No. 24-977

IN THE

Supreme Court of the United States

MERCK SHARP & DOHME CORPORATION,

Petitioner,

v.

DORIS ALBRECHT, ET AL.,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Third Circuit

REPLY IN SUPPORT OF PETITION FOR WRIT OF CERTIORARI

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INTRODUCTION

After canvassing the record and regulatory context, two district judges found that Merck informed the FDA about the possible connection between Fosamax and atypical femoral fractures, attempted to revise its label to warn of that risk, and was told that it could not because the science was not clear. The FDA agreed. It told this Court that Merck provided it with the relevant data about Fosamax's risks, but that it then told Merck the information did not warrant a change.

The Third Circuit still reversed. In light of the "strong presumption [against preemption]," it "ha[d] a duty to accept the reading [of the agency's Complete Response Letter] that disfavors pre-emption"; it was thus "[un]necessary" to *consider* "extrinsic evidence" proving that the CRL is best read to reject Merck's request on scientific grounds. Pet.App.62a, 65a, 66a n.27. That approach cannot be squared with *Albrecht*, the approach by other circuits since that decision, or the FDA's duty to require needed revisions. Pet.18-31.

Unable to defend the actual decision below, Respondents instead misrepresent it, skewing the factual and regulatory context and the decision's consequences. But the Third Circuit said what it said: courts must blind themselves to evidence of the true meaning of ambiguous agency documents—including the agency's own view—leaving pharmaceutical manufacturers and patients alike to suffer from a regulatory scheme outside the FDA's control. This Court should grant certiorari to again correct the Third Circuit's outlier approach.

I. RESPONDENTS MISREPRESENT THE DECISION BELOW AND THE REGULATORY FRAMEWORK.

A. Respondents Cannot Erase the Third Circuit's Mistaken Presumption.

Rather than ask whether the CRL, read in light of the entire record, the regulatory regime, and the FDA's own view, prohibited Merck from revising its warning, the Third Circuit demanded "abundant[] cl[arity]" under a "heavy *Albrecht* presumption." Pet.App.66a & n.27. That cannot be squared with this or any other court's approach. Pet.23-27.

1. Respondents first try to duck all this, arguing that the FDA rejected only a "warning about stress fractures" and so Merck could have revised its label despite the CRL. Opp.13. The Third Circuit, however, rejected that argument, recognizing that Merck's proposal sought to warn of atypical femoral fractures. Pet.App.54a-55a.

Respondents similarly seek to avoid the Third Circuit's presumption by arguing that Merck's not using "the CBE regulation to unilaterally change its label" is somehow "dispositive." Opp.14. But the courts below did not accept this argument, Pet.App.37a-38a, and for good reason. Changes made while seeking FDA approval (the CBE process) are subject to the same standard as those made with the agency's blessing (the PAS process). *See* 21 C.F.R. § 314.70(b), (c). So if the agency rejected Merck's PAS in part because of the science, it would have done the same with any CBE, leading again to preemption.

2. Turning to the Third Circuit's actual decision, Respondents insist it did not "overlay a new evidentiary requirement" on this Court's two-pronged

test. Opp.16. The Third Circuit, however, said otherwise. It claimed courts have "a duty to accept the reading" of the FDA's actions "that disfavors pre-emption," Pet.App.65a (quotation omitted), and stated that an ambiguous record "will seldom, if ever, be enough to overcome [its] presumption," Pet.App.66a n.27. That is the very thumb on the scale Respondents try to disclaim.

Respondents next suggest that the Third Circuit's repeated statements about the presumption are "shorthand" for the idea that "ambiguity does not amount to clear evidence." Opp.16. That repeats the Third Circuit's fundamental error. As *Albrecht* explained, "'clear evidence' is evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning required by state law" and that "the FDA, in turn, informed the drug manufacturer that the FDA would not approve a change to the drug's label to include that warning." *Merck Sharp & Dohme Corp. v. Albrecht*, 587 U.S. 299, 303 (2019). *Albrecht*'s two-part test is what it *means* in the drug-labeling context for federal and state law to "irreconcilably conflict." *Id.* at 315 (cleaned up). The Court never hinted that judges should conduct that inquiry with a jaundiced eye.

Respondents also divine support for the Third Circuit's presumption in this Court's statement that manufacturers will not "ordinarily" be able to show a conflict between state and federal law. Opp.16 (quoting *Albrecht*, 587 U.S. at 315). There, *Albrecht* made the basic point that, in light of the CBE process, manufacturers cannot invoke preemption simply by pointing to their federally-approved label; it in no way

suggested manufacturers who *try* to revise their label and get rebuffed face additional evidentiary burdens.

