**No. _____**

In the

Supreme Court of the United States

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GLAXOSMITHKLINE LLC,

*Petitioner*,

v.

UNITED FOOD AND COMMERCIAL WORKERS LOCAL 1776 AND PARTICIPATING EMPLOYERS HEALTH AND WELFARE FUND AND J.B. HUNT TRANSPORT SERVICES, INC.,

*Respondents*.

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

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# PETITION FOR WRIT OF CERTIORARI

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## QUESTION PRESENTED

Federal law preempts state-law tort claims challenging the adequacy of a brand-name drug's warnings whenever the drug's manufacturer "fully informed the FDA of the justifications for the warning [allegedly] required by state law and . . . the FDA, in turn, informed the drug manufacturer that the FDA would not approve changing the drug's label to include that warning." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1678 (2019). That is precisely what happened here: (A) Petitioner GlaxoSmithKline ("GSK") asked the FDA to approve new cardiovascular warnings for its diabetes drug Avandia; (B) GSK provided the FDA with all material information in GSK's possession that justified the change at the time of the FDA's decision; and (C) the FDA responded by denying GSK's proposed warning because the evidence did not support it.

The Third Circuit held, however, that GSK did not "fully inform[]" the FDA of the justification for its label change—and so claims against GSK are not preempted—for two related reasons. First, it faulted GSK for not providing emerging data that did not exist at the time of the FDA's rejection. Then, to make matters worse, it concluded that GSK should also have submitted other data that FDA regulations affirmatively discourage companies from providing, and which, once provided, had no impact on the FDA's decision. The result is that the Third Circuit has effectively closed the door to conflict preemption that *Merck* expressly left open

The question presented is:

Whether federal law preempts state-law tort

claims where a brand-name drug's manufacturer provides the FDA with all material information in its possession at the time the FDA resolves the manufacturer's label change request, or whether applicants must also provide the FDA with data and information that does not exist or that, under binding regulations, the FDA does not want and that the FDA did not rely upon in reaching its decision.

## PARTIES TO THE PROCEEDING

Petitioner, and Defendant-Appellee below, is GlaxoSmithKline LLC ("GSK").

Respondents are Plaintiff-Appellants United Food and Commercial Workers Local 1776, Participating Employers Health and Welfare Fund, and J.B. Hunt Transport Services, Inc.

## CORPORATE DISCLOSURE STATEMENT

GlaxoSmithKline LLC is owned, through several levels of wholly owned subsidiaries, by GlaxoSmithKline plc, a publicly traded public limited company organized under the laws of England. To the knowledge of GlaxoSmithKline LLC and GlaxoSmithKline plc, no publicly held company owns ten percent or more of GlaxoSmithKline plc's outstanding stock. However, BNYMellon (BNYM) acts as a Depositary for Ordinary Share American Depositary Receipts representing shares in GlaxoSmithKline plc. In that capacity, BNYM is the holder of more than ten percent of the outstanding shares in GlaxoSmithKline plc.

## STATEMENT OF RELATED PROCEEDINGS

This case arises from and is related to the following proceeding in the U.S. District Court for the Eastern District of Pennsylvania and the U.S. Court of Appeals for the Third Circuit:

- *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, No. 07-MD-1871 (E.D. Pa. Oct. 23, 2013), ECF No. 3618 (opinion denying GSK's motion to dismiss);
- *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, 804 F.3d 633, 646 (3d Cir. 2015) (opinion affirming district court's denial of GSK's motion to dismiss);
- *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, No. 07-MD-1871 (E.D. Pa. Dec. 7, 2017), ECF No. 5152 (opinion granting GSK's motion for summary judgment on preemption grounds);
- *In re Avandia Mktg., Sales Practices & Prod. Liab. Litig.*, No. 07-MD-1871 (E.D. Pa. May 31 & July 24, 2018), ECF Nos. 5201 & 5220 (orders granting in part and denying in part GSK's sealing motions);
- *In re Avandia Mktg., Sales Practices and Prods. Liab. Litig.*, 924 F.3d 662, 680 (3d Cir. 2019) (opinion vacating district court's sealing orders);
- *In re Avandia Mktg., Sales & Prod. Liab. Litig.*, 945 F.3d 749 (3d Cir. 2019) (opinion reversing district court's grant of summary judgment in favor of GSK).

There are no other proceedings in state or federal trial or appellate courts directly related to this case within the meaning of this Court's Rule 14.1(b)(iii).

