong reasons supporting review of the Fifth Circuit's holding that FDA's 2016 and 2021 actions were likely unlawful extend to the separate issues cross-petitioners seek to raise here. As the government has explained, the portions of the Fifth Circuit's decision affirming the district court's "stay" of the 2016 and 2021 modifications of mifepristone's conditions of use are unprecedented and threaten significant practical harm for women across the country, the pharmaceutical industry, and FDA. See Pet. 30-33. The Fifth Circuit's enforcement of the statute of limitations, however, breaks no new legal ground, is clearly correct, and respects the principles upon which the statute of limitations rests. Nor does leaving in place FDA's approval of mifepristone—a drug that has been on the market for more than two decades, during which its safety and efficacy have repeatedly been confirmed—threaten to up-

end the regulatory framework for drug approvals or undermine reliance interests. By contrast, granting cross-petitioners the relief they seek through their cross-petition—invalidating FDA's approval of mifepristone and upsetting a decades-long status quo—would be extraordinarily disruptive. See, *e.g.*, Pharmaceutical Companies Amicus Br. at 18, *FDA* v. *Alliance for Hippocratic Medicine*, No. 22A902 (Apr. 14, 2023). This Court should decline cross-petitioners' request to reinject such uncertainty into this litigation.

CONCLUSION

The conditional cross-petition for a writ of certiorari should be denied.

Respectfully submitted.

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