No. _____

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

PETITION FOR WRIT OF CERTIORARI

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QUESTION PRESENTED

This Court's preemption cases have long drawn a critical distinction when it comes to state-law claims implicating prescription-drug labels that have been approved by the Food and Drug Administration (FDA): While there may be room for such claims in circumstances where the manufacturer had the ability to unilaterally change the label, those claims cannot proceed when they are premised on the notion that the manufacturer was required as matter of state law to make a change that federal law prohibits it from making without the prior approval of the FDA. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011).

Respondent brought a state-law claim positing that petitioners should have unilaterally changed language that appears in the "Highlights" section of the label for one of their drugs. But petitioners were precluded as a matter of federal law from doing so, as the governing FDA regulations expressly state—twice—that the procedure that allows manufacturers to make certain changes to *other* aspects of their labels does not apply to changes implicating the Highlights section, which *always* require FDA preapproval. Yet the Eleventh Circuit nevertheless concluded that respondent's claim could go forward, while simply ignoring unambiguous regulatory text that prohibited petitioners from unilaterally making the changes that respondent insists they should have made.

The question presented is:

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.

PARTIES TO THE PROCEEDING

Petitioners (defendants-appellees below) are Shire US Inc. and Shire LLC.

Respondent (plaintiff-appellant below) is Mark Blackburn.

CORPORATE DISCLOSURE STATEMENT

Petitioners Shire US Inc. and Shire LLC in 2020 merged into Takeda Pharmaceuticals U.S.A., Inc. Shire US Inc. and Shire LLC therefore no longer exist. Takeda Pharmaceuticals U.S.A., Inc. is a subsidiary of Takeda Pharmaceutical Company Limited, a publicly traded company. No other publicly traded company directly or indirectly owns more than 10% of the shares of Takeda Pharmaceuticals U.S.A., Inc.

STATEMENT OF RELATED PROCEEDINGS

This case is directly related to the following proceedings in the U.S. Court of Appeals for the Eleventh Circuit and the Alabama Supreme Court:

Blackburn v. Shire U.S., Inc., No. 20-12258 (11th Cir.) (Nov. 7, 2022)

Blackburn v. Shire U.S., Inc., No. 20-12258 (11th Cir.) (Jan. 5, 2023) (denying rehearing)

Blackburn v. Shire U.S., Inc., No. 1210140 (Ala.) (Sept. 30, 2022)

Blackburn v. Shire U.S., Inc., No. 20-12258 (11th Cir.) (Nov. 29, 2021) (certifying questions)

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"[I]n recent years," this Court has "repeatedly" addressed "difficult pre-emption questions … in the prescription drug context" that have "vexed the Court" and "produced widely divergent views." *Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 492 (2013). This preemption case in the prescription-drug context is neither difficult nor vexing. To the contrary, in the decision below, the Eleventh Circuit simply misread regulations promulgated by the Food and Drug Administration (FDA) and allowed a state-law claim to proceed even though it is self-evidently preempted. That simple mistake has devastating consequences. Indeed, the decision below not only conflicts with this Court's preemption precedents, the plain language of the relevant regulations, the FDA's guidance regarding those regulations, and decisions from other lower courts, but also puts the pharmaceutical industry in the impossible position of facing liability for failing to make labeling changes that federal law precludes manufacturers from making without FDA approval. Whether by plenary review or summary reversal, this Court should not let that result stand.

The preemption question in this case concerns the labeling on prescription drugs. Before a manufacturer markets a drug, the FDA must approve every word that appears on the drug's label—most especially the language that appears in the "Highlights" section of the label, which summarizes the most important prescribing information. *See* 21 C.F.R. §201.57(a). Due to the overriding importance of the Highlights section, the FDA has promulgated a regulation that expressly states that, in all but two circumstances not

relevant here, any change to the Highlights section requires agency preapproval. *See id.* §314.70(b)(2)(v)(C). And although the FDA has promulgated another regulation—known as the "Changes Being Effected" (CBE) regulation—that permits manufacturers to make certain label changes *without* obtaining FDA preapproval, the CBE regulation expressly reiterates that changes to the Highlights section require FDA preapproval. *See id.* §314.70(c)(6)(iii).

Petitioners manufacture a drug called Lialda. The Highlights section of Lialda's label includes FDA-approved language recommending that patients undergo "periodic" evaluation of their kidney function while taking Lialda. After respondent took Lialda, and after a physician later diagnosed him with kidney disease, respondent brought a state-law failure-to-warn claim alleging that the FDA-approved recommendation on the Lialda label for "periodic" kidney testing is deficient and that petitioners should have utilized the CBE process to unilaterally alter the label to recommend testing at more specific intervals.

Petitioners moved to dismiss, arguing that respondent's claim is preempted because it would impose a duty on petitioners to violate federal law. Although the district court described respondent's arguments against preemption as "tenuous" and "shaky," it concluded that his claim escaped preemption just "barely" at the pleading stage, before ultimately going on to grant petitioners summary judgment on state-law grounds. App.128-29. Because the district court granted summary judgment on state-law grounds, it did not address petitioners' summary-

judgment arguments based on preemption. But after reversing on the state-law issue, the Eleventh Circuit turned to preemption, which petitioners advanced as an alternative ground for affirming the district court. Although the Eleventh Circuit recognized that unilateral changes to the Highlights section are prohibited under one FDA regulation, it nevertheless concluded that petitioners could have unilaterally altered that section under the CBE regulation. The court did so, however, without even *acknowledging*, let alone grappling with, the language in the CBE regulation that preserves the FDA-preapproval requirement for changes to the Highlights section.