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## PETITION FOR WRIT OF CERTIORARI

In *Wyeth v. Levine*, this Court held that federal law preempts state-law failure-to-warn claims against a brand-name drug manufacturer only where the manufacturer can provide "clear evidence that the FDA would not have approved a change to [the drug's] label" had the manufacturer attempted unilaterally to make one. 555 U.S. 555, 571, 573 (2009). But *Wyeth* itself gave little guidance about how to apply its "clear evidence" standard, and the lower courts struggled for years to formulate a cogent and consistent approach. So last Term, this Court sought to clear the water by holding that, under *Wyeth*, "clear evidence" that a label change would have been unavailing "is evidence that shows the court that the drug manufacturer fully informed the FDA of the justifications for the warning [allegedly] 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*, 139 S. Ct. 1668, 1672 (2019).

A straightforward application of *Merck* should have dictated the outcome here, where (A) GSK asked the FDA to approve new cardiovascular warnings for its diabetes drug Avandia; (B) GSK's submissions provided the FDA with all the information required by FDA regulations that was in GSK's possession and that justified the requested change; and (C) the FDA responded by rejecting GSK's proposed warning on the ground that it was actually *not* justified by the evidence GSK had provided. The FDA's explicit and formal rejection of GSK's request provides clear

evidence, *a fortiori*, that the FDA would have rejected an *earlier* attempt to implement that same label change—based on *even less* data—as Respondents allege GSK should have done to comply with state law.

But in the first—and, to date, only—appellate decision interpreting *Merck*'s "fully informed" prong, the Third Circuit misconstrued this Court's precedents and held that Respondents' state-law claims against GSK could proceed. *First*, it concluded that a manufacturer fails to "fully inform[]" the FDA about the basis for a labeling change whenever, when rejecting a label change, the Agency requests additional information, even if the manufacturer "did ***not*** have access to" the requested data, or the data *did not yet exist* by the time the FDA rejected the label change. App.15. This makes no sense.

*Second*, the Third Circuit compounded this impossibly capacious view of what it means to fully inform the FDA by holding that, even as to information that does exist, a manufacturer fails to fully inform the FDA *whenever*, when rejecting a label change, the FDA requests additional information from the manufacturer, *whatever* its purpose. In the Third Circuit's categorical view, it does not matter whether the FDA regulations instruct manufacturers not to submit that information in support of a label change, whether the information has no bearing on the warning the manufacturer sought, or whether—once it received the information—the FDA in fact relied on it. Rather, any information that an FDA official requests from a manufacturer automatically means that the FDA was not "fully informed" when it rejects

a proposed label change, with no further inquiry by a court required. This, too, makes no sense.

This is not and cannot be the law. These two irrational, newly concocted requirements are irreconcilable with this Court's conflict preemption doctrine, and—especially when combined—effectively make it impossible to invoke impossibility preemption. Manufacturers cannot base a label change on data or information they do not have, or on immaterial information that FDA regulations make clear should not be submitted and which do not justify the change sought. Given the Third Circuit's centrality to the pharmaceutical industry—it is, after all, home to many of the world's largest pharmaceutical companies—we respectfully ask this Court to intervene and prevent this unjustifiable decision from denying the nation's leading pharmaceutical firms the right to claim the benefit of federal preemption under *Wyeth* and *Merck*.

## OPINIONS BELOW

The Third Circuit's opinion is reported at 945 F.3d 749 and reproduced at App.1–24. The district court's opinion is unreported but is reproduced at App.27–62.

## JURISDICTION

The Third Circuit issued its opinion on December 17, 2019, and denied rehearing en banc on January 28, 2020. On March 19, 2020, the Court "extended" "the deadline to file any petition for a writ of certiorari" still then pending "to 150 days." This Court has jurisdiction under 28 U.S.C. § 1254(1).

## STATEMENT OF THE CASE

### I. Legal and Factual Background

#### A. Legal Framework

Drug labeling requires a careful balancing between adequate disclosure of likely side effects and risks, and the consequences of overdisclosure of more attenuated risks. *See Merck*, 139 S. Ct. at 1673. For this reason, the FDA carefully controls the labels of drugs offered for sale in the United States: it must approve the labeling before a new drug may be marketed and, except in limited circumstances, it must approve in advance any change that a manufacturer would like to make from that approved label. 21 U.S.C. § 355(a) & (d).

