No. 22-1180

In the
Supreme Court of the United States

SHIRE US INC.; SHIRE LLC,

Petitioners,

v.

MARK BLACKBURN,

Respondent.

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

REPLY BRIEF FOR PETITIONERS

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REPLY BRIEF

The Eleventh Circuit held below that a drug manufacturer must use the FDA's "Changes Being Effected" (CBE) regulation to unilaterally alter language implicating the "Highlights" section of a label to avoid failure-to-warn liability—while ignoring that the CBE regulation itself states that such a change requires FDA preapproval. As commentators and amici agree, that decision makes a hash of the regulations, defies this Court's preemption cases, and creates a lower-court conflict. And the stakes are high. The Highlights section contains the most important information for prescribing a drug safely and effectively. Thanks to the decision below, juries are now the ultimate editors of that section within the Eleventh Circuit, whereas courts in other jurisdictions correctly recognize that the FDA is. This Court should intervene and rescue manufacturers from the damned-if-they-do-damned-if-they-don't position in which the decision below leaves them.

Nothing in respondent's brief in opposition changes the calculus. Indeed, Blackburn does not even seriously defend the Eleventh Circuit's actual holding; he just insists that the court did not really mean what it said. His felt need to rewrite the decision is telling, but it is defeated both by the court's own words and by how everyone save him has read it. Blackburn thus is left pressing purported vehicle problems. But this Court has considered similar objections in other preemption cases in this context and found them wanting. If anything, this case—involving the most critical section of a drug label—is an even more obvious candidate for certiorari.

I. The Decision Below Conflicts With This Court's Precedent, With The Plain Text Of The Governing Regulations, And With The FDA's Repeated Interpretation Of Them.

The FDA regulations at issue make plain as day that, except in two circumstances that all agree are irrelevant here, a drug manufacturer is prohibited from making any change implicating the Highlights section of a label without FDA preapproval. In particular, 21 C.F.R. §314.70(b)(2)(v)(C) states that "[a]ny change to the information required by [21 C.F.R.] §201.57(a)"—*i.e.*, the regulation addressing the Highlights section—is a "major change[]" "requiring supplement submission and approval." And nothing in 21 C.F.R. §314.70(c)(6)(iii)—the CBE regulation—disturbs that conclusion. Indeed, although the CBE regulation allows label changes without FDA preapproval in limited circumstances, it explicitly states that the preapproval requirement continues to apply when the changes concern "information required in §201.57(a)." All that should have made this an easy case: Because Blackburn's state-law claim implicates Lialda's Highlights section, and because Shire could not have changed that section without FDA preapproval, it is preempted under precedents like *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), and *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472 (2013). The Eleventh Circuit clearly erred in holding otherwise. *See* Pet.17-24.

Rather than defend the Eleventh Circuit's actual decision, Blackburn tries to rewrite it, insisting that "[t]he court did not hold that the CBE process can be used to revise the Highlights section." BIO.17. That

is wishful thinking. Indeed, no one save Blackburn has read the decision that way. *See, e.g.*, PhRMA.Amicus.Br.4 ("[T]he Eleventh Circuit held that Shire could have unilaterally changed the Highlights section without FDA prior approval."); James M. Beck, Blackburn—*That's Just Plain Wrong*, Drug & Device Law (Dec. 19, 2022), https://bit.ly/3TlFWs4 (observing that the decision below "said 'no'" to the rule that "change[s] to drug 'highlights' … cannot be made through a CBE supplement"). And little wonder. After recounting Shire's argument that "it was precluded from changing the warning" on Lialda's label regarding "periodic" kidney testing because it implicated language "contained in the 'Highlights' section," the Eleventh Circuit "reject[ed]" it. Pet.App.7.

In doing so, the Eleventh Circuit never disputed that Blackburn's proposed alternative warning implicated the Highlights section. Rather, the court accepted that fact and agreed that 21 C.F.R. §314.70(b)(2)(v)(C) imposes a preapproval requirement for changes to the Highlights section. *See* Pet.App.7. But the court then proceeded to declare that requirement immaterial, on the theory that 21 C.F.R. §314.70(b)(2)(v)(A) supposedly "exempts" *all* label changes—including changes to the Highlights section—made pursuant to the CBE regulation from the preapproval requirement. Pet.App.7-8. The court did so, moreover, without even acknowledging that the CBE regulation *itself* explicitly preserves the preapproval requirement for labeling changes implicating the Highlights section. *See* 21 C.F.R. §314.70(c)(6)(iii)(C). *That* is the "disastrous" holding that has led commentators to denounce the decision as

one of "worst prescription drug/medical device decisions" in recent memory. James M. Beck, *The Agony of Defeat—The Ten Worst Prescription Drug/Medical Device Decisions of 2022*, Drug & Device Law (Dec. 22, 2022), https://bit.ly/3MirVtv.