The Eleventh Circuit's resolution of the preemption issue is plainly wrong, to put it mildly. As the FDA itself explained when it originally promulgated the regulations at issue here—and as it has stated on multiple occasions since—changes to the Highlights section *always* require FDA preapproval except in two situations that no one has ever claimed are relevant to this case. And this Court's preemption jurisprudence is clear that, if federal law prohibits a drug manufacturer from independently changing a label, then a state-law claim that would require the manufacturer to do just that is undoubtedly preempted. *See, e.g.*, *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011); *Mut. Pharm. Co.*, 570 U.S. 472. It thus comes as no surprise that industry observers have ranked the decision below as one of top-ten worst prescription-drug decisions issued by any federal or state court in all of 2022.

The Eleventh Circuit's decision is not just wrong, but consequential. Within the Eleventh Circuit,

manufacturers face a choice of either unilaterally changing the Highlights sections of their labels and risking exposure to sanctions from the FDA for violating agency regulations, or adhering to those agency regulations and risking exposure to state-law suits from enterprising plaintiff's lawyers. But outside the Eleventh Circuit, manufacturers are supposed to leave their Highlights sections untouched, as other courts have held that a change to the Highlights section is the kind of major change that requires FDA preapproval. And because manufacturers cannot change their Highlights sections on only a regional basis, all of this leaves manufacturers between a rock and a hard place. That state of affairs is untenable. This Court should intervene.

OPINIONS BELOW

The Eleventh Circuit's opinion after certification to the Alabama Supreme Court is unreported but available at 2022 WL 16729466. App.1-8. The Alabama Supreme Court's opinion is not yet reported but available at 2022 WL 4588887. App.11-49. The Eleventh Circuit's opinion before certification to the Alabama Supreme Court is reported at 18 F.4th 1310. App.50-70. The relevant district court opinions are unreported but available at 2020 WL 2840089, 2018 WL 2159927, 2017 WL 5013578, and 2017 WL 1833524. App.71-139.

JURISDICTION

The Eleventh Circuit issued its opinion on November 7, 2022, and denied a timely petition for rehearing on January 5, 2023. On March 29, 2023, Justice Thomas extended the time to file a petition for

certiorari until May 5, 2023. On April 25, 2023, Justice Thomas further extended the time to file a petition for certiorari until June 4, 2023. This Court has jurisdiction under 28 U.S.C. §1254(1).

CONSTITUTIONAL AND REGULATORY PROVISIONS INVOLVED

The Supremacy Clause of the U.S. Constitution, *see* Art. VI, cl. 2, and the relevant FDA regulations are reproduced at App.140-56.

STATEMENT OF THE CASE

A. Legal Background

Under the Federal Food, Drug, and Cosmetic Act, a drug manufacturer may not market a new drug in interstate commerce without obtaining FDA approval. *See* 21 U.S.C. §355(a). If the new drug is a brand-name drug, the manufacturer may obtain such approval only by filing a new drug application (NDA), which must contain an assortment of required information. *See id.* §355(b). Among other things, the NDA must include "the labeling proposed to be used for such drug," *id.* §355(b)(1)(A)(vi), and the FDA cannot approve an NDA without approving "the exact text in the proposed label," *Wyeth v. Levine*, 555 U.S. 555, 568 (2009); *see* 21 U.S.C. §355(d).

"Although we commonly understand a drug's 'label' to refer to the sticker affixed to a prescription bottle," the term "label" in this regulatory context "refers more broadly to the written material that is sent to the physician who prescribes the drug and the written material that comes with the prescription bottle when the drug is handed to the patient at the pharmacy." *Merck Sharp & Dohme Corp. v. Albrecht*,

139 S.Ct. 1668, 1672 (2019); *see* 21 U.S.C. §321(m) (defining "labeling"). Thus, the label is "often lengthy" and includes a bevy of "detailed information about the drug's medical uses and health risks." *Merck*, 139 S.Ct. at 1672-73. That detailed information is found in the "Full prescribing information" section of the label. *See* 21 C.F.R. §201.57(b)-(c).

In 2006, however, in an effort "to improve the accessibility, readability, and usefulness of information in prescription drug labeling and reduce the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information," the FDA promulgated a rule—commonly known as the Physician Labeling Rule—that requires manufacturers to include a "Highlights" section on the label, which precedes the Full Prescribing Information section and "contains a summary of the most important information for prescribing the drug safely and effectively." 71 Fed. Reg. 3,922, 3,930-32 (Jan. 24, 2006). The requirements relating to the Highlights section are codified in 21 C.F.R. §201.57(a), which specifies that the Highlights section must summarize sections in the Full Prescribing Information—including, as relevant here, the "most clinically significant information" found in the "Warnings and precautions" section. 21 C.F.R. §201.57(a)(10); *see also id.* §201.57(c)(6) (Warnings and Precautions section of Full Prescribing Information).