Respondents next insist that generic references to the presumption in pharmaceutical cases support the Third Circuit's "heavy" use of it in this impossibility preemption case, notwithstanding the *non obstante* nature of the Supremacy Clause. Opp.17-18. Here, Respondents have no answer for Merck's basic point: this Court has *never* used the presumption when applying a given test for impossibility preemption to the facts of a case. The Supremacy Clause itself dictates the outcome where a regulated party cannot comply with both federal and state law.

3. Respondents assert that "[t]he Third Circuit's reasoning does not foreclose consideration of 'extrinsic evidence.'" Opp.18. But the Third Circuit held that "extrinsic evidence" *could not* resolve "the ambiguities in the FDA's [CRL]" here given the court's "heavy *Albrecht* presumption." Pet.App.66a n.27. Indeed, it distinguished its own (supposedly permissible) use of "informal FDA communications to determine the impact of § 355(*o*)(4)(A)" from the district court's (supposedly impermissible) use of such materials "to interpret the [CRL]." Pet.App.73a n.32.

Anyway, Respondents don't actually believe what they are selling. In the next breath, they defend the Third Circuit's (now-admitted) "h[o]ld[ing]" that "reliance on informal communications" to resolve ambiguity is "legal error." Opp.18. The "legal error" runs the other way. This Court specifically said district judges "may have to resolve subsidiary factual disputes" that arise in the preemption inquiry.

Albrecht, 587 U.S. at 317 (quoting *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 574 U.S. 318, 327 (2015)).

As this Court recognized, that task may involve extrinsic evidence. Determining the "meaning and scope" of a decision "reject[ing]" an application for "insufficient" information might require the court to examine "what information the FDA had before it" without an administrative record. *Id.* at 317. That inquiry does not differ in kind from using the agency's informal back-and-forth with the regulated party to interpret its CRL, as the district court did here. *See Teva*, 574 U.S. at 326-27 (explaining how judges consider extrinsic evidence in patent construction).

Respondents further insist that the Third Circuit in fact "evaluat[ed] … the contested extrinsic evidence" and simply "interpret[ed]" it in Respondents' favor. Opp.18-19. Their quotations give that game away. The Third Circuit "conclud[ed] that 'it is not clear' that the 'extrinsic evidence … helps Merck.'" Opp.19 (quoting Pet.App.66a n.27) (second alteration Respondents'). Saying it is "not clear" that the evidence "helps Merck" is not an assessment of that evidence, let alone a holding that the district court *clearly erred* in concluding otherwise.

The Third Circuit only multiplied its errors by disregarding the other "clear extrinsic evidence" *favoring* preemption, *i.e.*, the FDA's own view of the CRL. Pet.App.67a n.27. That view was not a mere "conclusion that state law is pre-empted," *id.* (quotation omitted), but an application of "substantive expertise" about the FDA's own CRL process, expressed "in an *amicus curiae* brief in this Court,"

Kisor v. Wilkie, 588 U.S. 558, 577, 579 n.6 (2019) (quotation omitted); *see* C.A.App.1523-24.

Respondents similarly claim that Merck simply seeks "a different interpretation of the [CRL] and extrinsic evidence." Opp.19. No. Merck wants a preemption analysis that asks whether the CRL—read in light of the FDA's own view and all other evidence, and with no thumb on the scale—reflected the agency's determination that Merck could not add the warning in question. What it got was an analysis skewed by the Third Circuit's "heavy *Albrecht* presumption," one which made examination of the complete record "[un]necessary." Pet.App.66a n.27.

4. Respondents next argue that the Third Circuit's approach does not differ from other circuits. Opp.23-25. But Respondents begin by repeating their claim that the Third Circuit "adopted no … 'evidentiary presumption,'" Opp.23, which is wrong for the reasons just given, *supra* pp.2-4.

Respondents' walk through the cases fares no better. Start with the decisions in *Dolin v. GlaxoSmithKline LLC*, reported at 901 F.3d 803 (7th Cir. 2018) and 951 F.3d 882 (7th Cir. 2020). Respondents claim there was "no ambiguity" there, Opp.24, but that is beside the point. In setting out the *legal* standard, the Seventh Circuit mentioned no "heavy *Albrecht* presumption," and it relied on "discussions between the FDA" and the manufacturer in reaching its pro-preemption conclusion. 901 F.3d at 814; *see* 951 F.3d at 889-91. Both of those steps were erroneous under the Third Circuit's approach.