Unable to deny what the Eleventh Circuit actually said, Blackburn argues that the court could not possibly have meant it given "the complaint and the appellate briefing." BIO.13. Those arguments are self-defeating. While Blackburn applauds himself for "not mention[ing] the Highlights section" in his complaint and "focus[ing]" only on the supposedly deficient "periodic" warning that appears in the "Warnings and Precautions" part of the "Full Prescribing Information" section, BIO.7, 12-13—an expected omission from a plaintiff seeking to avoid preemption—*Shire* most definitely made the argument that those changes could not be made without requiring corresponding changes to the Highlights section, which FDA regulations (twice) prohibit manufacturers from making without agency preapproval. *See, e.g.*, CA11.Shire.Br.50-52; CA11.Shire.En.Banc.Pet.5-14. Indeed, Blackburn himself ultimately concedes that certain changes to the Warnings and Precautions part of the Full Prescribing Information section *necessarily* would demand a change to the Highlights section. *See* BIO.16. That is precisely the situation here.

For instance, citing his Eleventh Circuit reply brief, Blackburn admits that, under 21 C.F.R. §201.57(a)(5), "substantive changes … to [the] Warnings and Precautions" part of the Full Prescribing Information section—"including CBE

changes"—"requir[e]" a change to "Highlights." BIO.16. He just insists that his alternative "proper interval" warning would "require no change to … the Highlights," on the theory that Shire's "periodic" warning is "consistent with" his proposed "proper interval" warning. BIO.16. At the outset, that argument is fatally inconsistent with Blackburn's theory of his case, as Shire's warning could hardly have been so hopelessly deficient as to entitle Blackburn to handsome compensatory damages, punitive damages, and attorneys' fees if there is *no "substantive" difference whatsoever* between Shire's warning and his warning.

But more to the point, although the *district court* accepted that contradictory argument (albeit while labeling it "tenuous" and "shaky," Pet.App.128-29), Blackburn does not identify anything in the decision below hinting that the Eleventh Circuit followed that course. Nor could he: The court repeatedly stated that he had demanded a much "*stronger* monitoring instruction" than the "periodic" instruction on Lialda's label. Pet.App.5, 6, 7 (emphasis added). And changing the Warnings and Precautions part of the Full Prescribing Information section to include a stronger warning is plainly a substantive change that, as a result of 21 C.F.R. §201.57(a)(5), would require a corresponding change to the Highlights section. Indeed, "substantive" changes under 21 C.F.R. §201.57(a)(5) encompass all changes other than "minor revisions such as correcting typographical errors or grammatical changes." FDA, *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content*

and Format Requirements 8 (Feb. 2013), https://bit.ly/3VPCIhS.

Furthermore, Blackburn's selective recap of the proceedings below conveniently omits that the Eleventh Circuit *also* heard that a separate regulation—21 C.F.R. §201.57(a)(10)—would require Shire to change the Highlights section to accommodate his alternative warning. *See, e.g.*, CA11.Shire.Br.51. Blackburn has never disputed that point, and understandably so: Section 201.57(a)(10) requires the Highlights section to include "recommendations for patient monitoring that are critical to safe use of the drug." As the Eleventh Circuit explained when rejecting Shire's preemption argument, that perfectly describes Blackburn's alternative warning: "Blackburn's proposed language … is a recommendation"—or a "monitoring instruction"—"for how to administer LIALDA in a way that increases its safe use." Pet.App.7-8. Accordingly, far from suggesting that the decision below has some secret meaning, the complaint and appellate briefing confirm that the Eleventh Circuit meant what it (incorrectly) said: Blackburn's state-law claim is not preempted even though it plainly *does* implicate the Highlights section, because Shire can unilaterally change the Highlights section via the CBE process.

The closest Blackburn comes to defending that misguided holding is his assertion (which partially quotes the CBE regulation) that "changes to 'add or strengthen a contraindication, warning, [or] precaution' are *not* 'major' changes and *are* permitted through the CBE process, without FDA pre-approval." BIO.12. But that argument just repeats the Eleventh

Circuit's mistake. Like the court below, Blackburn fails to even *mention* that the CBE regulation expressly states that the FDA-preapproval requirement remains alive and well when it comes to "changes to the information required in §201.57(a)"—*i.e.*, the Highlights section. 21 C.F.R. §314.70(c)(6)(iii). As the FDA already concluded when it approved the now-challenged Highlights section of Lialda's label, information regarding the frequency of kidney testing is "information required in" that section. FDA regulations thus *prohibited* Shire from "independently" revising that language. *PLIVA*, 564 U.S. at 620; *see also* Erika Fisher Lietzan & Sarah E. Pitlyk, *Thoughts on Preemption in the Wake of the* Levine *Decision*, 13 J. Health Care L. & Pol'y 225, 238 (2010) ("Important safety changes to prescribing information … must also be reflected in the *Highlights* section," and "corresponding changes to the *Highlights* section cannot legally take the form of a CBE supplement.").