As the FDA has explained, the Highlights section is an "essential element" of the label that serves to "improve the accessibility, readability, and usefulness of information in prescription drug labeling and

reduce[s] the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information." 71 Fed. Reg. at 3,930-31. Considerable time and energy therefore go into the approval of the Highlights section itself; indeed, the FDA has described "developing Highlights" as one of the single "most challenging aspects" of prescription-drug regulation. FDA, *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements* 2 (Feb. 2013), https://bit.ly/3VPCIhS.

After the FDA approves an NDA and the text of a label, "preapproval by the FDA" is "ordinarily … necessary to change a label." *PLIVA*, 564 U.S. at 614. As the principal FDA regulation governing that process explains, "[c]hanges in labeling" are generally classified as "major changes," and major changes "requir[e] supplement submission and approval [from the FDA] prior to distribution of the product made using the change." 21 C.F.R. §314.70(b)(2)(v)(A). That supplement submission is known as a "Prior Approval Supplement." *Id.* §314.70(b)(3). Subsection (b)(2) of the preapproval regulation also identifies certain categories of labeling changes that are *always* treated as "major changes" that require FDA preapproval. Underscoring the importance of the Highlights section, changes to that section are included on that list: Paragraph (b)(2)(v)(C) states that "[a]ny change to the information required by §201.57(a) of this chapter"—*i.e.*, any change implicating the Highlights section—is a "major change[]" that requires a Prior Approval Supplement. *Id.* §314.70(b)(2)(v)(C). That rule is subject to only two enumerated exceptions, one

for the removal of a "recent major change" from the Highlights section because it no longer qualifies as recent and the other for a change to the most recent revision date of the labeling. *See id.* §314.70(b)(2)(v)(C)(1)-(2).

While this federal regulatory regime creates a default rule that approval is needed for label changes, there is a provision of the regime "that permits a manufacturer to make certain changes to its label before receiving the agency's approval." *Wyeth*, 555 U.S. at 568; *see also, e.g.*, *PLIVA*, 564 U.S. at 614-15. That provision—known as the "Changes Being Effected," or CBE, regulation, which is found at 21 C.F.R. §314.70(c)(6)(iii)—is specifically exempted from the Prior Approval Supplement requirement. *See* 21 C.F.R. §314.70(b)(2)(v)(A) (explaining that "[c]hanges in labeling" require a Prior Approval Supplement, "except those described in paragraph[] (c)(6)(iii) … of this section"). Thus, under the CBE regulation, it is permissible for a manufacturer that has "newly acquired information" to unilaterally revise the label to (among other things) "add or strengthen a contraindication, warning, precaution, or adverse reaction." *Id.* §314.70(c)(6)(iii)(A); *see also id.* §314.3(b) (defining "[n]ewly acquired information"); *Wyeth*, 555 U.S. at 582-83 (Thomas, J., concurring).

In keeping with exalted status of the Highlights section, however, the CBE regulation explicitly prohibits the CBE process from being utilized to make changes that implicate the Highlights section of the label. In particular, the CBE regulation states that manufacturers may utilize the CBE process to make "[c]hanges in the labeling to reflect newly acquired

information, *except for changes to the information required in §201.57(a) of this chapter*"—*i.e.*, the Highlights section—"*which must be made under paragraph (b)(2)(v)(C) of this section.*" *Id.* §314.70(c)(6)(iii)(C) (emphasis added)). As noted, paragraph (b)(2)(v)(C) is the paragraph deeming "[a]ny change to the information required by §201.57(a)"—*i.e.*, the Highlights regulation—a "major change[]" that "requir[es a] supplement submission and approval prior to distribution of the product made using the change." *Id.* §314.70(b)(2)(v)(C).

As the FDA therefore summarized things when it originally promulgated the Physician Labeling Rule in 2006, "[u]nder §§314.70(b)(2)(v)(C) *and* (c)(6)(iii)"—*i.e.*, both the paragraph deeming changes to the Highlights section a "major change" and the CBE regulation—manufacturers "are required to obtain prior approval of any labeling changes to Highlights, except for editorial or similar minor changes, including removal of a listed section(s) from 'Recent Major Changes' or a change to the most recent revision date of the labeling." 71 Fed. Reg. at 3,932 (emphasis added).

All of that has important consequences under this Court's preemption jurisprudence, as the Court has long drawn a distinction between labeling changes that can be made unilaterally pursuant to the CBE process, and labeling changes that can be made only with prior approval of the FDA. While the Court has generally held that state-law failure-to-warn claims are not preempted when a manufacturer could have made the labeling change required by state law pursuant to the CBE process, *see Wyeth*, 555 U.S. at

573; *Merck*, 139 S.Ct. at 1678, it has concluded that state-law claims cannot go forward when they turn on an allegation that a manufacturer was required as a matter of state law to make a labeling change that federal law prohibits it from making without prior FDA approval, *see PLIVA*, 564 U.S. at 618-24. As the governing regulations make abundantly clear—twice—that is precisely the situation when it comes to changes to the Highlights section of a label.

