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 Petition for Writ of Certiorari to the United States Court of Appeals for the Fifth Circuit

REPLY BRIEF FOR CROSS-PETITIONERS

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CORPORATE DISCLOSURE STATEMENT

The Corporate Disclosure Statement in the Conditional Cross-Petition for Writ of Certiorari remains unchanged.

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INTRODUCTION

Cross-Petitioners agree there is no compelling reason for this Court to grant interlocutory review of the modest decision below. Yet Cross-Respondents ask this Court to intervene mid-litigation to review fact-bound and splitless issues. Then, seeking to have their cake and eat it too, Cross-Respondents ask the Court to limit its review to half a case. The Court should deny all three petitions and allow the parties to develop a full record in the district court. But if the Court is inclined to review any issue, it should review them all.

FDA and Danco ask this Court to examine the FDA's 2016 and 2021 actions while denying the cross-petition. But the cross-petition provides the regulatory framework for—and presents questions intertwined with—the very issues FDA and Danco insist are cert-worthy. For example, FDA and Danco say in their petitions that the Fifth Circuit's decision will wreak regulatory havoc. Yet in their brief opposing the cross-petition, they say that the 2016 and 2021 changes did not alter the basic regulatory scheme. Both arguments cannot be true. If reinstating safeguards for women's health upends the regulatory regime, so does removing them.

Cross-Petitioners' challenge to the 2000 Approval is timely under the reopening doctrine, and FDA's approval of mifepristone under Subpart H was fatally flawed under both the FDCA and the APA. If the Court agrees that interlocutory review is warranted, it should grant this cross-petition and review the Fifth Circuit's entire decision now.

REPLY ARGUMENT

I. FDA reopened its 2000 Approval when it overhauled the mifepristone regimen in 2016 and authorized mail-order abortion in 2021.

Danco and FDA spill much ink disparaging the reopening doctrine. But the doctrine is well-established in the D.C. Circuit—whose docket consists of 33% administrative law cases.[1]

Far from undermining the cross-petition, Cross-Respondents' arguments highlight the need for this Court's guidance. On Danco's telling, the Eighth Circuit in *North Dakota Retail Association* v. *Board of Governors of the Federal Reserve System,* 55 F.4th 634 (8th Cir. 2022), cast shade on the reopening doctrine, potentially limiting it in conflict with D.C. Circuit precedent. Danco.BIO.13–14. So too have other courts of appeal that Danco references. Danco.BIO.12 n.2 (citing *Outdoor Amusement Bus. Ass'n* v. *Dep't of Homeland Sec.*, 983 F.3d 671, 682 n.5 (4th Cir. 2020); *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)). That means there is more of a circuit split on the first issue in the cross-petition than those in FDA and Danco's petitions. If those petitions warrant this Court's review, so does the cross-petition.

Moreover, the reopening doctrine applies here because FDA (1) expressly reopened the 2000 Approval by reexamining it and (2) constructively reopened

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[1] Hyland Hunt, *Notice & Comment D.C. Circuit Review – Reviewed: A Quiet Week*, Yale J. on Regul. (Oct. 8, 2023), https://perma.cc/TG4K-543K.

it by removing safeguards it previously found indispensable to mifepristone's safe use.

A. Express Reopening

FDA admits that a new limitations period begins to run upon an agency's reconsideration of a decision. FDA.BIO.13. Here, because FDA removed the pre-requisites on which mifepristone's approval was based, the limitations period "beg[an] anew." *Nat'l Ass'n of Reversionary Prop. Owners* v. *Surface Transp. Bd.*, 158 F.3d 135, 141 (D.C. Cir. 1998). Whether viewed "as a timely challenge to the new decision," FDA.BIO.13 (emphasis omitted), or an express reopening of the initial approval, Cross-Petitioners' challenge can proceed.

FDA disputes this straightforward application of reopening by arguing that the only question in 2016 "was whether mifepristone would remain safe and effective without [the post-marketing] conditions." FDA.BIO.15 (emphasis omitted). That ignores the statutory framework. In 2000, FDA deemed the drug to be *un*safe without post-marketing limitations (later known as Elements to Assure Safe Use or ETASUs). Those FDA-imposed limitations were necessary antecedents to FDA's approval. 21 U.S.C. 355-1(f)(1)(A) (certain dangerous drugs "approved only if, or would be withdrawn unless, such elements are required"). When FDA removed those antecedents, the question became whether the drug nevertheless was safe for approval. This literal reopening was "a serious, substantive reconsideration" of the 2000 Approval. *Nat'l Mining Ass'n* v. *U.S. Dep't of Interior*, 70 F.3d 1345, 1352 (D.C. Cir. 1995).

