No. 23-395

IN THE
Supreme Court of the United States

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Cross-Petitioners,

v.

U.S. FOOD AND DRUG ADMINISTRATION, ET AL.,
Cross-Respondents,

and

ALLIANCE FOR HIPPOCRATIC MEDICINE, ET AL.,
Cross-Petitioners,

v.

DANCO LABORATORIES, L.L.C.,
Cross-Respondent.

On Conditional Cross-Petition for a Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

BRIEF IN OPPOSITION FOR DANCO LABORATORIES, LLC

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QUESTIONS PRESENTED

More than 23 years ago, the Food and Drug Administration (FDA) approved Danco's drug Mifeprex, in combination with another FDA-approved drug misoprostol, for termination of early pregnancy. The six-year statute of limitations to challenge that approval came and went. Then, in November 2022, anti-abortion doctors and associations of anti-abortion doctors—none of whom prescribe Mifeprex—filed an untimely challenge to FDA's September 2000 approval of Mifeprex. As relevant here, they argued that FDA was not authorized to impose use restrictions in 2000 under a set of regulations known as Subpart H. The Fifth Circuit held this challenge was time-barred. The questions presented are:

1. Whether this Court should adopt the D.C. Circuit's judge-made "reopening" doctrine and find that FDA's lifting of certain Mifeprex use restrictions in response to post-approval clinical data and real-world drug experience restarted the statute of limitations for challenging the drug's 2000 approval.

2. Whether Mifeprex's 2000 approval can be preliminarily enjoined in 2023 based on FDA's use of Subpart H to initially impose use restrictions.

PARTIES TO THE PROCEEDING

Cross-Petitioners are Alliance for Hippocratic Medicine; American Association of Pro-Life Obstetricians & Gynecologists; American College of Pediatricians; Christian Medical & Dental Associations; Shaun Jester, D.O.; Regina Frost-Clark, M.D.; Tyler Johnson, D.O.; and George Delgado, M.D. They were plaintiffs in the District Court and appellees in the Court of Appeals.

Cross-Respondents are Danco Laboratories, LLC, who was an intervenor in the District Court and an appellant in the Court of Appeals, and the U.S. Food and Drug Administration (FDA); Robert M. Califf, M.D., in his official capacity as Commissioner of Food and Drugs; Janet Woodcock, M.D., in her official capacity as Deputy Commissioner of Food and Drugs; Patrizia Cavazzoni, M.D., in her official capacity as Director of FDA's Center for Drug Evaluation and Research; the U.S. Department of Health and Human Services (HHS); and Xavier Becerra, in his official capacity as Secretary of HHS, who were defendants in the District Court and appellants in the Court of Appeals.

CORPORATE DISCLOSURE STATEMENT

Pursuant to Supreme Court Rule 29.6, Danco Laboratories, LLC hereby states that it is a wholly-owned subsidiary of Danco Investors Group, LP. No publicly held corporation owns 10% or more of the stock of either entity.

RELATED PROCEEDINGS

Supreme Court of the United States:

- *Danco Laboratories, LLC* v. *Alliance for Hippocratic Medicine, et al.*, No. 23-236 (Sept. 12, 2023) (petition for a writ of certiorari)
- *U.S. Food & Drug Administration, et al.* v. *Alliance for Hippocratic Medicine, et al.*, No. 23-235 (Sept. 12, 2023) (petition for a writ of certiorari)
- *Danco Laboratories, LLC* v. *Alliance for Hippocratic Medicine, et al.*, No. 22A901 (Apr. 21, 2023) (granting application for stay)
- *U.S. Food & Drug Administration, et al.* v. *Alliance for Hippocratic Medicine, et al.*, No. 22A902 (Apr. 21, 2023) (granting application for stay)

United States Court of Appeals (5th Cir.):

- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration, et al.*, No. 23-10362 (Aug. 16, 2023) (opinion)
- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration, et al.*, No. 23-10362 (Apr. 12, 2023) (partially granting and partially denying stay pending appeal)

United States District Court (N.D. Tex.):

- *Alliance for Hippocratic Medicine, et al.* v. *U.S. Food & Drug Administration et al.*, No. 2:22-cv-223 (Apr. 7, 2023) (opinion)

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BRIEF IN OPPOSITION FOR DANCO LABORATORIES, LLC

INTRODUCTION

Plaintiffs' conditional cross-petition starts by asking this Court to adopt a new legal doctrine to excuse their failure to timely file suit—an issue presenting no conflict with this Court's precedent, involving no circuit split, and that the court below found was inapplicable to the facts here. Plaintiffs next ask this Court to address an obsolete regulatory mechanism FDA once used to implement use

restrictions on approved drugs—prior to 2008—even though that regulation does not govern Mifeprex's use restrictions today, or the use restrictions of any other drug either. In any event, that mechanism was properly used. This Court should reject Plaintiffs' requests.

The Fifth Circuit correctly held that Plaintiffs' challenge to FDA's 2000 approval of Mifeprex was untimely; Plaintiffs filed suit after the statute of limitations expired. So Plaintiffs are left to argue that this Court should grant certiorari to recognize—for the first time—the "reopening" doctrine, a judge-made exception to the statute of limitations created by the D.C. Circuit. And because the Fifth Circuit held that this doctrine would be inapplicable even if it could validly excuse a failure to timely file suit, Plaintiffs also ask this Court to find that the Fifth Circuit's fact-bound analysis of that issue was wrong.

Equally uncertworthy, this Court should not opine on a purely academic question that the Fifth Circuit did not address: whether FDA acted within its regulatory authority when it imposed use restrictions under regulations known as Subpart H at the time it initially approved Mifeprex. The answer to that question is yes. But neither the question nor the answer matter one whit, because FDA's use of its Subpart H regulatory authority to require Mifeprex use restrictions was superseded by Congress in 2008. When Congress gave FDA statutory authority to impose use restrictions in the form of a Risk Evaluation and Mitigation Strategy (REMS), all drugs with Subpart H use restrictions transitioned to a REMS. The use restrictions for Mifeprex have been

under FDA's REMS authority for the past fifteen years, and remain so today.

Indeed, it is truly difficult to come up with a less certworthy question than whether FDA in 2000 properly applied a long-since-superseded regulation—unless, perhaps, it is the question whether the Fifth Circuit erred in finding the D.C. Circuit's "reopening" doctrine inapplicable to revive Plaintiffs' long-expired claims.

The questions presented in Plaintiffs' cross-petition are not intertwined with the questions presented in Danco's or FDA's petitions. Those petitions ask this Court to address Article III standing and FDA's 2016 and 2021 administrative actions with respect to Mifeprex—questions far removed from the validity of the "reopening" doctrine and FDA's obsolete interpretation of Subpart H. As Danco's certiorari petition detailed, the Fifth Circuit's approach conflicts with this Court's precedents and creates multiple circuit splits. The cross-petition offers nothing remotely similar.