There are two ways to change a drug's label following FDA approval—both of which require new FDA approval. First, and most common, the manufacturer can ask the FDA's permission to change the label by filing a Prior Approval Supplement ("PAS"). 21 C.F.R. § 314.70(b)(2)(v). Alternatively, where the manufacturer wishes to change the label "to reflect newly acquired information" that "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA," it can sometimes file a Changes Being Effected, or CBE, supplement, which allows the manufacturer to change the label unilaterally, subject to FDA review afterward. *Id.* §§ 314.3; 314.70(c)(6)(iii). But the FDA will forbid a new label—either *ex ante* or *ex post*—if, among other things, it disagrees that "sufficient evidence of a causal association" supports it. Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical

Devices, 73 Fed. Reg. 49603, 49608 (Aug. 19, 2008); *see also* 21 C.F.R. § 201.57(c)(6)(i); *Wyeth*, 555 U.S. at 571. By expressly requiring that label changes be based on sufficient evidence of a causal association, the FDA ensures "that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, and . . . prevent[s] overwarning, which may deter appropriate use of medical products, or overshadow more important warnings." Labeling Changes, 73 Fed. Reg. at 49605–06.

The FDA also explicitly delineates what "[c]linical data" must be provided to the FDA to support a label change, whether by PAS or CBE. *See* 21 C.F.R. §§ 314.50(d)(5); 314.71 (requiring the same procedures for all label changes). As relevant here, a manufacturer must present a "description and analysis" of controlled clinical studies, *id.* § 314.50(d)(5)(ii); a "description and analysis of any other data or information . . . obtained or otherwise received by the applicant" that is "relevant to an evaluation of the safety and effectiveness of the drug," *id.* § 314.50(d)(5)(iv); and a "summary . . . of safety information" that includes "an integrated summary of all available information about the safety of the drug product" along with a "description of any statistical analyses performed in analyzing safety data," *id.* § 314.50(d)(5)(vi)(a)–(b). Notably, FDA regulations do not ask for every piece of data, however marginal, that the manufacturer "obtained or otherwise received," but rather seek "relevant" descriptions, analysis, and "integrated summaries" of the data. The regulations could not be otherwise, as the FDA has neither the capacity nor resources to review such mountainous

submissions of data. *Wyeth*, 555 U.S. at 578 & n.11. A label change based on information that falls short of the "sufficient evidence" threshold will be rejected as insufficient—or inadequate—to support a label change, even if the manufacturer provides the FDA with complete descriptions, analysis, and integrated summaries of the evidence it possesses supporting the request.

### B. Avandia's Regulatory History

When the FDA approved Avandia in 1999, it concluded that Avandia's "cardiac safety profile" "seem[ed] to be benign." CA3.JA.914. By 2001, however, a link between Avandia and heart failure emerged. GSK proposed and the FDA approved an updated label, which warned that Avandia "may exacerbate or lead to heart failure," and "should be discontinued if any deterioration in cardiac status occurs." CA3.JA.632.

GSK sponsored many studies over the ensuing years to monitor Avandia's effect on cardiac health. These studies included short-term clinical studies, meta-analyses (which analyze the results of completed short-term studies), and long-term studies. Of these, the FDA has explained that long-term studies are by far the most reliable. *E.g.*, CA3.JA.1639–40, 1655–56. In this case, GSK's most relevant long-term cardiovascular outcome study—the gold standard of clinical trials, *see* CA3.JA.1656—was called RECORD. RECORD began in 2001 and finished in 2009.

In August 2005 GSK completed, and shared with the FDA, its first post-approval meta-analysis reported cardiovascular events from 37 controlled trials, aptly called ICT-37. The purpose of ICT-37

included "evaluat[ing] the association (if any) between rosiglitazone and . . . myocardial ischemia." CA3.SA.279. But the results showed "no consistent pattern," CA3.SA.280, and "did not further inform understanding of the degree of any association," CA3.SA.304.

In May 2006, GSK completed, and shared with the FDA, a second meta-analysis including five additional studies, dubbed ICT-42. CA3.SA.467. ICT-42 showed a stronger association between Avandia and myocardial ischemia, CA3.SA.497–98, but GSK noted that this result was inconsistent with data from long-term studies and did not include data from others, CA3.SA.495–98.