Danco contends that, even if the 2016 Major Changes reopened the 2000 Approval, Cross-Petitioners' challenge would still be untimely because it was filed more than six years after their issuance. Danco.BIO.16. Not so. Under 21 C.F.R. 10.45(b), those changes became final only in December 2021 when FDA denied the 2019 Citizen Petition.

FDA also suggests that it could not have reopened its 2000 Approval because some of the Cross-Petitioners filed a citizen petition. FDA.BIO.16. But the relevant inquiry is what action the *agency*—not Cross-Petitioners—took. FDA's removal of crucial safeguards in 2016 and 2021 was not "merely" a response to a citizen petition, *ibid.*, but transformative agency action that removed crucial safeguards.

FDA is likewise wrong that its 2021 actions did not expressly reopen the 2000 Approval because judicial review is limited to the "narrow issues" defined in a citizen petition. FDA.BIO.16. Again, the appropriate inquiry is the scope of the agency's action—not the citizens'. Because FDA necessarily reconsidered its original decision, reopening applies. Regardless, the 2019 Citizen Petition expressly urged FDA to "not further erode patient protections" and thus keep the in-person dispensing requirement—precisely what FDA eliminated in 2021. ROA.765.

None of Cross-Respondents' cases suggest that the filing of a citizen petition defeats reopening when an agency dramatically changes course. FDA.BIO.16 (citing cases). Indeed, Danco admits that an agency's response to a petition "could conceivably reopen an administrative proceeding," but without a hint of irony, says such an intent must be "clear from the

administrative record." Danco.BIO.17 n.5. Here, that record remains in cold storage. Oral Arg. at 24:49 (5th Cir. May 17, 2023). Danco thus appears to support Cross-Petitioners' point that FDA should produce, and the district court should rule based on, a full record before this Court's review.

B. Constructive Reopening

The 2016 and 2021 actions also constructively reopened the 2000 Approval. A constructive reopening occurs when the revision of regulations "significantly alters the stakes of judicial review as the result of a change that could have not been reasonably anticipated." *Sierra Club* v. *EPA*, 551 F.3d 1019, 1025 (D.C. Cir. 2008) (quotation omitted). This standard is met here.

As every panel member below concluded, erasing crucial safeguards in 2016 and 2021 "meaningfully altered" the drug regimen. FDA.Pet.App.47a. Danco suggests that these changes did not "significantly alter[] the stakes of judicial review," *Sierra Club*, 551 F.3d at 1025, because eliminating "a more stringent requirement in favor of an alternative does not work such a sea change." Danco.BIO.20 (cleaned up). That cannot be correct. Such a theory would immunize agencies anytime they swap out a stringent requirement for a more lenient one. Indeed, the D.C. Circuit found the elimination of a crucial safeguard to work just a sea change in *Sierra Club*.

Hard put to deny the sea-change occasioned by the 2016 and 2021 actions, Cross-Respondents pull a stray line from *Sierra Club* to suggest that reopening applies only where the initial action "may not have been worth challenging" on its own. Danco.BIO.21.

But the standard is whether the new agency action "significantly altered" the prior one, including "by stripping out virtually all of the [previous safeguards]." *Sierra Club*, 551 F.3d at 1025 (cleaned up). And just because agency action was initially worth challenging does not foreclose the reopening doctrine. That some Cross-Petitioners might have challenged the 2000 Approval no more defeats reopening here than did the challengers' submitted comments opposing the initial rule in *Sierra Club*. *Id.* at 1026 (noting that commenters raised objections to the initial 1994 rule). It is similarly irrelevant whether Cross-Petitioners personally oppose abortion. Cf. Danco.BIO.21.

Cross-Respondents also contend that since drug applicants can ask FDA to make "revision[s]" to a REMS, Danco.BIO.20, it was "entirely foreseeable" that FDA would modify mifepristone's post-marketing restrictions in a drastic way, FDA.BIO.17. Hardly. The basic assumption of the 2000 Approval was that mifepristone's safety depended on the included safeguards. See *Nat'l Biodiesel Bd.* v. *EPA*, 843 F.3d 1010, 1017 (D.C. Cir. 2016). It was not "reasonably foreseeable"—much less entirely so—that FDA would strip away *nine* safeguards it once determined necessary for safety. Nor was it foreseeable that FDA would erase the "cornerstone" safeguard of an in-person dispensing requirement. FDA.Pet.App.229a. FDA's changes are not garden-variety REMS modifications or efficacy supplementation, cf. Danco.BIO.22 & n.7, but specific ETASUs that FDA once determined were "necessary to assure safe use," 21 U.S.C. 355-1(f)(1). Only 63 drugs have active ETASUs and removing those elements does not occur with any frequency. See FDA Risk Evaluation and Mitigation Strategy

(REMS) Public Dashboard, https://perma.cc/N787-MQ2F.