B. Factual and Procedural Background

1. Petitioners Shire US Inc. and Shire LLC (collectively, Shire) manufacture a brand-name drug called Lialda, which the FDA first approved in 2007. *See* App.2, 115. Lialda is one of multiple FDA-approved mesalamine-containing brand-name drugs for the treatment of ulcerative colitis, a chronic inflammatory bowel disease. Due to a risk of kidney impairment associated with Lialda, the Highlights section of Lialda's label has included the following FDA-approved recommendation under the heading "Warnings and Precautions": "Renal impairment may occur. Assess renal function at the beginning of treatment and periodically during treatment. (5.1)." D.Ct.Dkt.41-2 at 2. The reference to "5.1" at the end of that recommendation refers to §5.1 of the label's Full Prescribing Information, which is the unabridged "Warnings and Precautions" section. *See* 21 C.F.R. §201.56(d)(3) ("Any reference in Highlights to information appearing in the full prescribing information must be accompanied by the identifying number (in parentheses) corresponding to the location of the information in the full prescribing information."). The Warnings and Precautions section

similarly states: "It is recommended that patients have an evaluation of renal function prior to initiation of Lialda therapy and periodically while on therapy." D.Ct.Dkt.41-2 at 3. One way to evaluate renal function is by conducting a blood test on a patient—specifically, by measuring the amount of creatinine in the blood. *See* App.53.

Respondent Mark Blackburn is a golf instructor who "reported persistent gastrointestinal issues" to one of his golf students, who doubled as Blackburn's "*de facto* primary care physician." App.52. That physician later referred Blackburn to a gastroenterologist, who concluded that he did not need to order initial bloodwork before treating Blackburn. *See* App.52. Eventually, the gastroenterologist diagnosed Blackburn with Crohn's disease, the "'sister' disease" to ulcerative colitis. App.52. As treatment, Blackburn's gastroenterologist in October 2013 prescribed him Lialda. App.52.

Although the gastroenterologist scheduled a follow-up appointment with Blackburn for two months thereafter, "either he or Blackburn cancelled it." App.53. Blackburn later moved to a different area, which prompted the gastroenterologist to provide a referral to another doctor. App.53. But Blackburn "never followed up." App.53. The gastroenterologist continued to allow Blackburn to fill Lialda prescriptions in the meantime, but Blackburn's "renal function went unmonitored during that time." App.53. In April 2015, Blackburn finally underwent a blood test, and that test revealed an excessive amount of creatinine in the blood. *See* App.54. A physician later

diagnosed Blackburn with stage-four kidney disease. *See* App.54.

2. Blackburn sued Shire in June 2016, contending that Lialda was a proximate cause of his kidney disease. *See* App.55. As relevant here, the operative complaint (the first amended complaint) included a state-law failure-to-warn claim. Blackburn did not and could not deny that Lialda's FDA-approved label warned—twice—that "[r]enal impairment may occur," and hence recommended—again, twice—that prescribing physicians "[a]ssess renal function at the beginning of treatment and periodically during treatment. (5.1)." D.Ct.Dkt.41-2 at 2; *see also* D.Ct.Dkt.41-2 at 3 ("It is recommended that patients have an evaluation of renal function prior to initiation of Lialda therapy and periodically while on therapy."). But he nevertheless contended that the label provided "a defective and unsafe instruction for safe use of Lialda" because it recommended kidney renal function assessment "periodically" instead of at specified intervals. D.Ct.Dkt.41 at 4. In Blackburn's view, Shire should have unilaterally altered the label to capture a concept that Blackburn described as "Proper Interval Testing"—*i.e.*, "evaluation of renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year." D.Ct.Dkt.41 at 5.

Blackburn received inspiration for that "Proper Interval Testing" theory from the labels affixed to different drugs marketed in the United Kingdom. *See* App.74. But Blackburn's preferred warning does not appear in the labeling of any mesalamine product

approved by FDA. Instead, the labeling for all of those FDA-approved products contains the same recommendation for "periodic" renal assessment found in Lialda's labeling. *See, e.g.*, *ASACOL HD*, DailyMed (last updated Nov. 16, 2022), https://rb.gy/xasi3; *DELZICOL*, DailyMed (last updated Nov. 16, 2022), https://rb.gy/4rgkp; *APRISO*, DailyMed (last updated Nov. 7, 2022), https://rb.gy/nk75e.

Shire moved to dismiss, arguing that federal law preempts Blackburn's failure-to-warn claim because it would require a prohibited unilateral change to the Highlights section of Lialda's label. *See* D.Ct.Dkt.45. at 13-15. The district court concluded that Blackburn's claim survived dismissal—but "just barely." App.129. As the court explained, the recommendation for "periodic" renal-function testing appeared both in the Highlights section and the Full Prescribing Information section of Lialda's label. App.129. And the court agreed that federal law prohibited Shire from unilaterally altering the Highlights section. App.124-27. But it accepted for purposes of the motion to dismiss Blackburn's theory that Shire "could have changed the recommendation for 'periodic' testing in the FPI section" through the CBE process, "but left [the] recommendation for 'periodic' testing in the Highlights section," App.128-29—even though the entire point of the Highlights section is to "*summarize*[] the information from the FPI," not to provide competing information, 71 Fed. Reg. at 3,931 (emphasis added). In doing so, however, the court acknowledged that this "tenuous" theory was at odds with Blackburn's own argument "that the term 'periodic' is defective because it typically connotes semi-annual or annual testing." App.128-29. And it

cautioned that this internal conflict between Blackburn's arguments "may place [him] on shaky ground going forward." App.129.