Despite these mixed signals, GSK filed a PAS in August 2006, asking the FDA's permission to add a warning about myocardial ischemia to Avandia's label based on the results of ICT-42. CA3.SA.539, 565. Underscoring the scientific uncertainty, however, GSK informed the FDA in a May 2007 meeting that "all subsequent work" following ICT-42 "has yielded information that is inconsistent with an increased risk of myocardial ischemic events." CA3.SA.611. GSK was therefore working to clarify the situation by "progressing an interim analysis of RECORD with the highest possible urgency." CA3.SA.611. GSK also offered to help the FDA independently "contact[] the [Data and Safety Monitoring Board ("DSMB")] for RECORD" to allow the FDA to gain access to information from the ongoing RECORD study "while protecting the integrity of the study." CA3.SA.611. The FDA agreed that interim results from RECORD would be important "to inform FDA's deliberations" on

the PAS, but explained that it would need to discuss internally whether it wanted to seek such information from RECORD's DSMB, and, if so, how to do it without compromising the study's integrity. CA3.SA.611. The FDA made the same comment about another in-progress long-term study called BARI-2D. CA3.SA.612. At that point, however, none of this data existed or was available to GSK.

On May 18, 2007, GSK supplemented its PAS by proposing to add "a new subsection entitled 'Myocardial Ischemic Events' in the WARNINGS section" of Avandia's label. CA3.SA.616, 635. The proposed warning stated that "pooled data from 42 controlled clinical studies" showed "[a]n increased risk of myocardial ischemic events." CA3.SA.616, 635. Critically, however, interim results from RECORD and other long-term studies still were not yet available; the FDA had yet to indicate a desire to obtain them; and the FDA and GSK both acknowledged that the meta-analyses that served as the basis for the PAS had "substantial methodological limitations" (although neither suggested that such limitations were any fault of GSK's). CA3.SA.616.

On June 4, 2007, the FDA rejected the PAS by issuing a "Not Approvable" letter under 21 C.F.R. § 314.120. App.63–66. The FDA explained that it was rejecting a myocardial-ischemia warning because "the information presented is inadequate" to justify it, adding that "we have concluded that the pooled data"—*i.e.*, the short-term studies underlying ICT-42—"require further analysis to adequately convey the potential risk for increased cardiac ischemia associated with [Avandia]." App.63–64. Specifically,

the FDA noted that it had "identified *certain subgroups* of patients . . . that may be particularly vulnerable to experiencing an ischemic event while on [Avandia]," meaning that the FDA was unconvinced that the data supported the universal warning GSK proposed for *all* Avandia users. App.64 (emphasis added). The FDA continued that "[f]urther analyses" and "additional studies" were necessary to evaluate ischemic risks among those "subgroups of patients," for whom a more targeted warning might be appropriate. App.64.

To facilitate these additional reviews, the FDA instructed GSK to provide the agency with four categories of data: (1) "[i]nformation from on-going RECORD and BARI-2D trials," (2) "primary datasets" from a long-term study called DREAM, (3) targeted information specific to those subgroups from DREAM and another long-term study called ADOPT, and (4) certain studies underlying a third-party meta-analysis that was recently published in the New England Journal of Medicine.[1] App.64–65. The FDA's letter explained that no ischemic-risk warning could not be approved absent this "additional data recently requested, ***and*** *accruing information from ongoing clinical trials*," meaning the still non-existent RECORD data. App.65 (emphasis added).[2] And the

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[1] This meta-analysis, by Dr. Steven Nissen, also relied on 42 Avandia studies, but there was not a complete overlap between the studies he chose and those in ICT-42.

[2] Importantly, neither the FDA's non-approvable letter nor anything else in the record suggests that the FDA believed that GSK *should* have provided any of this information earlier or that

FDA decided that all such evidence would need to be considered by an Advisory Committee of independent experts on July 30, 2007. App.65. "The outcome of this meeting," the FDA said, "will be particularly germane to any labeling or other regulatory action needed for [Avandia]." App.65.

That same day, the FDA's Director of Metabolism and Endocrinology Products, Dr. Mary Parks, told GSK that the "FDA wants further consultation, including review of recent and newly emerging information, in order to 'make the right decision'" and that "it is 'not an easy matter' to take action without additional data." CA3.SA.663. The material data that existed when GSK filed its application was not enough to convince the FDA that the requested label change was appropriate. Before it was comfortable taking any action on Avandia's label, the FDA would await the opportunity for an Advisory Committee to review the "newly emerging information" from RECORD, data which did not yet exist. In other words, until RECORD data emerged, the FDA would not approve any changes to Avandia's label.