Perhaps recognizing that the Eleventh Circuit's reasoning is indefensible, Blackburn resurrects alternative arguments from his briefing below. He suggests that Shire could have sought a "waiver" of the FDA-preapproval requirement, which the agency "'typically'" grants "where a revision to the Full Prescribing Information to enhance safety" affects "the Highlights." BIO.17. That argument goes nowhere. An FDA regulation expressly states that the agency may grant a waiver only after "[a]n applicant … ask[s] the Food and Drug Administration" for such a waiver. 21 C.F.R. §314.90(a). And this Court has already held that state-law claims "are pre-empted" when they would require a drug manufacturer to

"ask[] for the FDA's help" before making a labeling change. *PLIVA*, 564 U.S. at 624.

Blackburn is thus left complaining that, if "new or revised Warnings and Precautions necessarily required changing the Highlights" and securing FDA preapproval, it would render the CBE regulation and this Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009), a "nullity." BIO.15. He is wrong on both counts. As to the former, the very waiver process that he emphasizes presupposes that FDA preapproval is the default rule for changes to the Warnings and Precautions part of the Full Prescribing Information section that implicate the Highlights section, and that a special dispensation is necessary absent such approval. Enforcing a regulatory scheme according to its terms hardly renders it a nullity. As to the latter, *Wyeth* involved a drug first approved in 1955 and used in 2000, *see* 555 U.S. at 558-59, and the Highlights-related regulations apply only to certain drugs approved in 2001 or later, *see* 21 C.F.R. §201.56(b). Applying the Highlights regulations as written by the FDA thus would not disturb the bottom-line in *Wyeth*, and would preempt additional state-law claims only to the extent that they conflict with the FDA's post-*Wyeth* regulations.[1]

[1] Blackburn also posits that "Shire's argument concerning Highlights would not support its preemption argument" anyway "because the Highlights section regulations did not apply to Lialda for several years after it entered the market"—*i.e.*, between 2007 and 2009. BIO.17. But Blackburn began taking Lialda in 2013, *see* BIO.5, when the Highlights regulations indisputably applied.

Ultimately, Blackburn is right about one thing: the "brevity" of the analysis below. BIO.13. But while that brevity may explain how the Eleventh Circuit managed to issue a decision that is "dead wrong," Beck, Blackburn—*That's Just Plain Wrong*, *supra*, it does not make that decision any less dead wrong. Because the court below refused to correct its glaring error when given the opportunity, it falls to this Court to intervene.

II. The Eleventh Circuit's Stark Departure From The Longstanding Consensus Reading Of Unambiguous Regulatory Text Threatens Untenable Results.

This Court has granted certiorari in prescription-drug-related preemption cases even in the absence of any lower-court conflict given the sheer "importance of the pre-emption issue." *PLIVA*, 555 U.S. at 563. This case likewise raises a preemption question of "substantial importance." PhRMA.Amicus.Br.1. And it involves a lower-court conflict to boot, making the case for review even stronger.

Blackburn resists that conclusion, claiming that the Eleventh Circuit's decision is "consistent with" decisions from "the courts of appeals." BIO.17. But he does not deign to identify any such decision. That is unsurprising; in reality, the circuits are stacked against the Eleventh Circuit. Whereas the court below held that a drug manufacturer can make "major changes" under 21 C.F.R. §314.70(b)(2)—*i.e.*, changes to the Highlights section—even without FDA preapproval, other courts of appeals have consistently held that *all* "major changes" *always* require FDA preapproval. *See Gustavsen v. Alcon Lab'ys, Inc.*, 903

F.3d 1, 11 (1st Cir. 2018) ("[I]f a change fits under any of the categories listed in section (b)(2), that change … requir[es] FDA pre-approval."); *Ignacuinos v. Boehringer Ingelheim Pharms. Inc*, 8 F.4th 98, 102-03 (2d Cir. 2021) ("[C]laims are preempted to the extent that they would require any change listed in §314.70(b)(2)."); *Yates v. Ortho-McNeil-Janssen Pharms., Inc.*, 808 F.3d 281, 298 (6th Cir. 2015) ("[T]he manufacturer is prohibited from making any major changes … without … the agency's approval[.]"); *Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.*, 586 F.3d 500, 510 (7th Cir. 2009) ("[M]ajor changes[] requir[e] the FDA's approval.").