Danco is unaware of any case in which this Court granted a conditional cross-petition raising separate, distinct issues involving a separate, distinct agency action. The conditional cross-petition should be denied.

STATEMENT OF THE CASE

A. Factual Background

1. FDA approved Mifeprex in 2000 as safe and effective for use in combination with misoprostol to terminate intrauterine pregnancy through 49 days gestation. ROA.600; *see* 21 U.S.C. § 355.

The New Drug Application (NDA) for Mifeprex, submitted in 1996, presented extensive data on the drug's safety and efficacy, including data from multiple clinical trials with thousands of participants showing that mifepristone was effective for 92.1% to 95.5% of women, meaning further intervention to terminate the pregnancy was not required. ROA.642-647, ROA.591-598.

FDA imposed certain use restrictions with Mifeprex's approval, including that the drug would be dispensed by a doctor in-person and that there would be an in-person follow-up appointment. FDA included these restrictions under its Subpart H authority, which—in separate provisions—sets out a mechanism for imposing use restrictions and a pathway for accelerating approval of certain new drugs. 21 C.F.R. §§ 314.520, 314.510; *see* ROA.596; ROA.600-601. FDA relied on Subpart H only for its use-restriction authority; the Mifeprex NDA was not accelerated, and in fact took more than four and a half years to approve.

2. In 2007, Congress amended the Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to impose certain restrictions on drugs in the form of a Risk Evaluation and Mitigation Strategy (REMS) when the agency concluded use restrictions were necessary "to ensure that the benefits of the drug outweigh the risks of the drug." 21 U.S.C. § 355-1(a)(1). Congress "deemed" drugs previously approved with use restrictions under Subpart H to have a REMS in effect while the drugs' sponsors supplemented their approved NDAs to include a REMS. *See* Food and Drug Administration Amendments Act of 2007, Pub. L. 110-85, Title IX, § 909(b)(1), (3), 121 Stat. 823, 950-

951 (codified at 21 U.S.C. § 331 note); Identification of Drug and Biological Products, 73 Fed. Reg. 16,313 (Mar. 27, 2008). The amendment took effect 180 days after its enactment. § 909(a), 121 Stat. at 950. In accordance with the amendment, Danco submitted a supplemental New Drug Application (sNDA) for the Mifeprex REMS, which FDA approved in 2011. ROA.672-675. Since this statutory amendment, Mifeprex's use restrictions have been governed by FDA's REMS authority—not by Subpart H, which is no longer the basis for any drug's use restrictions.

3. Some of the Plaintiffs—self-described organizations that "have consistently opposed abortion and continue to do so"—filed a citizen petition in 2002 with FDA asserting that Mifeprex was improperly approved under Subpart H and not safe and effective as approved. ROA.355; *see* ROA.353-444. Plaintiffs never sought to compel FDA to act on the petition. *See* 5 U.S.C. § 706(1). FDA ultimately denied the petition in March 2016, meticulously documenting and reaffirming that Mifeprex is safe and effective for its approved use and explaining why the agency initially relied on Subpart H in setting use restrictions. ROA.635-667. Plaintiffs had six years to sue after this denial of their citizen petition. 28 U.S.C. § 2401(a).

4. FDA also took a number of other actions related to mifepristone that are not part of the conditional cross-petition. In March 2016, FDA approved an sNDA that Danco had submitted with an extensive scientific record seeking to amend Mifeprex's labeling and to modify its REMS based on data post-dating the 2000 approval. The sNDA changed the dosing regimen, altered the mode of administration for

misoprostol, extended the approved gestational age from 49 to 70 days, allowed at-home administration of misoprostol, authorized flexibility in how follow-up care occurs, changed references from "physician" to "health care provider" reflecting that certain non-physicians are authorized to prescribe drugs by state law, and modified the prescriber reporting requirements for certain adverse events. ROA.689-696; ROA.2142-2337. In 2019, some Plaintiffs filed a citizen petition challenging these changes.

Also in 2019, FDA approved a generic version of mifepristone. ROA.768-773.[1]

In April 2021, FDA determined that it would temporarily exercise enforcement discretion during the COVID-19 public health emergency as to whether mifepristone must be dispensed in person. ROA.786-788.

In December 2021, FDA denied the 2019 citizen petition challenging the 2016 changes. ROA.802-842; *see* ROA.740-766. The petition had urged FDA to "(I) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (II) retain the Mifeprex [REMS], and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber." ROA.741. In denying the petition, FDA reiterated its view from April 2021 that "mifepristone may be safely

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[1] Danco, the manufacturer of Mifeprex, did not intervene as to Count Four, which is Plaintiffs' challenge to FDA's approval of generic mifepristone. *See* ROA.2000; ROA.179. That is why Danco "did not respond to" Plaintiffs' "challenge to the 2019 Generic Approval in the district court proceedings." Cross-Pet. 33 n.1.

used without in person dispensing" and directed Danco to propose modifications to the mifepristone REMS effectuating that change. ROA.829.

In January 2023, FDA approved Danco's application to modify the mifepristone REMS, including removing mandatory in-person dispensing of the drug. *See* Ctr. for Drug Evaluation & Rsch., *Approval Package for: Application Number 020687Orig1s025* (Jan. 3, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/020687Orig1s025.pdf. Although Plaintiffs had already filed suit and sought a preliminary injunction at this time, they did not amend their complaint or otherwise challenge FDA's approval of the 2023 REMS modification. No documents pertaining to that approval are in the record.

B. Procedural History

1. After FDA denied Plaintiffs' citizen petition challenging the approval of Mifeprex in March 2016, Plaintiffs had six years to file suit challenging that denial. *See* 28 U.S.C. § 2401(a). But March 2022 came and went.

Eight months after the statute of limitations expired, Plaintiffs filed suit challenging FDA's 2000 approval of Mifeprex. They "admit[ted] that they did not raise a claim as to FDA's denial of their 2002 citizen petition within six years, as required for civil actions filed against the United States." Danco.Pet.App. 46a. Instead, they argued that their challenge to the 2000 approval was timely under a judge-made exception to the statute of limitations called the "reopening doctrine." ROA.173-174. According to Plaintiffs, in taking subsequent actions related to mifepristone, FDA had "reopened" its 2000

decision to approve Mifeprex. *See* ROA.173-174; ROA.3333; ROA.3341-3344; ROA.4460-4461.

The District Court excused Plaintiffs' failure to meet the six-year statute of limitations and held that FDA must have reopened its 2000 approval. In the court's view, the 2016 changes "significantly departed" from the original approval; the court also noted that FDA referenced conducting a "full review" of the mifepristone REMS in 2021 in its citizen petition denial, which the court thought must mean FDA had "necessarily consider[ed] the possibility that [mifepristone] is too dangerous to be on the market." Danco.Pet.App. 191a-192a. The District Court went on to find that FDA exceeded its authority in using Subpart H to impose use restrictions in 2000 and, on that basis, "stayed" the 2000 approval "and all subsequent challenged actions" from taking effect. *Id.* at 213a-225a, 249a.