After GSK collected and, at least with respect to RECORD, for the first time gained access to the data the FDA sought, it provided it to the FDA, which then convened an Advisory Committee review of Avandia's cardiovascular risk. CA3.JA.1080–86. The Advisory Committee's July 30, 2007 meeting confirmed that the FDA had rejected GSK's label change because the universe of evidence that existed at the time had not

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this data—which the FDA sought by name and so clearly knew existed—was improperly withheld.

been sufficient to justify it. FDA officials voiced concern about the meta-analyses' unavoidable limitations, including "the short duration of the [underlying] trials; the quality of the data; low number of cardiac events; lack of cardiac event-adjudication; and . . . the heterogeneity of the study population." CA3.JA.1083. Those limitations and others made "the study data difficult to interpret." CA3.JA.1083–84. By contrast, the "[m]ost notabl[e]" data presented at the meeting were "the interim results of the RECORD trial," which had not been available when the FDA rejected GSK's PAS on June 4, 2007, and which the FDA had already expressed was the key information it was awaiting before it would be willing to reach a decision regarding Avandia's ischemic risk. CA3.JA.1643, 1084.

After reviewing this newly available, preliminary RECORD evidence, a majority of the committee voted that "the available data support[s] a conclusion that Avandia increases cardiac ischemic risk in type 2 diabetes," although some members "qualified their vote by adding that current data could be categorized as 'suggestive of' rather than 'evidence of' an increased cardiac ischemic risk." CA3.JA.1085. Notably, consistent with the FDA's indication in the not approvable letter that a narrower label targeting high-risk sub-populations might be warranted instead of GSK's proposed universal label, "many" members "qualified their" vote on "the question of greater risk with Avandia, by identifying subgroups at increased risk." CA3.JA.1085.

Accordingly, in October 2007, the FDA directed the following addition to an existing boxed warning on

Avandia's label: "A meta-analysis of 42 clinical studies . . . showed Avandia to be associated with an increased risk of myocardial ischemic events . . . . Three other studies . . . have not confirmed or excluded this risk. In their entirety, the available data on the risk of myocardial ischemia are inconclusive." CA3.JA.1096–97. The FDA reached this decision after "carefully weigh[ing] several complex sources of data, some of which show conflicting results," and the most important of which—RECORD—was unavailable prior to the FDA's earlier rejection. CA3.JA.1096. This warning was, on its face, more measured than the one GSK had proposed in its PAS and that the FDA rejected as unsupported by sufficient evidence.

GSK continued studying Avandia and myocardial ischemia over the following years, including running a third meta-analysis called ICT-52 in 2010. CA3.JA.1187. The most critical development, however, was the completion of RECORD, whose results the FDA reviewed in 2010 and again in 2013 following a re-adjudication. CA3.JA.1637. The results severely undermined the meta-analyses' suggestion that Avandia caused an increased risk of myocardial ischemia. The FDA concluded that RECORD "provide[d] considerable reassurance regarding the cardiovascular safety of" Avandia, CA3.JA.1657, so directed the "[r]emoval of the [myocardial-ischemia warning] from the current boxed warning," CA3.JA.1641. It allowed that "[s]ome description of the meta-analysis findings and observational data could remain in another section . . . in order to convey that there is a small amount of residual uncertainty." CA3.JA.1641. But the FDA concluded that "the

totality of the available evidence does not support a marked signal of cardiovascular harm." CA3.JA.1656.

## II. District Court's Decision

Respondents filed suit in 2010, alleging, inter alia, state-law failure-to-warn claims. Respondents allege that "GSK falsely promoted Avandia from its launch in 1999 until the FDA forced GSK to reveal its true cardiovascular risks in 2007. Thus, the critical time period in this case is 2000 to 2006." Brief of Plaintiff-Appellants, 2018 WL 3218448, at 62. And Respondents' argument is "that GSK could and should have added cardiovascular warnings, *like those on the current label,* prior to 2007." *Id.* at 68.

The district court granted summary judgment to GSK on preemption grounds, among others. App.27–28. The district court concluded that the FDA's June 2007 "rejection of GSK's proposed label on the basis of inconclusive data, considered with other evidence, constitutes clear evidence that the FDA would not have approved of the label change Respondents claim was necessary." App.59–60. The court also emphasized that "'the RECORD trial, and its re-adjudication, provide considerable reassurance regarding the cardiovascular safety of rosiglitazone.' . . . [T]he Court cannot ignore the FDA's current conclusion that a link between Avandia use and increased cardiovascular risk does not exist." App.61–62.

## III. Third Circuit's Decision

Purporting to apply *Merck* (which came down after the district court's decision), the Third Circuit reversed. The panel held that GSK could not meet either of *Merck*'s prongs.