3. After more than three additional years of litigation, the district court granted Shire summary judgment on Blackburn's failure-to-warn claim on state-law grounds. *See* App.71. But after Blackburn appealed, and after the Eleventh Circuit certified state-law questions to the Alabama Supreme Court, *see* App.50, the court of appeals reversed.[1]

After resolving the state-law issues, the Eleventh Circuit addressed Shire's argument regarding federal preemption, which Shire advanced as an alternative ground for affirming the district court's judgment. The court acknowledged that, under 21 C.F.R. §314.70(b)(2)(V)(C), FDA preapproval is "require[d]" for "'[a]ny change to the information required by' the Highlights section." App.7-8. But the court nonetheless held that Shire could have independently revised the Highlights section of its label *without* FDA preapproval.

In reaching that puzzling conclusion, the court noted that, under 21 C.F.R. §314.70(b)(2)(V)(A), "[c]hanges in labeling … described in paragraph[] (c)(6)(iii)" of 21 C.F.R. §314.70—*i.e.*, changes made under the CBE regulation—are "exempt[]" from the FDA-preapproval requirement, which it criticized Shire for purportedly "overlook[ing]." App.7-8. But the court inexplicably omitted from its partial quotation of the CBE regulation the language that

[1] The Eleventh Circuit rejected Blackburn's effort to reinstate his three other claims. *See* App.58-60.

goes on to expressly exempt from *its* scope "changes to the information required in §201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section)," 21 C.F.R. §314.70(c)(6)(iii)—*i.e.*, changes to the Highlights section. The court thus erroneously concluded that Shire could have used the CBE process to unilaterally alter a part of its label, even though the CBE regulation itself prohibited Shire from unilaterally making that alteration.

Shire filed a petition for rehearing to provide the Eleventh Circuit an opportunity to correct its glaring error. The court denied the petition.

REASONS FOR GRANTING THE PETITION

This Court regularly grants certiorari in cases that raise important preemption questions in the prescription-drug context. *See, e.g.*, *Wyeth v. Levine*, 552 U.S. 1161 (2008); *PLIVA, Inc. v. Mensing*, 562 U.S. 1104 (2010); *Mut. Pharm. Co. v. Bartlett*, 568 U.S. 1045 (2012); *Merck Sharp & Dohme Corp v. Albrecht*, 138 S.Ct. 2705 (2018). The Court should do so again here, as the Eleventh Circuit's decision effectively nullifies FDA regulations that address how drug manufacturers should go about communicating the most important prescribing information and thereby exposes manufacturers to state-law claims that are indisputably preempted. As a result, it leaves manufacturers in an impossible position, unable to eliminate a risk of significant state tort-law liability without violating federal law. That is precisely what federal preemption is supposed to prevent.

This Court's precedent leaves no doubt that a state-law claim is preempted if it places a duty on a drug manufacturer to take unilateral action that

federal law prohibits. That describes Blackburn's state-law failure-to-warn claim to a tee. His claim is premised on the proposition that Shire should have independently altered language that appears in the Highlights section of Lialda's label, yet FDA regulations state plain as day—twice—that a manufacturer cannot change that language without obtaining FDA preapproval. The Eleventh Circuit acknowledged that one FDA regulation says as much, but it ultimately concluded that the CBE regulation trumps that regulation. But as the text of the CBE regulation makes plain, and as the FDA has confirmed time and again, the CBE regulation *itself* states that changes to the Highlights section require FDA preapproval. The court below concluded otherwise only by pretending as though that language did not exist.

The Eleventh Circuit's profound misreading of the governing regulations leaves drug manufacturers in an impossible position. On the one hand, they will now face increased pressure to make unilateral and potentially confusing revisions to the Highlights sections of their drug labels, even though the FDA has admonished that such unilateral changes are impermissible precisely because the need for agency oversight is paramount in this context. On the other hand, manufacturers that decline to make these unilateral changes will face the prospect of tort litigation that will only increase costs for the pharmaceutical industry—to the ultimate detriment of consumers. Making matters worse, numerous other federal courts have correctly held that *all* major changes to prescription-drug labeling—which the regulations themselves define to include changes to

the Highlights section—require FDA preapproval, leaving manufacturers barred by federal law in some states from making changes that other states may now demand. That situation is untenable—especially in the context of what the FDA itself has deemed the most important information for prescribing drugs safely and effectively.

There is a better way. The Court should grant plenary review or summarily reverse and make clear once and for all that unilateral changes to the Highlights section are impermissible and that state-law claims embodying the contrary view are preempted. Simply put, a decision that failed to even acknowledge the most critical language in regulations governing one of the most critical aspects of drug labels should not be the last word on an issue of this magnitude.

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.