2. Danco and the Government appealed and sought an emergency stay of the District Court's order. A stay panel of the Fifth Circuit granted relief as to the 2000 approval, concluding that Plaintiffs' challenge was likely untimely. *Id.* at 140a-149a. The court found that the reopening doctrine was inapplicable because nothing indicated that FDA had "substantively reconsider[ed]" its 2000 approval of Mifeprex at a later date or "significantly alter[ed] the stakes of judicial review" in an unanticipated way. *Id.* at 144a-149a.

The stay panel left in place the District Court's injunction of the 2016 changes to the Mifeprex REMS and the 2021 non-enforcement decision. *Id.* at 163a. This Court stayed the District Court's ruling pending resolution of any certiorari petition. *Id.* at 111a.

3. A merits panel of the Fifth Circuit likewise held Plaintiffs' challenge to the 2000 approval was untimely. *Id.* at 52a. The panel did not address "whether the reopening doctrine is a legitimate exception to a statute of limitations" because it "ultimately conclude[d] that the doctrine does not apply here." *Id*. at 47a n.6. It noted, however, that this Court has "cast some doubt on whether the reopening doctrine is a legitimate exception to a statute of limitations." *Id.* (citing *Biden* v. *Texas*, 142 S. Ct. 2528, 2545 n.8 (2022)). Because it held the challenge untimely, the panel majority did not address the merits of Plaintiffs' challenge to the 2000 approval.

The Fifth Circuit affirmed the preliminary injunction as to the later FDA actions. That decision is the subject of pending petitions for certiorari from Danco and the Government. *See* Nos. 23-236, 23-235.

In a partial dissent, Judge Ho explained that he would have found that FDA's actions in 2016 and 2021 were a "constructive reopening" of the 2000 approval. Danco.Pet.App. 86a. Judge Ho also disagreed that Subpart H authorized FDA to impose use restrictions on Mifeprex at the time it was approved. *Id.* at 98a.

REASONS FOR DENYING THE CONDITIONAL CROSS-PETITION

I. REVIEW IS NOT WARRANTED OF A DOCTRINE THE FIFTH CIRCUIT DID NOT ADOPT AND THAT IT FOUND WOULD NOT MAKE PLAINTIFFS' CHALLENGE TIMELY IN ANY EVENT.

Plaintiffs asked the Fifth Circuit to apply the D.C. Circuit's "reopening" doctrine to find timely their

challenge to Mifeprex's 2000 approval. The Fifth Circuit declined to do so. The merits panel explained that it need not reach whether the reopening doctrine "is good law in this circuit," because it would not apply on the facts here. Danco.Pet.App. 47a n.6. The Court should deny Plaintiffs' request for review of this issue.

A. Whether The "Reopening" Doctrine Is A Valid Exception To The Statute Of Limitations Does Not Warrant Review.

1. The "reopening" doctrine was created by the D.C. Circuit as "an exception to statutory limits on the time for seeking review of an agency decision." *Environmental Def.* v. *EPA*, 467 F.3d 1329, 1333 (D.C. Cir. 2006) (citation omitted). Despite recognizing that "statutory time limits reflect Congress's express preference for regulatory finality," *Public Emps. for Env't Resp.* v. *EPA*, 77 F.4th 899, 915 (D.C. Cir. 2023), the D.C. Circuit's "reopener doctrine allows an otherwise untimely challenge to proceed" if the agency later "reexamine[s] its former choice" in that rule, *National Biodiesel Bd.* v. *EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016) (citation omitted). As the D.C. Circuit sees it, the period for judicial review of the original rule "runs anew" from the date of reopening. *National Ass'n of Reversionary Prop. Owners* v. *Surface Transp. Bd.*, 158 F.3d 135, 141 (D.C. Cir. 1998).

In what the D.C. Circuit calls "express" reopening, an agency "literal[ly]" reopens a previous decision. *Natural Res. Def. Council* v. *EPA*, 571 F.3d 1245, 1265-66 (D.C. Cir. 2009). This can happen when "an agency conducts a rulemaking or adopts a policy on an issue at one time, and then in a later rulemaking restates the policy or otherwise addresses the issue again without altering the original decision."

National Ass'n of Reversionary Prop. Owners, 158 F.3d at 141. For it to apply, the agency must "undertake[] a serious, substantive reconsideration of the existing rule." *Growth Energy* v. *EPA*, 5 F.4th 1, 21 (D.C. Cir. 2021) (citation and brackets omitted). This strain of reopening does not apply when an agency "merely responds to an unsolicited comment by reaffirming its prior position," or "respond[s] to a comment that addresses a settled aspect of some matter." *Sierra Club* v. *EPA*, 551 F.3d 1019, 1024 (D.C. Cir. 2008) (citation omitted).

In a few cases, the D.C. Circuit has applied a different strain of the reopening doctrine for rules it describes as having been "constructively"—but "not actually"—reopened. *Natural Res. Def. Council*, 571 F.3d at 1266 (citation omitted). This doctrinal strain requires an agency to promulgate a new rule effecting such a "sea change" to "the basic regulatory scheme" that it "significantly alters the stakes" of seeking judicial review of the earlier rule in a way the plaintiff could not have anticipated at the time of the earlier rule. *National Biodiesel Bd.*, 843 F.3d at 1017 (citations omitted). The facts must show that the original rule was not "worth challenging" for the plaintiff, but the "completely changed" regulatory context is. *Sierra Club*, 551 F.3d at 1025-26 (citations and emphasis omitted). The D.C. Circuit has made clear its view that an agency's "elimination" of a "more stringent requirement" "in favor of an alternative" does "not work such a sea change" to the original rule. *Natural Res. Def. Council*, 571 F.3d at 1266.

2. Relying exclusively on D.C. Circuit caselaw, Plaintiffs contend that the Fifth Circuit erred in its analysis of the reopening doctrine. *See* Cross-Pet. 16-

23. But Plaintiffs identify no conflict between the Fifth Circuit's analysis and this Court's precedents, and no disagreement among the courts of appeals concerning the legal standard.

Indeed, as the panel below noted, the Fifth Circuit has yet to decide "whether the reopening doctrine is a legitimate exception to a statute of limitations." Danco.Pet.App. 47a n.6. The panel did "not address that threshold question" because it "ultimately conclude[d] that the doctrine does not apply here." *Id.* No other Fifth Circuit case has ruled on the doctrine's validity, either. The Fifth Circuit previously analogized to the reopening doctrine in analyzing when agency action becomes final in *Texas* v. *Biden*, 20 F.4th 928, 951-955 (5th Cir. 2021), *rev'd*, 142 S. Ct. 2528 (2022), but no party defended that analogy in this Court, which noted that the doctrine appeared "inapposite" to the finality question at issue, 142 S. Ct. at 2545 n.8.