Respondents' discussion of *In re Zofran (Ondansetron) Products Liability Litigation*, 57 F.4th

327 (1st Cir. 2023), misfires for the same reason. The First Circuit did not suggest that courts should apply this Court's two-part test with a "heavy *Albrecht* presumption," even if such a presumption could have been rebutted on that case's facts.

Finally, Respondents distinguish the Second, Fourth, Fifth, and Tenth Circuits' cases because they assessed whether there was newly available information such that the manufacturer could have updated its label under the CBE regulation, not whether the manufacturer sought permission to revise its label and the agency said no. Opp.24-25. Why would a "heavy *Albrecht* presumption" apply when determining whether the agency blocked the manufacturer's request, but not whether there was newly available information that could have justified a revision in the first place? Respondents have no answer.

B. Respondents Cannot Explain the Statutory and Regulatory Context.

The Third Circuit's presumption itself justifies review, but there is more. Congress instructed the agency to start discussions and order a label change if it "becomes aware of new information" that "should be included." 21 U.S.C. § 355(*o*)(4)(A). FDA regulations also make clear that it does not reject warnings over "editorial" differences, but rather proposes "changes" if needed. 21 C.F.R. § 314.105(b); *see id.* § 314.110(a)(4).

Justice Alito explained the upshot: "if the FDA declines to require a label change," the "logical conclusion" is that it "determined" a revision "was unjustified." *Albrecht*, 587 U.S. at 324 (Alito, J.,

concurring in the judgment). Rather than accept that "highly relevant" inference, *id.* at 325, the Third Circuit said the FDA may have been "still assessing evidence," "not fully convinced" of a link, Pet.App.71a.

The Third Circuit failed to recognize the preemptive force of its reasoning. If the FDA was not yet convinced, then Merck could not have revised its label. Here, too, the Third Circuit's misunderstanding warrants certiorari. Pet.27-31.

1. In response, Respondents point out that the Third Circuit "held that FDA may have rejected petitioner's warning because it improperly warned about stress fractures." Opp.21 (citing Pet.App.61a-62a). That just highlights the facts supporting Justice Alito's inference. The Third Circuit held that Merck "fully informed the FDA about the risks of atypical femoral fractures," Pet.App.43a (cleaned up), and it held that Merck "offered a warning for atypical femoral fractures, not 'garden-variety' stress fractures," Pet.App.54a (cleaned up). If so—and if the FDA believed the data *supported* a warning—then the agency was obligated to redline Merck's proposal with its own. It did not, and so the obvious inference is that it believed Merck's "justification" was "inadequate." Pet.App.57a. The FDA agrees. C.A.App.1524.

Respondents next recite the Third Circuit's claim that "'the FDA had not fully considered the information that Merck … had submitted'" before issuing its CRL. Opp.21 (quoting Pet.App.71a). This misunderstands the CRL process. A "*complete* response letter" "reflects FDA's *complete* review of the data submitted." 21 C.F.R. § 314.110(a)(2) (emphases added); 73 Fed. Reg. 39588, 39592, 39594 (2008)

(expounding on this). Indeed, the only scenario in which a CRL would not provide the agency's "complete review" is "[i]f FDA determines … that the data submitted are inadequate to support approval." 21 C.F.R. § 314.110(a)(3); *see* 73 Fed. Reg. at 39592 (the FDA denies in such circumstances "without first … reviewing" the label). No one claims that happened here. Because the FDA issued a CRL partially granting and partially rejecting Merck's application, we know its review was complete—and that it felt no warning was justified. Here, too, the FDA agrees. C.A.App.1524.

Anyway, accepting the Third Circuit's understanding of the CRL still would not change the outcome. If the link was unclear at the time of the CRL, Merck *could not* have revised the label to warn about it then. Per the regulations, "the labeling must be revised … as soon as there is reasonable evidence of a causal association"—but no sooner. 21 C.F.R. § 201.57(c)(6)(i). That makes sense, because *over*warning is just as problematic as underwarning. 73 Fed. Reg. 49603, 49605-06 (2008).

Respondents next insist that "[t]he record" indicates the "FDA was still assessing whether a different warning from the one [Merck] had proposed would be appropriate." Opp.21. But again, if the agency was still deliberating about whether there was sufficient risk, Merck could not add a warning. Indeed, Merck *accepts* that the agency was not fully convinced on the science when it rejected Merck's request: it asked Merck to "hold off" on a warning so that the agency could "close out" Merck's request and *then* determine whether a revision was "warranted." Pet.App.154a.