1. The Supremacy Clause provides that the laws and treaties of the United States "shall be the supreme Law of the Land … any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const., art. VI, cl. 2. In light of the Supremacy Clause, it is well-settled that, "[w]here state and federal law 'directly conflict,' state law" is preempted and "must give way." *PLIVA*, 564 U.S. at 617; *see also, e.g.*, *M'Culloch v. Maryland*, 17 U.S. (4 Wheat.) 316, 427 (1819); *Maryland v. Louisiana*, 451 U.S. 725, 746 (1981); *Gade v. Nat'l Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 108 (1992). In short, if "it is 'impossible for a

private party to comply with both state and federal requirements,'" then federal law prevails. *Bartlett*, 570 U.S. at 480; *see also, e.g.*, *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990); *Fla. Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963).

Applying those principles in the prescription-drug context, this Court has repeatedly drawn a critical distinction: While state tort-law claims may be able to proceed in instances where a manufacturer had the ability to make the changes at issue to its label on its own through the CBE process, they may *not* proceed when, as here, the CBE process was unavailable and FDA preapproval was required. In *PLIVA*, for instance, the plaintiffs argued that state law required generic drug manufacturers to "use a different, stronger label than the label they actually used." 564 U.S. at 617. More precisely, the plaintiffs asserted that the CBE regulation "allowed the Manufacturers to change their labels when necessary" and that they "need not wait for preapproval by the FDA, which ordinarily is necessary to change a label." *Id.* at 614. In response, this Court explained that "[t]he question for 'impossibility' is whether the private party could independently do under federal law what state law requires of it." *Id.* at 620. Under that standard, the Court easily found the plaintiffs' claims preempted because "[f]ederal drug regulations, as interpreted by the FDA, prevented the Manufacturers from independently changing their generic drugs' safety labels," which had to "be the same at all times as the corresponding brand-name drug labels." *Id.* at 617-18.

It made no difference that the manufacturers "could have asked the FDA for help" in trying to

change the label. *Id.* at 619. That argument, the Court noted, "would render conflict pre-emption largely meaningless because it would make most conflicts between state and federal law illusory," as "[w]e can often imagine that a third party or the Federal Government *might* do something that makes it lawful for a private party to accomplish under federal law what state law requires of it." *Id.* at 620. Instead, the Court emphasized, the preemption inquiry is more straightforward: "[W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency," state-law claims are "preempted"—full stop. *Id.* at 623-24.

The Court reached a similar conclusion in *Bartlett*, which likewise addressed a state-law claim that would have "effectively required [a generic drug manufacturer] to change [a drug's] labeling to provide stronger warnings." 570 U.S. at 475. The Court had no trouble finding preemption there too. As the Court put it, state-law claims that "place a duty on manufacturers to render a drug safer by … altering its labeling" are preempted if federal law "prohibit[s] manufacturers from unilaterally altering … labeling." *Id.* at 490. And because federal law "prohibited" generic drug manufacturers "from making any unilateral changes to a drug's label," "it was impossible for [the manufacturer] to comply with both its state-law duty to strengthen the warnings on [the] label and its federal-law duty not to alter [the] label." *Id.* at 477, 480. Indeed, this Court has applied the same basic principles to conclude that state-law claims requiring different labels are preempted even

when the CBE process is available to a manufacturer as a matter of *law*, but not as a matter of *fact* because the FDA has rejected the very change that state law would command. *See Wyeth*, 555 U.S. at 573; *Merck*, 139 S.Ct. at 1678. *A fortiori*, such claims cannot proceed when federal law forecloses resort to the CBE process entirely.

2. All of that should have made the preemption question in this case very straightforward. Blackburn contends that the FDA-approved kidney-related warning on Lialda's label recommending "periodic" evaluation of renal function "constitutes a defective and unsafe instruction for safe use of LIALDA" and that "an appropriate label for LIALDA" under state law should have included a warning akin to what appears on the labels of other drugs in the United Kingdom: "instructions recommending 'evaluation of renal function by a simple serum (blood) test of creatinine levels on a monthly basis for the first three months after initiation of therapy and then on a quarterly basis for at least one year.'" App.75. But that is precisely the kind of label change that Shire could *not* have made "unilaterally" or "independently" under federal law. *PLIVA*, 564 U.S. at 620.

That is because the FDA-approved "periodic" renal-function recommendation is found in the Highlights section of Lialda's label. *See* D.Ct.Dkt.41-2 at 2. And FDA regulations make crystal clear that virtually "[a]ny change to the information required by §201.57(a)"—*i.e.*, virtually any change to information required in the Highlights section—is a "major change[]" "requiring supplement submission and approval prior to distribution of the product made

using the change," 21 C.F.R. §314.70(b)(2)(v)(C)—*i.e.*, "a Prior Approval Supplement … , which requires FDA approval before the changes are made," *Merck*, 139 S.Ct. at 1682 (Thomas, J., concurring); *see also id.* at 1685 (Alito, J., concurring in the judgment). The FDA has recognized only two minor "exceptions" to that rule: (1) when a manufacturer "remov[es]" from the Highlights section the listing of a recent major change because it is no longer recent and (2) when there is a "[c]hange[] to the most recent revision date of the labeling." 21 C.F.R. §314.70(b)(2)(v)(C). Because it is undisputed that neither of those exceptions is applicable here, it follows ineluctably that Blackburn's state-law claim "imposed a duty on [Shire] *not* to comply with federal law"—which is just the kind of claim that falls in the heartland of this Court's FDA preemption jurisprudence. *Bartlett*, 570 U.S. at 475.