Plaintiffs also do not argue that the legal standard the panel applied diverged from the D.C. Circuit's standard.[2] While Plaintiffs say (at 22) that this case is "on all fours" factually with *Sierra Club* v. *EPA*, 551 F.3d 1019 (D.C. Cir. 2008)—which is wrong, *see infra*

[2] Danco has not identified any other circuit that has applied the D.C. Circuit's reopening doctrine to excuse an untimely claim. *See, e.g.*, *Outdoor Amusement Bus. Ass'n* v. *Department of Homeland Sec.*, 983 F.3d 671, 682 n.5 (4th Cir. 2020) ("Even assuming this Court would adopt the doctrine—an issue we need not reach today—we agree with the district court that it would not apply here."); *Utah ex rel. Utah Dep't of Env't Quality, Div. of Air Quality* v. *EPA*, 750 F.3d 1182, 1185-86 (10th Cir. 2014) ("We need not decide here whether to adopt the doctrine. Even if we were to do so, it would not apply."). Plaintiffs have not identified any such circuit either.

pp. 20-22—they notably never contend that the Fifth Circuit applied a different legal standard. Plaintiffs instead complain (at 23) that the panel's assessment of the facts was "simply untrue." This sort of fact-bound application does not merit review.

3. Plaintiffs also do not argue that the validity of the reopening doctrine is an important federal question. Instead, Plaintiffs suggest in a single sentence that this issue has "greater importance" because of a petition the Court granted in another case to resolve a clear circuit split related to when a claim accrues under the Administrative Procedure Act. *See* Cross-Pet. 18 (citing *Corner Post, Inc.* v. *Board of Governors, FRS*, No. 22-1008).

Since Plaintiffs offer no further explanation, Danco will. The plaintiffs in *Corner Post* made two arguments in asserting their challenge to the rule at issue was timely despite the APA's six-year statute of limitations. First, they argued that a "clarification" of the 2011 rule by the agency in 2015 "renewed the statute of limitations under the D.C. Circuit's reopening doctrine." *North Dakota Retail Ass'n* v. *Board of Governors, FRS*, 55 F.4th 634, 638 (8th Cir. 2022). The Eighth Circuit rejected that argument. It explained that "[t]his court has not adopted or even referenced the D.C. Circuit's reopening doctrine," which it concluded would not apply "[e]ven if the reopening doctrine has any validity," because the agency's clarification was "not a 'later rulemaking' and did not 'actually reconsider the rule.'" *Id.* at 639 (citation omitted). Second, the plaintiffs argued that for one plaintiff (Corner Post), the challenge to the 2011 rule "first accrued when Corner Post opened in 2018" and became subject to the rule, "rather than

when [the rule] was published in 2011," so the statute of limitations did not begin to run until 2018. *Id.* The Eighth Circuit rejected that theory too. *Id.*

Corner Post sought and was granted certiorari only on the second theory—whether an APA claim "first accrues" under 28 U.S.C. § 2401(a) when an agency issues a rule or when the rule first harms an individual plaintiff. *See Corner Post, Inc.* v. *Board of Governors, FRS*, No. 22-1008 (U.S. Sept. 29, 2023). The answer to that question has no relevance here, and Plaintiffs never made a claim-accrual argument akin to *Corner Post* below. Claim accrual concerns whether a lawsuit is timely in the first instance—not whether there are valid excuses for *failing* to timely assert a claim.[3]

4. Even if the validity of the reopening doctrine were a question worthy of this Court's review, this case is a poor vehicle to address it. Because the Fifth Circuit did "not address [the] threshold question" whether to adopt the reopening doctrine, Danco.Pet.App. 47a n.6, this Court thus lacks the Fifth Circuit's considered views on the validity of the reopening doctrine. If the Court is inclined to address

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[3] To the extent Plaintiffs suggest (at 18) that *Corner Post* might be relevant here because one Plaintiff was supposedly injured "just last year," that argument is both forfeited and unsupported by the record. Plaintiffs never pressed this argument below, ROA.153-166, and three sentences in a conditional cross-petition hardly suffices to raise it for this Court's review. Nor is it supported by the record. Plaintiff Shaun Jester—the Plaintiff identified by the cross-petition—made no such claim. *See* ROA.955-962. He received his medical license in 1999, has been a board-certified obstetrician and gynecologist since 2007, and offered one undated example of treating a patient who had experienced an adverse event after a medication abortion. ROA.957; ROA.959.

the "reopening" doctrine at some point, it should grant review of a decision that has adopted and applied the doctrine. This case checks none of those boxes. Even the District Court admitted that there was no precedent for applying the doctrine "in the precise context of FDA's approval of an NDA." Danco.Pet.App. 192a n.18.

B. Even If "Reopening" Could Theoretically Restart A Limitations Period, The Fifth Circuit Correctly Found It Inapplicable Here.

Plaintiffs ask this Court to correct a purported error in how the Fifth Circuit analyzed whether the facts here demonstrate the D.C. Circuit's reopening doctrine applies. That is not the province of this Court, and there are no errors to be corrected. Plaintiffs' contention that three subsequent FDA actions involving mifepristone "reopened" FDA's initial approval of the drug is plainly wrong. The Fifth Circuit's rejection of Plaintiffs' meritless, fact-bound arguments does not warrant further review.

1. Express Reopening Is Inapplicable To The Facts Here.

Plaintiffs identify two actions they say "expressly" reopened FDA's 2000 approval of Mifeprex: (1) FDA's March 2016 approval of Danco's sNDA requesting to amend certain aspects of Mifeprex's approval, including its indication, dosing regimen, and REMS, and (2) FDA's December 2021 denial of Plaintiffs' citizen petition (filed in 2019) contesting the 2016 changes. *See* Cross-Pet. 19. Neither fits the bill.

For starters, FDA's approval of the sNDA making changes to the label and REMS in 2016 cannot

support application of the reopening doctrine for a simple reason: Plaintiffs waited more than 6 years from that sNDA approval to file suit. Thus, *even if* FDA's actions in March 2016 somehow reopened FDA's 2000 approval of Mifeprex, the six-year statute of limitations would have run in March 2022. Plaintiffs sued in November 2022. Therefore, "even assuming such a * * * reopening occurred, the challenge is still untimely." *Growth Energy*, 5 F.4th at 26.