Danco says constructive reopening hasn't applied outside the rulemaking context. Danco.BIO.20. But there's no reason to exempt agency adjudication from the prohibition on bait-and-switch maneuvers applied in *Sierra Club*. Otherwise, an agency could fundamentally alter the "package deal that [it] devised and sold to the public as adequate protection," *Sierra Club*, 551 F.3d at 1026—exactly what happened here. Tellingly, the D.C. Circuit has already suggested that the "alteration" of an original adjudication *can* constitute reopening. *Sendra Corp.* v. *Magaw*, 111 F.3d 162, 167 (D.C. Cir. 1997) (considering reopening where agency "altered its original decision" even though the order stated "only that it [was] denying reconsideration").

II. FDA violated the APA and the FDCA when approving mifepristone under Subpart H.

Cross-Respondents' procedural arguments cannot hide the 2000 Approval's glaring deficiencies. FDA improperly classified pregnancy as an "illness" and asserted without basis that chemical abortion provides a "meaningful therapeutic benefit" over surgical abortion. FDA also lacked evidence and satisfactory explanations for excluding safeguards employed in every clinical trial. The 2000 Approval violated the APA and the FDCA.

A. Subpart H applies only to drugs that treat illnesses, but pregnancy is not an illness.

Subpart H approvals are only for new drugs "treating serious or life-threatening illnesses." 21

C.F.R. 314.500. But pregnancy is not an illness. Cross-Pet.25. FDA and Danco know this. *Ibid*. So they argue that Subpart H also applies to drugs that treat "conditions"—a term absent from the regulation. Their basis for that argument is Subpart H's preamble. FDA.BIO.22–23; Danco.BIO.26–27. But the preamble does not extend the regulation to drugs that treat "conditions." FDA.Pet.App.92a–93a, 161a. Equally important, a preamble cannot override clear regulatory text. *Dist. of Columbia* v. *Heller*, 554 U.S. 570, 578 n.3 (2008); *Cuomo* v. *Clearing House Ass'n*, 557 U.S. 519, 533 (2009). FDA's efforts to contort Subpart H cannot justify the 2000 Approval. Cross-Pet.26.

B. Chemical abortion does not provide a meaningful therapeutic benefit over surgical abortion.

Subpart H also requires that a new drug have a "meaningful therapeutic benefit," defined as the "ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy." 21 C.F.R. 314.500. But chemical abortion does not provide such a benefit over surgical abortion, and the 2000 Approval did not say it did. Instead, FDA said merely that mifepristone potentially enabled women to avoid surgical abortion. FDA.BIO.23. Crediting this justification would read the requirement of a therapeutic benefit right out of Subpart H.

Danco cites post-hoc studies that purportedly show "various benefits over surgical abortion." Danco.BIO.28. Yet "[i]t is a foundational principle of administrative law that judicial review of agency action is limited to the grounds that the agency

invoked when it took the action." *Dep't of Homeland Sec.* v. *Regents of Univ. of Cal.*, 140 S. Ct. 1891, 1907 (2020) (cleaned up).

Finally, Danco references a 2008 Government Accountability Office report that compared FDA's approval "processes" for mifepristone with other Subpart H approvals. Danco.BIO.27. But Cross-Petitioners have never challenged FDA's approval *processes* for mifepristone. Instead, they have shown that Subpart H was an improper vehicle for the 2000 Approval. FDA.Pet.App.90a–97a, 160a–172a.

C. The 2000 Approval violated the FDCA and the APA.

FDA acknowledges that the 2000 Approval must comply with the FDCA and the APA. FDA.Pet.App.95a; FDA.BIO.19. But it failed to do so.

The FDCA requires FDA to reject any new drug application if clinical studies "do not include adequate tests … to show whether or not such drug is safe for use under the conditions prescribed … in the proposed labeling," 21 U.S.C. 355(d)(1), or if "there is a lack of substantial evidence that the drug will have the effect it purports … to have under the conditions of use prescribed," *id.* 355(d)(5). Cf. FDA.BIO.20 (omitting these requirements when explaining FDA's FDCA obligations).

FDA's 2000 Approval relied on clinical studies that included (1) ultrasounds to determine gestational age and identify life-threatening ectopic pregnancies and (2) an observation period after misoprostol administration. Cross-Pet.30. But the 2000 Approval included neither of these safeguards. *Ibid.*

As to the first deficiency, FDA argues that the 2000 Approval "explained why an ultrasound requirement was unnecessary": a doctor could use "other clinical methods" to determine gestational age and diagnose ectopic pregnancies. FDA.BIO.21. But FDA cited no "adequate tests," 21 U.S.C. 355(d)(1), or "substantial evidence," *id.* 355(d)(5), to support its conclusory statement. ROA.595. That violates the FDCA. And FDA's failure to explain how it could extrapolate key conclusions about safety without such data is arbitrary and capricious under the APA. See *Motor Vehicle Mfrs. Ass'n of U.S., Inc.* v. *State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

As to the second shortcoming, FDA excuses the lack of an observation period after misoprostol administration by noting that its 2000 Approval listed "[in]adequate access to emergency services" as a contraindication. FDA.BIO.21. This falls short of a reasonable explanation. All it does is reinforce Cross-Petitioners' standing by confirming that FDA always envisioned that emergency room doctors—like Cross-Petitioner doctors and association members—would be a crucial component of the mifepristone regimen. See Resp'ts.BIO.24–26 (discussing FDA's position that emergency room doctors are "critical for the safe" use of mifepristone).