3. The Eleventh Circuit's contrary conclusion is inexplicable. The court acknowledged the "default rule" that, "[o]nce a label is approved, the manufacturer is generally not permitted to alter it without the [FDA's] approval." App.4. And the court conceded that 21 C.F.R. §314.70(b)(2)(v)(C) explicitly "requires a supplement for '[a]ny change to the information required by' the Highlights section." App.7. But it then accused Shire of "overlook[ing]" 21 C.F.R. §314.70(b)(2)(v)(A), which "exempts '[c]hanges in labeling … described in paragraph[] (c)(6)(iii)" of 21 C.F.R. §314.70 from the FDA-preapproval requirement—*i.e.*, changes covered by the CBE regulation. App.7.

In reality, it is the Eleventh Circuit that appears to have overlooked a critical aspect of the governing

regulations. Paragraph (c)(6)(iii) of 21 C.F.R. §314.70 *itself* states in no uncertain terms that the CBE process is *not* available for changes implicating the Highlights section of a label: "[T]he holder of an approved NDA may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change" for "[c]hanges in the labeling to reflect newly acquired information, *except for changes to the information required* [*by*] *§201.57(a) of this chapter (which must be made under paragraph (b)(2)(v)(C) of this section).*" 21 C.F.R. §314.70(c)(6)(iii) (emphasis added). As the italicized language makes clear beyond cavil, there is only one way to alter the Highlights section: by proceeding under 21 C.F.R. §314.70(b)(2)(v)(C), which bars a manufacturer from altering the Highlights section unless and until the FDA approves a Prior Approval Supplement.

If there were any doubt about that pellucid text, it would be eliminated by the FDA's repeated pronouncements that Shire's understanding is correct. To begin with, when the agency originally promulgated the Physician Labeling Rule in 2006, it expressly addressed in the preamble to that rule both 21 C.F.R. §314.70(b)(2)(v)(C)—*i.e.*, the regulation governing changes to the Highlights section—and 21 C.F.R. §314.70(c)(6)(iii)—*i.e.*, the CBE regulation. And far from embracing the Eleventh Circuit's theory that the CBE regulation reigns supreme, the agency instead said that, under *both* "§§314.70(b)(2)(v)(C) *and* (c)(6)(iii)," drug manufacturers "are required to obtain prior approval of any labeling changes to Highlights," except in two limited circumstances not relevant here. 71 Fed. Reg. at 3,932 (emphasis added); *see also id.* at 3,934 (explaining, in a section addressing preemption,

that "a sponsor may not use a CBE supplement to make most changes to Highlights"). The agency later reinforced the point during another rulemaking in 2008, when it explained that "Highlights cannot be amended by a CBE supplement." 73 Fed. Reg. 2,848, 2,850 n.4 (Jan. 16, 2008). And the agency did the same thing yet again during a 2013 rulemaking, when it explained that "changes to the information required in the Highlights … are classified as a 'major change' that must be made by a prior approval supplement." 78 Fed. Reg. 67,985, 67,993 (Nov. 13, 2013).

Unsurprisingly, commentators likewise have long recognized that changes to the Highlights section cannot be made without first securing FDA approval, which makes state-law claims requiring such changes preempted under a straightforward application of *PLIVA* and *Bartlett*. *See, e.g.*, Arameh O'Boyle & Clancy Galgay, *"Newly Acquired Information" and Federal Preemption Defenses in Pharmaceutical Products Liability Cases*, Am. Bar Ass'n (June 28, 2018), https://bit.ly/3I2nlga ("[I]f the claims relate to … the 'Highlights' section of the label, they do not fall under the CBE and must be preempted. 21 C.F.R. §314.70(b)(2)(v)(C)."); 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 & n.79 (2010) (citing 21 C.F.R. §§314.70(b)(2)(v)(C) and (c)(6)(iii)) (explaining that "FDA regulations require submission of a prior approval supplement for any change to the Highlights information, except for certain minor changes"). Yet that is precisely the type of claim that the decision below allows to proceed.

In short, there is no denying that the Eleventh Circuit's decision simply reads language out of the regulation, in contravention of bedrock principles of textual interpretation, and allows state-law claims that are obviously preempted to nevertheless move forward. *See, e.g.*, *Nat'l Ass'n of Home Builders v. Defs. of Wildlife*, 551 U.S. 644, 669 (2007) ("caution[ing] against reading a text in a way that makes part of it redundant"); *Leocal v. Ashcroft*, 543 U.S. 1, 12 (2004) ("[W]e must give effect to every word of a [text] wherever possible[.]"). That readily explains why leading commentators in the field have derided the decision below as "plain wrong," "fatally flawed," and "simply a mistake." James M. Beck, Blackburn—*That's Just Plain Wrong*, Drug & Device Law (Dec. 19, 2022), https://bit.ly/3TlFWs4. In fact, the decision below is so "disastrous" and "flat-out wrong" that it has earned the ignominious distinction as one of "the ten worst prescription drug/medical device decisions of 2022." 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.