Plaintiffs' delay aside, nothing in the existing record shows that FDA's 2016 sNDA approval "expressly" reopened FDA's 2000 decision to approve the drug as safe and effective.[4] Plaintiffs never assert FDA "explicitly" said it had "undertaken a serious, substantive reconsideration" of its 2000 Mifeprex approval decision. *Growth Energy*, 5 F.4th at 21 (citations and brackets omitted). They say that FDA did so silently, because it also denied their citizen petition challenging the 2000 approval at the same time. Cross-Pet. 20 But as the Fifth Circuit explained, this "context" assertion is "really just an end-run around the fact that [Plaintiffs] were too late to challenge FDA's denial of their [2002] citizen petition." Danco.Pet.App. 48a; *see also id.* at 144a (same conclusion by stay panel).

It does not show that FDA "actually reconsidered" whether it should have approved mifepristone in the first place. *Growth Energy*, 5 F.4th at 21 (citation omitted). Action on separate pending matters at the

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[4] Plaintiffs' assertion that FDA's 2016 sNDA approval "chang[ed] the safeguards essential to th[e] original approval," Cross-Pet. 19, is an argument about constructive reopening and addressed *infra* pp. 19-23.

same time is not a valid basis to infer otherwise. *See National Ass'n of Reversionary Prop. Owners*, 158 F.3d at 142 ("[A]nything less than a direct relationship between the two rules would be too lax a standard for triggering the reopening doctrine."). "FDA took the restrictions imposed in 2000 as a given, and considered only whether the [labeling and] REMS amendments were safe and effective." Danco.Pet.App. 48a.

FDA's 2021 denial of Plaintiffs' citizen petition is also unhelpful for them. As the D.C. Circuit itself confirmed a few months ago, the denial of a petition, like Plaintiffs' citizen petition, does not trigger the reopening doctrine. The D.C. Circuit applies the "reopening" doctrine only to "a voluntary and affirmative agency action," which "is the hallmark of a reopening"—not to an agency action that is "required or reactive." *Public Emps. for Env't Resp.*, 77 F.4th at 914 (finding reopening inapplicable). Indeed, the D.C. Circuit has *never* found that "an agency reopened an issue by merely responding to a petition * * * submitted by a third party." *Id*. at 913.[5] That is because "if a party were allowed to goad an agency into a reply, and then sue on the grounds that

[5] And while the D.C. Circuit recently speculated that an agency's "response to a petition" "could conceivably reopen an administrative proceeding," it emphasized that "the party challenging the denial of such a petition must show that the agency's intention to initiate a reopening is clear from the administrative record," which "requires showing that the agency did much more than merely take legally required steps to respond to the petition." *Public Emps. for Env't Resp.*, 77 F.4th at 914 (citations and internal quotation marks omitted). Of course, Plaintiffs never asserted that FDA's supposed intention to reopen the 2000 approval was "crystal clear" when FDA denied their petition in 2021. *Id.*

the agency re-opened the issue, the agency's thorough answer would put it at risk of reopening, while a taciturn response would put it at risk of being faulted for acting without reasoned decisionmaking." *American Rd. & Transp. Builders Ass'n* v. *EPA*, 588 F.3d 1109, 1114 (D.C. Cir. 2009) (citations, internal quotation marks, and ellipses omitted). This Court should not grant certiorari to address whether the reopening doctrine applies in a context where even the D.C. Circuit would not apply it.

Moreover, the petition that FDA denied in 2021 requested that FDA *return to the use restrictions that accompanied the 2000 approval*—not that it rethink that approval in the first place. *See* ROA.741. Plaintiffs seize on FDA's remark that the agency had conducted a "full review" of the mifepristone REMS in 2021. Cross-Pet. 20 (quoting ROA.808). That gets them nowhere. It is nonsensical that FDA's review of the use restrictions *in the REMS as of 2021*—which are not the initial use restrictions—would reopen FDA's 2000 approval or the original use restrictions. *Cf. Charter Commc'ns, Inc.* v. *FCC*, 460 F.3d 31, 38 (D.C. Cir. 2006) (by saying the agency had "review[ed] the effectiveness of the rules," agency did not "reopen[] the question of its statutory authority to adopt the rules in the first place"; "nothing in those notices suggested that, in reviewing the 'effectiveness' of the rules, the [agency] intended to review their statutory basis as well" (citation omitted)).

As the Fifth Circuit merits panel emphasized, "FDA had no reason to reevaluate" the 2000 approval of Mifeprex in the course of addressing Plaintiffs' 2019 petition because Plaintiffs "did not actually ask FDA to reconsider its approval of mifepristone" in that

petition; instead, they merely "requested that FDA 'restore' previous restrictions and 'retain' others currently in place." Danco.Pet.App. 50a (quoting ROA.741).

2. Constructive Reopening Is Inapplicable To The Facts Here.

Plaintiffs next ask this Court to review whether, even if FDA did not expressly reopen its 2000 approval of Mifeprex, FDA's 2016 changes, 2021 petition denial, and 2021 non-enforcement decision "constructively" did so. Cross-Pet. 21. This argument is just as fact-bound as Plaintiffs' express-reopening argument, and is poorly suited for certiorari review for all the same reasons.

Plaintiffs' argument is also based on a misunderstanding of the "constructive" version of the D.C. Circuit's reopening doctrine. That court has invoked "constructive reopening" to permit an otherwise untimely challenge in less than a handful of cases, and only in the rulemaking context.[6]

Even in the rulemaking context, moreover, the D.C. Circuit has held that "'constructive' reopening" occurs only when a new rule results in such a "sea change" to "the basic regulatory scheme" that it "significantly alters the stakes" of seeking judicial review in a way that the plaintiffs could not have "reasonably anticipated" when they chose not to challenge that scheme in the first instance. *National Biodiesel Bd.*, 843 F.3d at 1017 (citations omitted);

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[6] And these cases, except for one, have "limited the constructive reopening doctrine to cases involving regulated entities," rather than "challenges from third parties" like Plaintiffs. *Sierra Club*, 551 F.3d at 1029 (Randolph, J., dissenting).

accord Kennecott Utah Copper Corp. v. *Department of Interior*, 88 F.3d 1191, 1214-15, 1227 (D.C. Cir. 1996) (applying doctrine in rulemaking context); *National Ass'n of Mfrs.* v. *Department of Interior*, 134 F.3d 1095, 1104-05 (D.C. Cir. 1998) (same). An agency's "elimination" of a "more stringent requirement" "in favor of an alternative" does "not work such a sea change." *Natural Res. Def. Council*, 571 F.3d at 1266.