Blackburn does not argue that Shire has misread those decisions. To the contrary, he concedes that each one holds that "the CBE process is not available for 'major' changes." BIO.11-12 & n.1. His attempt to deny the circuit split thus rests entirely on his theory that Shire and everyone else in the industry has "misread[]" the decision below, which purportedly agreed with him that this case does "*not*" involve a "major" change or implicate the Highlights section. BIO.12, 17. As explained above, that theory remains divorced from reality.

Blackburn's footnoted effort to reconcile the Eleventh Circuit's decision with the relevant district court decisions is equally unavailing. He posits that *Brashear v. Pacira Pharmaceuticals, Inc.*, 2023 WL 3075403 (S.D. Ohio Apr. 25, 2023), hinted that a manufacturer could use the CBE process to make a substantive change to the Warnings and Precautions part of the Full Prescribing Information section without ever having to secure FDA approval. *See*

BIO.16 n.3. In fact, *Brashear* held that "*any*" such change to the Warning and Precautions part—which plainly encompasses one initiated through the CBE process—"*requires* a change to the … Highlights section," which in turn "*requires* prior FDA approval." 2023 WL 3075403, at *4 (emphases added). And while Blackburn seems to think that *Patton v. Forest Laboratories, Inc.*, 2018 WL 5269239 (C.D. Cal. Sept. 19, 2018), "does not" undermine his or the Eleventh Circuit's reading of the regulations, BIO16 n.3, that is only because he ignores *Patton*'s admonition that manufacturers "may not make any changes to the Highlights section of a drug's labeling without prior FDA approval"—a categorical statement that comes *immediately* after explicating the CBE process, 2018 WL 5269239, at *3.

Blackburn is thus left arguing that the decision below does not "place manufacturers in [a] 'damned-if-you-do, damned-if-you-don't position'" because it is "unpublished." BIO.11. That is an argument only plaintiffs' lawyers could love. Indeed, nothing prevents plaintiffs within the Eleventh Circuit from invoking the decision below to assert state-law claims premised on a manufacturer's failure to unilaterally alter language implicating Highlights sections. *See* 11th Cir. R. 36-2 (unpublished decisions "may be cited"). Thus, absent this Court's intervention, manufacturers will increasingly find themselves in the impossible position of facing the prospect of state-law liability (or at least *in terrorem* settlement pressure) for failing to take action that other courts have said they are prohibited from taking as a matter of federal law. That is why the pharmaceutical industry is urging this Court to step in. *See*

PhRMA.Amicus.Br.4 ("The Eleventh Circuit's ruling has the effect of creating a patchwork system of liability that will ultimately hamper manufacturer innovation and harm patient health."). And the undeniable fact that unpublished decisions can cause such mischief presumably explains why "plenty of unpublished decisions have been accepted for review and reversed by the Supreme Court." Hon. Danny J. Boggs & Brian P. Brooks, *Unpublished Opinions & the Nature of Precedent*, 4 Green Bag 2d 17, 20-21 (2000).

Blackburn's other purported vehicle problems face insurmountable roadblocks too. He protests that "[t]he petition challenges an interlocutory decision under a summary judgment standard." BIO.18. Such pleas have not moved the Court in prescription-drug-related preemption cases previously, *see, e.g.*, *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S.Ct. 1668, 1676 (2019) (granting certiorari after court of appeals vacated grant of summary judgment); *PLIVA*, 564 U.S. at 610-11 (granting multiple petitions in interlocutory posture), and this is hardly the time to chart a new course, as this case involves regulations governing "the *most important information* for prescribing [a] drug safely and effectively," 71 Fed. Reg. 3,922, 3,930-32 (Jan. 24, 2006) (emphasis added). Blackburn's only other argument is that "facts remain in dispute." BIO.18. But none of those disputes has anything to do with the question presented. Indeed, Blackburn forgets that the Eleventh Circuit remanded only after *rejecting* Shire's Highlights-based preemption defense *as a matter of law*. As a result, the only question presented here is a purely legal one: whether a state-law claim is preempted if it places a duty on a drug manufacturer to unilaterally change

FDA-approved language that appears in the Highlights section of a drug label. Because the answer to that question is plainly no, and because that question is of profound importance to the pharmaceutical industry and everyone affected by it, this Court should grant plenary review or summarily reverse.

CONCLUSION

The Court should grant the petition.

Respectfully submitted,

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