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

The Eleventh Circuit's decision is both profoundly wrong and profoundly disruptive, as it departs from the settled understanding not just of the FDA, but of numerous courts throughout the country. Several courts of appeals have correctly recognized that, "if a change fits under *any* of the categories listed in section

(b)(2), that change … require[es] FDA pre-approval." *Gustavsen v. Alcon Lab'ys, Inc.*, 903 F.3d 1, 11 (1st Cir. 2018) (emphasis added); *see also, e.g.*, *Ignacuinos v. Boehringer Ingelheim Pharms. Inc*, 8 F.4th 98, 102 (2d Cir. 2021) ("[W]e agree with the First Circuit[.]"); *Yates v. Ortho-McNeil-Janssen Pharms., Inc.*, 808 F.3d 281, 298 (6th Cir. 2015) ("Yates's post-approval design defect claim is clearly preempted by federal law. FDA regulations provide that once a drug, whether generic or brand-name, is approved, the manufacturer is prohibited from making any major changes[.]"); *Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.*, 586 F.3d 500, 510 (7th Cir. 2009) ("[T]he changes Schering wants the defendants to make in their labeling … are major changes, requiring the FDA's approval."). No other circuit recognizes an exception to subsection (b)(2)(v)(C) for changes to the Highlights section.

On top of that, multiple district courts have addressed preemption questions involving the Highlights section in particular, and in stark contrast to the Eleventh Circuit, they have repeatedly concluded that changes implicating that section require FDA preapproval. *See, e.g.*, *Brashear v. Pacira Pharms., Inc.*, 2023 WL 3075403, at *4 (S.D. Ohio Apr. 25, 2023) ("[A]ny change to the Highlights section requires prior FDA approval of a supplement to the drug's labeling before distribution can occur."); *Patton v. Forest Lab'ys, Inc.*, 2018 WL 5269239, at *3 (C.D. Cal. Sept. 19, 2018) ("NDA holders may not make any changes to the Highlights section of a drug's labeling without prior FDA approval."). Again, no other circuit court has permitted unilateral changes to the Highlights section.

The Eleventh Circuit's opinion is impossible to square with these decisions and has the effect of pulling drug manufacturers in diametrically opposed regulatory directions. Within the Eleventh Circuit, manufacturers are expected to utilize the CBE process to make unilateral changes to the Highlights sections of their drug labels—even if that means facing repercussions from the FDA for failing to comply with regulations specifically prohibiting those very kinds of changes. And those manufacturers that fail to get in line expose themselves to time-consuming and expensive state-law tort suits—as this seven-year-long (and counting) case vividly illustrates. Meanwhile, in other circuits, manufacturers are expected to refrain from utilizing the CBE process in the exact same circumstances. This dynamic is unsustainable. After all, manufacturers do not and cannot make labels for use only within the Eleventh Circuit or any other region; they make drug labels for use on a national basis. The decision below thus places manufacturers in an impossible damned-if-you-do, damned-if-you-don't position.

As this Court has repeatedly recognized, "[t]he importance of the pre-emption issue" to the pharmaceutical industry can be reason enough to grant certiorari. *Wyeth*, 555 U.S. at 563; *see PLIVA*, 564 U.S. at 610-11; *cf. Merck*, 139 S.Ct. at 1676. This case is no exception. A muddled regulatory scheme serves no one's interests, but a muddled regulatory scheme that implicates the Highlights section of drug labels is particularly intolerable. The FDA has emphasized that the Highlights section is an "essential element" of its regulatory mission because it "improve[s] the accessibility, readability, and

usefulness of information in prescription drug labeling and reduce[s] the number of adverse reactions resulting from medication errors due to misunderstood or incorrectly applied drug information." 71 Fed. Reg. at 3,930-31. Unsurprisingly given the high stakes, producing a Highlights section is no mean feat. As the FDA has candidly acknowledged, "developing Highlights" is one of the single "most challenging aspects" of prescription-drug regulation. FDA, *Guidance for Industry*, *supra*, at 2. That is precisely why the FDA has declared it "essential" that it "review and approve … proposed changes to the information in Highlights"—and that manufacturers refrain from taking matters into their own hands without the agency's expert input. 71 Fed. Reg. at 3,932. Yet the decision below not only permits—but requires—manufacturers to do exactly that.

In short, the Eleventh Circuit's decision upends a carefully calibrated scheme that has prevailed for nearly two decades. The end result is to throw into disarray a regulatory framework governing how manufacturers should go about communicating the most important information for prescribing drugs safely and effectively. That has nothing to recommend it. Indeed, the decision so plainly misreads the relevant regulations, and reaches a result so plainly at odds with this Court's cases, that the Court may wish to consider summary reversal. In all events, whether through plenary review or summary reversal, this Court should not leave the Eleventh Circuit's decision as the last word on an FDA preemption question of surpassing importance.

CONCLUSION

For the foregoing reasons, this Court should grant the petition.

Respectfully submitted,

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