This case does not involve a challenge to a rulemaking. Plaintiffs are thus asking this Court to grant certiorari to address a question *no* court has addressed: whether a "constructive reopening" doctrine applies outside the rulemaking context. And in all events, FDA's subsequent actions on mifepristone did not "alter[] the "regulatory framework" for drug approvals. *National Biodiesel Bd.*, 843 F.3d at 1017. The agency's rules have long "establish[ed]" that applicants "may seek approval" of revisions to a product's labeling and REMS, *id.*; *see* 21 U.S.C. § 355-1(g)(4)(A); 21 C.F.R. § 314.70, meaning that FDA's subsequent actions on mifepristone "neither alter[ed] that regulatory framework nor work[ed] a change that [Plaintiffs] could not have reasonably anticipated." *National Biodiesel Bd.*, 843 F.3d at 1017.

Plaintiffs also do not contend that FDA's 2000 approval of Mifeprex was not "worth challenging" until FDA changed the use restrictions. *Sierra Club*, 551 F.3d at 1026 (citation omitted). Nor could they; after all, several Plaintiffs filed a citizen petition challenging the 2000 approval. ROA.353-444.

Plaintiffs maintain, in the face of all this, that this case is "on all fours" with the D.C. Circuit's decision in *Sierra Club*. Cross-Pet. 22. It is not. For starters,

Sierra Club involved a rulemaking. There, the initial EPA rule crafted a narrow exemption to emissions limits for certain operational events where an emitting source received approval of a plan to minimize emissions during such events. Later EPA rulemakings, however, eliminated the need for an emitting source to obtain approval of a plan to minimize emissions during those events. Environmentalists then challenged the exemption as unlawful and arbitrary. A divided D.C. Circuit panel held that the initial rule "may not have been worth challenging" "from the perspective of environmental petitioners' interests" because EPA had crafted it so that it would not be a "blanket exemption" to Clean Air Act requirements. *Sierra Club*, 551 F.3d at 1026 (citation omitted). The new rule, in contrast, "*completely* changed the regulatory context," by creating in effect the very blanket exemption EPA had earlier disclaimed. *See id.* at 1025 (citation omitted). Two judges found this sufficient to constructively reopen EPA's initial rulemaking.

Compare that to this case. Here, FDA approved Mifeprex in 2000 after concluding the drug sponsor's application showed it was safe and effective for the indicated use; this was not a rulemaking crafting an exemption to otherwise applicable law. And Plaintiffs cannot say with a straight face that FDA's subsequent actions so "significantly altered the stakes of judicial review" that only after the 2016 changes did Plaintiffs view Mifeprex's approval as worth challenging "from the perspective of [their] interests." *Sierra Club*, 551 F.3d at 1025-26 (citations and brackets omitted). After all, Plaintiffs "have consistently opposed abortion." ROA.355; *see also* ROA.232; ROA.239; ROA.252. From that perspective, FDA's approval of

Mifeprex in 2000 was certainly "worth challenging in its own right," *Natural Res. Def. Council*, 571 F.3d at 1270, as Plaintiffs "had an ample incentive at that time to protest" the decision, *Kennecott*, 88 F.3d at 1215. In fact, some did. *See* ROA.355.

Plaintiffs suggest (at 23) that this Court should find "constructive reopening" because Danco's sNDA only became public when FDA approved it. That cannot be right. It would mean every drug approval is reopened with every sNDA amendment or REMS revision, because applications for those changes are never publicly filed. Actual notice of a specific amendment is not the question anyway. The question is whether Plaintiffs could have reasonably anticipated that the use restrictions or indication might change over time based on scientific studies and real-world experience with the drug. Of course they could. FDA frequently authorizes new uses, changes to indications, and amended use restrictions based on new data and real-world experience. *See* PhRMA Amicus Br. 16, ECF No. 312, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362 (5th Cir. May 2, 2023) ("FDA has approved more than 300 REMS since 2008 and has made more than 800 modifications to REMS.").[7]

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[7] FDA approved over 100 efficacy supplements in 2021 and 2022 that, for example, added a new or modified indication, new dosing regimen, or new route of administration; approved use of a drug in a new patient population; or changed a drug from prescription to over-the-counter. *See* FDA, CY 2022 New Drug Application (NDA) & Biologic License Application (BLA) Efficacy Supplement Calendar Year Approvals as of December 31, 2022, https://www.fda.gov/media/165825/download?attachment; FDA, CY 2021 New Drug Application (NDA) & Biologic License

Even in the rulemaking context that the D.C. Circuit has limited this doctrine to, a litigant may "reasonably anticipate[]" that an agency might "subsequently eliminate" a rule's "more stringent requirement[s]" "in favor of an alternative" that would "allow more liberal use" of the original rule. *Natural Res. Def. Council*, 571 F.3d at 1266 (citation omitted). Such an "elimination" of stricter requirements "does not provide a ground to conclude that the broader issue" of the merits of the original rule "has been reopened." *Id.*

* * *

This is not the case to address the "reopening" doctrine. The Fifth Circuit did not address that question below. And Plaintiffs do not even have support from the D.C. Circuit for their position here.

II. THIS COURT SHOULD NOT REVIEW AN ACADEMIC QUESTION ABOUT THE SCOPE OF A SUPERSEDED REGULATION THAT HAS NOT GOVERNED MIFEPREX'S USE RESTRICTIONS SINCE 2008.

Plaintiffs also ask this Court to address the scope of Subpart H—a statutory provision that *has not applied to Mifeprex since 2008*. That academic question is legally irrelevant to Mifeprex today, and this Court should not reach it for four reasons.

First, the panel majority did not address the scope of Subpart H. This Court should not pass on an issue that the court below did not decide.

Application (BLA) Efficacy Supplement Calendar Year Approvals as of December 31, 2021, https://www.fda.gov/media/158154/download?attachment.

Second, Plaintiffs' argument has a glaring vehicle problem: Subpart H does not govern the use restrictions for *any drug*, including Mifeprex. Danco is unaware of any case in which this Court has granted review to opine on the scope of a defunct regulation.

Third, Plaintiffs are wrong when they contend that FDA could not have relied on Subpart H to set use restrictions prior to 2008. This Court does not grant review to decide fact-bound error-correction arguments about an agency's interpretation of an obsolete regulation more than two decades ago.

Fourth, nothing supports Plaintiffs' contention that FDA may only approve a drug on the precise terms of a completed clinical trial protocol. This issue is outside the scope of Plaintiffs' question presented, which is limited to Subpart H, and has no basis in the law. It would mean that virtually every drug on the market was wrongly approved.

A. Plaintiffs' Subpart H Argument Was Not Addressed Below And There Is No Circuit Split.

The panel decision did not reach Plaintiffs' Subpart H argument. This Court should decline to reach a question that was not passed on below. *See, e.g.*, *Zivotofsky* v. *Clinton*, 566 U.S. 189, 201 (2012) ("Ours is a court of 'final review and not first view.'" (citation omitted)); Stephen M. Shapiro et al., *Supreme Court Practice* § 6.26.(B) (11th ed. 2019).