2. Next, Respondents argue that the FDA's regulations did not require it to do anything if it simply disliked Merck's phrasing. Respondents assert that the agency satisfied its duty under 21 C.F.R. § 314.110(a)(4) to "recommend actions" Merck could take to secure approval by inviting Merck to "resubmit." Opp.22.

Hardly. If the agency disliked Merck's phrasing, its regulations required it to "recommend" phrasing that would meet with the agency's approval. And indeed, that is *exactly* what the FDA did with respect to Merck's proposed alteration to the Adverse Reactions section: it suggested revisions that, if implemented, would lead to acceptance. Pet.App.89a.

Respondents' rejection of 21 C.F.R. § 314.105(b)—which requires the agency to note "editorial or similar minor deficiencies"—misses as well. They assert the FDA may not have suggested revisions because Merck's proposal was "misleading." Opp.22 (discussing 21 C.F.R. § 314.125(b)(6)). But the whole point of suggesting revisions is to *eliminate* potentially misleading terminology so that patients can be properly warned about actual risks. That the agency did not do so proves that its concerns ran deeper.

Finally, Respondents insist that Merck's (and the district court's and the FDA's) inferences from the statutory and regulatory background "shift[] the responsibility for [Merck's] label to FDA." Opp.23. Not so. Merck discharged its duties by fully informing the FDA on the latest science and requesting a label change based on that science. Pet.App.43a-49a, 55a. If the FDA believed a warning was necessary, it should have and would have recommended revisions to

Merck's proposed phrasing—just as the FDA itself told this Court years ago. C.A.App.1523-24. This error, too, warrants this Court's intervention.

II. THE DECISION BELOW PUTS DRUG MANUFACTURERS IN AN IMPOSSIBLE POSITION.

The Third Circuit's decision puts pharmaceutical manufacturers to an impossible choice: submit request after request to make sure it really is impossible to update the label, or risk decades of litigation. This Court has often granted certiorari to prevent disruption to the pharmaceutical industry, even without sharp circuit conflict. It did so in *this* case, to correct a similar error. Pet.32-34.

1. Respondents insist Merck "could have followed up with FDA" or "updat[ed] the Precautions section through the CBE supplement." Opp.26. Respondents' first proposal only highlights Merck's concerns. The agency had already told Merck that its "*justification* for the proposed PRECAUTIONS section language [was] inadequate," Pet.App.22a (emphasis added), and had asked it to "agree to hold off" on a warning so that the agency could "close out" Merck's supplement and then further study whether a warning was "warranted," Pet.App.154a. Manufacturers should not have to file seriatim requests to get the agency's views (yet again), let alone do so simply because of boilerplate language telling *all* manufacturers they may resubmit. Pet.App.155a (explaining how the FDA "rebuffed" Merck's attempts to "initiate further discussion" (emphasis omitted)).

Respondents' other proposal is worse. Respondents apparently believe Merck should have disregarded its back-and-forth with the agency and unilaterally

changed its label anyway, waiting for the agency to express its disapproval (again) on the backend. Opp.26-27. Asking for forgiveness rather than permission may have virtues in some contexts; the pharmaceutical industry is not one of them. Merck could not circumvent the agency's actions through the CBE process, *supra* p.2, and no rational system of regulation would expect it to anyway.

2. Respondents insist the Third Circuit's decision leaves the FDA regime "as Congress and FDA intended"—under that regime, it was Merck's job to update its label, not the FDA's duty to propose an alternative. Opp.27. We know the "FDA" part of that claim is not true; it told this Court that Merck could not have updated its label because of the agency's concerns about the science. C.A.App.1523-24.

Respondents' claim about Congress fares no better. Under Congress's scheme, manufacturers must ultimately obtain the FDA's approval for label changes. While manufacturers must "maintain [their] label[s] in accordance with existing requirements," 21 U.S.C. § 355(*o*)(4)(I), the FDA must also "promptly notify" them if it "becomes aware" of "new safety information," *id.* § 355(*o*)(4)(A), and "may … direct[]" revisions unilaterally if necessary, *id.* § 355(*o*)(4)(E).

Merck followed that process to a tee: it told the FDA about the possible risk of atypical femoral fractures, Pet.App.43a-49a, proposed a warning attempting to target that risk, Pet.App.55a, and then heeded the FDA's request to withdraw its submission while the agency studied the issue, Pet.App.122a. Respondents would replace the FDA's expert supervision of drug labeling with a patchwork of state-tort-law decisions

unless and until the agency expresses its conclusions with indisputable precision in the CRL itself, and regardless of the FDA's own view of its CRLs. That is no way to run a railroad.

CONCLUSION

The petition should be granted.

MAY 23, 2025

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