Danco says Cross-Petitioners did not reference the lack of an observation period below. Danco.BIO.33. That's wrong. The complaint specifically highlighted that the U.S. clinical trial required women to be "monitored for four hours for adverse events after taking misoprostol" and that "FDA's 2000 Approval did not require th[is] safeguard[]." ROA.119. The brief in support of the motion for a preliminary injunction made this same argument. ROA.1057. And the

district court noted this in finding the 2000 Approval arbitrary and capricious. FDA.Pet.App.173a.

Cross-Petitioners' argument is simple: FDA must comply with the FDCA's stringent requirements for adequate testing, sufficient information, *and* substantial evidence of safety and effectiveness under the labeled conditions of use. 21 U.S.C. 355(d). If FDA's action lacks such data, the agency must adequately explain how it could determine that a drug was nevertheless safe under the conditions for use. *State Farm*, 463 U.S. at 43. FDA's characterization of these well-established requirements as a "study match" mandate is misplaced. FDA.BIO.20. The problem is that a discrepancy between the studies and the approved label exists, yet FDA failed to justify the discrepancy with additional data or a reasonable explanation. *State Farm*, 463 U.S. at 43.

D. The FDAAA provides no refuge for FDA's unlawful 2000 Approval.

Abandoning Subpart H, Cross-Respondents turn to the FDAAA. FDA.BIO.22; Danco.BIO.25. This statutory amendment provides them no refuge.

The FDAAA "did not approve any drugs. It only approved [REMS] for those drugs that the FDA had *already* validly approved under § 314.520 of Subpart H," FDA.Pet.App.96a (Ho, J., concurring and dissenting in part)—and only on a temporary basis. But as explained above, FDA failed to validly approve mifepristone under Subpart H. *Ibid.* So FDAAA does not help Cross-Respondents.

What's more, the FDAAA only temporarily deemed approved drugs to have REMS and required

Danco to submit a supplemental drug application that FDA approved in 2011. That 2011 approval "did not re-approve the drug apart from Subpart H." FDA.Pet.App.97a (Ho, J., concurring and dissenting in part). Rather, it "made clear that the agency continued to rely on Subpart H for its approval of mifepristone." *Ibid.* (citing FDA Suppl. Approval Letter to Danco Labs at 1).

In sum, the FDAAA is not a "glaring vehicle problem" for Cross-Petitioners. Contra Danco.BIO.24. It's a glaring merits problem for FDA and Danco.

III. Cross-Petitioners have standing to challenge the unlawful 2019 Generic Approval.

The 2019 Generic Approval relied on the previous mifepristone submissions and approvals. Cross-Pet.31–32. In particular, FDA approved generic mifepristone under the 2016 Major Changes regimen. Cross-Pet.32. Cross-Petitioners have submitted substantial evidence demonstrating that the 2000 Approval and the 2016 Major Changes have injured and will continue injuring them. ROA.1226-1294. This harm flows in part from the approval of generic mifepristone, which comprises roughly two-thirds of the chemical abortion market. Cross-Pet.33. This establishes Cross-Petitioners' standing to challenge the 2019 Generic Approval.

In fact, standing to challenge that action exists doubly so. In addition to the harm to Cross-Petitioners, three states have moved to intervene, D.Ct.Doc.151, based on evidence showing that the 2019 Generic Approval has injured them, D.Ct.Doc.151-1 at 2–3, 68 & Exhibits 36, 38. The district court is poised to rule on that intervention

request in December. D.Ct.Doc.159. This is yet another reason why the interlocutory nature of this litigation supports denying the petitions and cross-petition.

Once standing is established, the merits of the challenge to the 2019 Generic Approval rise or fall with the rest of the case. FDA agrees that Cross-Petitioners' "challenge to the approval of generic mifepristone is entirely derivative of their challenge to FDA's [2000] approval," meaning if the latter succeeds, so does the former. FDA.BIO.24. Likewise, if the 2016 Major Changes fall, the same fate awaits the 2019 Generic Approval.

CONCLUSION

The petitions should be denied. But if they are granted, the cross-petition should also be granted.

Respectfully submitted,

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