There is also no conflict between the circuits, or between the panel decision and this Court's precedents. As Plaintiffs acknowledged in response to Danco's and the Government's emergency stay

applications, no court of appeals has ever ruled on this issue. *See* Plaintiffs' Opp. to App. for Stay 13-14, No. 22A901 (Apr. 18, 2023) (noting that "even when the Fifth Circuit completes its expedited merits review," there could be "no cases that will conflict"). That fact counsels against deviating from the Court's "ordinary practice of denying petitions insofar as they raise legal issues that have not been considered by additional Courts of Appeals." *Box* v. *Planned Parenthood of Ind. & Ky., Inc.*, 139 S. Ct. 1780, 1782 (2019) (per curiam); *see also* Sup. Ct. R. 10.

B. Subpart H Does Not Govern Mifeprex's Use Restrictions Today.

Whatever the historical relevance of Subpart H for Mifeprex, it was superseded by Congress's amendment to the FDCA in 2007 authorizing FDA to impose use restrictions through a REMS and by FDA's approval of the Mifeprex REMS. Since 2007, no new drugs have been approved with use restrictions under Subpart H and no drugs that were already on the market in 2007 have use restrictions governed by Subpart H.

When Congress enacted the REMS authority, it specifically "deemed" drugs with Subpart H use restrictions—including Mifeprex—"to have in effect an approved [REMS]." § 909(b)(1), 121 Stat. at 950. By doing so, Congress superseded FDA's earlier decision to implement use restrictions under Subpart H. And in 2011, FDA expressly approved Danco's REMS proposal. ROA.672-675. Plaintiffs' acknowledgement (at 18-19) that Subpart H has been superseded by statute underscores that certiorari is

not warranted here. This Court does not review regulatory dinosaurs.[8]

C. Plaintiffs' Subpart H Arguments Are Wrong On The Merits.

Plaintiffs' arguments about the scope of Subpart H also are meritless. Subpart H includes a regulation that FDA used, prior to its REMS authority, to impose use restrictions. ROA.596. That regulation refers to "new drug products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments." 21 C.F.R. § 314.500. Plaintiffs contend (at 24-28) that pregnancy is not an "illness," and that medication abortion lacks a meaningful therapeutic benefit compared to surgical abortion, such that use restrictions could not have been imposed under Subpart H.

Consistent with FDA's interchangeable use of "illness," "condition," and "disease" under the FDCA, the agency reasonably concluded that it could use

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[8] At times, Plaintiffs appear to suggest that Subpart H was the source of FDA's authority to approve Mifeprex as safe and effective for its intended use. That is wrong. As Plaintiffs recognize elsewhere, Cross-Pet. 4, FDA's approval authority in 2000 and today is found at 21 U.S.C. § 355(d). Subpart H is a regulation that FDA used prior to 2007 when it determined use restrictions were warranted. *See* 21 C.F.R. § 314.520. Today, FDA is authorized to require use restrictions under its REMS authority, codified at 21 U.S.C. § 355-1. Plaintiffs are also wrong to proclaim that without Subpart H, FDA would have denied approval of Mifeprex. For example, another FDA-approved mifepristone product—Korlym, which is approved to treat Cushing's disease—was approved by FDA with restrictions that were not in the form of a REMS or Subpart H use restrictions.

Subpart H to approve drugs to treat a variety of conditions even if they are not considered an "illness"—including Mifeprex. *See* New Drug, Antibiotic, and Biological Drug Product Regulations, 57 Fed. Reg. 58,942, 58,946 (Dec. 11, 1992). An independent review by the U.S. Government Accountability Office (GAO) confirmed that FDA's approval and oversight processes for Mifeprex were consistent with its processes for other drugs with Subpart H use restrictions. GAO, GAO-08-751, *FDA: Approval and Oversight of the Drug Mifeprex* (Aug. 2008), https://www.gao.gov/assets/gao-08-751.pdf.

Mifeprex is not an outlier: FDA cited Subpart H when approving use restrictions for drugs treating, for example, acute acne and severe diarrhea-predominant irritable bowel syndrome. *See id.* at 4-5; Former FDA Officials Amicus Br. 12, ECF No. 307, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362 (5th Cir. May 2, 2023). And FDA has similarly interpreted illness and condition interchangeably in other contexts as well. *See* FDA, *Guidance for Industry, Expedited Programs for Serious Conditions—Drugs and Biologics* 3 (May 2014) https://www.fda.gov/media/86377/download (using terms interchangeably). FDA's reasonable interpretation of its own regulation as encompassing serious or life-threatening conditions easily meets this Court's standard in *Kisor* v. *Wilkie* for granting deference to an agency. 139 S. Ct. 2400, 2412 (2019) (plurality) ("[T]he agency that promulgated a rule is in the better position to reconstruct its original meaning." (citation and brackets omitted)).

Plaintiffs' argument (at 26-27) that FDA acted unlawfully in finding that Mifeprex provides a

"meaningful therapeutic benefit" is also wrong on the merits. FDA evaluated data from multiple clinical trials comparing medication abortion to surgical abortion and reasonably concluded that Mifeprex confers various benefits over surgical abortion, including avoiding an invasive surgical procedure and avoiding anesthesia, each of which has complications and reactions that make it inappropriate for some patients. ROA.639; *see* ECF No. 29, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362, at 71-73 ¶¶ 10-11, 13-14 (Goldberg Decl.) (5th Cir. Apr. 7, 2023) (explaining that medication abortion is preferable for some patients); *id.* at 82, 86-88 ¶¶ 8, 18-19, 21 (Schreiber Decl.) (same).

Plaintiffs argue that a Merriam-Webster dictionary limits the definition of "therapeutic" to the "treatment or curing of a disease or disorder" and that mifepristone would have to treat all "pregnancy-related complications," including ectopic pregnancies, to fall within Subpart H. Cross-Pet. 27. But the same dictionary also defines "therapeutic" as "producing a useful or favorable result or effect," such as "the therapeutic benefits of yoga," "laughter," and "[g]ardening." Merriam-Webster Dictionary, *Therapeutic*, https://www.merriam-webster.com/dictionary/therapeutic (last visited Nov. 7, 2023). Other dictionaries similarly recognize a broader meaning for "therapeutic" than just relating to illness. The *American Heritage Dictionary*, for example, defines "therapeutic" as "[o]f or relating to the medical treatment of a disease *or condition*." American Heritage Dictionary of the English Language, *Therapeutic* (5th ed. 2022), https://ahdictionary.com/word/search.html?q=therapeutic (last visited Nov. 7, 2023) (emphasis added).

As for Plaintiffs' argument (at 27) about pregnancy-related complications, they offer no rationale for why medication abortion would have to treat every possible pregnancy-related complication, including ectopic pregnancies, to qualify as "therapeutic." And the amicus brief below from the American College of Obstetricians and Gynecologists, the American Medical Association, and the Society for Maternal Fetal Medicine explains that mifepristone is, in fact, used off-label for a number of pregnancy-related complications, including to treat miscarriages, "to reduce the duration of bleeding or hemorrhaging during certain serious pregnancy complications," and for its "beneficial effects on the cervix in full-term pregnancies, which may in turn affect the likelihood of successful labor." American College of Obstetricians and Gynecologists et al. Amicus Br. 25-26, ECF No. 354, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362 (5th Cir. May 4, 2023).

Plaintiffs also assert (at 27-28) that FDA could not have found mifepristone provides meaningful therapeutic benefit because a very small number of patients might need a follow-up surgical procedure. But the fact that a drug may require additional follow-up care in some circumstances does not mean it lacks therapeutic effect. For the 92.1% to 95.5% of women who the pre-2000 approval studies showed did *not* need follow up care, the pregnancy was successfully terminated with no further intervention. ROA.591. Requiring every drug to work for every patient in order to obtain FDA approval would prevent nearly all drugs from reaching the market. *See* Patient and Provider Advocacy Organizations Amicus Br. 2, ECF No. 346, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362 (5th Cir. May 4, 2023) (explaining that the

District Court's "decision would cast uncertainty over the continued availability of *all* FDA-approved drugs"); *see also* Food and Drug Scholars Amicus Br. 9-10, ECF No. 308, *Alliance for Hippocratic Med.* v. *FDA*, No. 23-10362 (5th Cir. May 2, 2023).

D. Plaintiffs' Argument That FDA Must Match The Terms Of A Drug's Approval Exactly To The Protocol Of A Supporting Clinical Trial Is Outside The Questions Presented And Wrong.

Plaintiffs chose to limit their second question presented to whether FDA's approval of Mifeprex "under Subpart H" was unlawful. Cross-Pet. i. Plaintiffs nevertheless contend in their cross-petition that FDA was required to reject the Mifeprex NDA because the proposed labeling did not exactly match the protocol under which the drug was used in the clinical trials on which FDA relied to make its safety and efficacy determination.

Review of this issue can and should be denied because Plaintiffs did not raise it in their questions presented, and it is not a subsidiary question to the issue of Subpart H approval. *See Yee* v. *City of Escondido*, 503 U.S. 519, 537 (1992) (even a "*related*" question is not reviewable if it is not "fairly included" within the question presented); Sup. Ct. R. 14.1(a).

And in any event, Plaintiffs' argument is meritless. According to Plaintiffs, FDA cannot approve a drug unless there is a clinical trial using the precise conditions under which the drug is ultimately approved. Cross-Pet. 30. Plaintiffs have no support for their position. FDA must consider whether there is "substantial evidence" of effectiveness from "adequate and well-controlled investigations" and

sufficient evidence of safety, and whether the drug's benefits outweigh any risks. 21 U.S.C. § 355(d). A team of experts (including physicians, statisticians, chemists, pharmacologists, and other scientists) reviews each application and carefully assesses all relevant data in light of the drug's proposed labeling and intended use. If the applicant has demonstrated the drug is safe and effective under the conditions of use in the proposed labeling and satisfies certain other conditions, FDA *must* approve the drug. 21 U.S.C. § 355(c)-(d).

These intentionally flexible standards allow FDA to rely on a range of data in evaluating an NDA and to extrapolate from various sources as it deems appropriate. *See* 21 C.F.R. § 314.105(c). That flexibility is particularly important because clinical trials often employ more restrictive conditions than those ultimately recommended for approved labeling, a practice intended to protect study participants *before* FDA has concluded a drug is safe and effective for a particular use. *See* ROA.662; *see also* ROA.3292-3293.

No statutory or regulatory provision prohibits FDA from approving an NDA without a clinical trial evaluating a drug under all of the approved conditions of use. FDA can, in its scientific judgment, determine that the existing studies show the drug is safe for use under the proposed labeling. That is what occurred here, and what occurs with virtually every drug on the market. *See* PhRMA Amicus Br. 12-15. This Court has made clear that agencies can form a "reasonable predictive judgment" based on the evidence before them. *FCC* v. *Prometheus Radio Project*, 141 S. Ct. 1150, 1160 (2021). That is what FDA did here.

Plaintiffs nevertheless ask this Court to conclude that FDA acted unreasonably when it approved Mifeprex in 2000 without requiring prescribers to perform an ultrasound to check for an ectopic pregnancy and for gestational dating. Cross-Pet. 30. They ignore that FDA has consistently required that certified prescribers be able to accurately "assess the duration of the pregnancy" and "diagnose ectopic pregnancies," ROA.813-814, whether through an ultrasound or "other clinical methods" that elicit that information effectively, ROA.652. The agency "carefully considered" "[t]he role of the ultrasound," and it reasonably explained its decision to leave the method of dating pregnancies and ectopic-pregnancy diagnosis to "the medical judgment of the physician." ROA.595; *see also* ROA.651-653 (discussing alternative methods and noting that, among women with reported ectopic pregnancies who took mifepristone and received ultrasounds, more than half of the ultrasounds failed to detect the ectopic pregnancy). The rarity of ectopic pregnancies in women who have been prescribed mifepristone over the past 23 years—further evidenced by the fact that no Plaintiff identified ever treating a woman with an ectopic pregnancy after taking mifepristone—suggests that FDA was right in its judgment call. *See* FDA, Mifepristone U.S. Post-Marketing Adverse Events Summary Through 12/31/2022, https://www.fda.gov/media/164331/download (documenting 97 total instances of ectopic pregnancies out of the millions of women who have had medication abortions).

Plaintiffs also argue that FDA erred by not requiring women to remain under a doctor's observation for multiple hours after taking

misoprostol (the second drug in the approved regimen) because the clinical trials on which the approval was based had included such observation. Cross-Pet. 31. But Plaintiffs never made this argument below, making it unfit for this Court's review. *See, e.g.*, *Zivotofsky*, 566 U.S. at 201. Their Complaint likewise did not allege this observation period was included in each clinical trial supporting Mifeprex's approval. ROA.74-186. Moreover, again, there is no requirement that clinical trial protocols dictate a drug's approved labeling. Clinical trials of unapproved drugs routinely implement stringent safety measures to account for the fact that safety and efficacy have not yet been established. These measures are often unnecessary once the drug is approved. Former FDA Officials Amicus Br. 19-20.

FDA's considered exercise of its expert scientific judgment—based on a huge array of evidence—to determine that some conditions of use imposed in clinical trials need not be included in a drug label does not render the agency's choice unreasonable. *See Motor Vehicle Mfrs. Ass'n of U.S., Inc.* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Plaintiffs' position, which lacks any legal support and has never been accepted by any court, would undermine the approval of nearly all FDA-approved drugs on the market today. Certiorari review is plainly unwarranted.

CONCLUSION

The conditional cross-petition should be denied.

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