On the first prong, GSK argued that its PAS included more than enough data to fully inform the FDA of the justifications for a myocardial-ischemia warning, and that the additional data the FDA requested either did not yet exist—most notably, the interim RECORD results—or was immaterial both in light of the regulations governing the content of label change applications and the FDA's ultimate decision regarding the label change.

The Third Circuit did not completely disagree. It accepted that GSK "did not have access to the information that the FDA requested until after [the FDA] issued the [not approvable] Letter." App.15–16. Nevertheless, the panel determined that the unavailability of the evidence was itself "unavailing." App.16. The Third Circuit elaborated: "we read *Merck* as holding that, in order to prove impossibility preemption, the drug manufacturer must show . . . that the FDA was 'fully informed . . . of the justifications for the [proposed] warning' *at the time that the FDA rejected the proposed warning*." App.16–17. Thus, it reasoned, "[b]y arguing that it did not have the FDA's requested data and information until after the FDA issued its letter, . . . GSK is, in effect, conceding that the FDA was not 'fully informed' at the time of the Letter's issuance." App.17. Accordingly, it concluded that to rely upon a not approvable letter "as proof that the FDA rejected its proposed label change, [GSK] must also demonstrate that the FDA possessed all the information it deemed necessary to decide whether to approve or reject the proposed warning *at the time it issued the Letter*." App.17.

The Third Circuit did not, however, accept GSK's materiality argument. It reasoned, uncontroversially, that the FDA "is the entity with power to approve or refuse a change to a drug's label" and thus that "the FDA, and only the FDA, can determine what information is 'material' to *its own* decision to approve or reject a labelling change." App.16. Pointing only to the fact that "the FDA *actually requested*" the information in the not approvable letter, the Third Circuit rejected GSK's position that the data was immaterial to the FDA's resolution of the label change request. App.16. Perplexingly, the panel *never* concluded that the FDA—the "only" entity that can make a materiality determination—in fact considered this additional information to be material to its decision on GSK's proposed label, or that GSK had in fact withheld any material information from the FDA. On *Merck*'s second prong, given its conclusion on prong one, the Third Circuit concluded that the FDA's not approvable letter could not qualify as a rejection of GSK's proposed warning because the letter—and the record itself—indicated that the warning might become justified in the future, if enough new information later came to light. App.17–18.

## REASONS FOR GRANTING THE PETITION

### I. The Third Circuit's Decision Is Incorrect.

Under *Merck*, to merit preemption, a manufacturer must show that it sought to comply with state law by "fully inform[ing] the FDA of the justifications" for the label change, but that the FDA rejected it. 139 S. Ct. at 1678–79. Given that *Merck* aims to answer whether the manufacturer could have revised the label in a way that complied with both

federal and state law, the information that the manufacturer must have provided to the FDA is the information that the manufacturer possessed at the time the FDA rejected the change. Information that did not exist by that time could not have been a justification for the change that the manufacturer could or should have shared with the FDA. If with the benefit of all the material information justifying the label change, the FDA still rejects it, there is clear evidence that the manufacturer could not at an earlier time have made such a label change.

In this case, GSK sought to add a stronger cardiovascular warning to Avandia's label and provided to the FDA all the information in its possession that justified the warning and that the FDA regulations instructed it to provide, but the FDA nevertheless rejected the warning as unsupported by that comprehensive body of information. This is *precisely* the kind of evidence that, under *Merck*, entitles a manufacturer to a preemption defense. But the Third Circuit denied preemption based on two unsupportable theories: that, to "fully inform" the FDA, a manufacturer must provide the FDA with information (1) that did not exist at the time of the FDA's decision or (2) that the FDA regulations instruct manufacturers *not* to provide and which the FDA in fact did not rely on. Under the Third Circuit's profoundly wrong revision of *Merck*, in order to merit a preemption defense, a manufacturer must defy space, time, and FDA regulations to "fully inform" the FDA *with information that the manufacturer does not have* or that official FDA policy establishes *that the FDA does not want*. The Third Circuit's rule would deny impossibility preemption in precisely the

circumstance when it is impossible for a manufacturer to comply with state law.

### A. The Third Circuit's "Fully Informed" Rule Defies Settled Conflict Preemption Doctrine, FDA Regulations, and Common Sense.

This and every court to address the issue have held that where a manufacturer could not unilaterally have changed a drug's label at the time it allegedly should have done so to comply with state law, state law tort claims are preempted. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011) (citing *Wyeth*, 555 U.S. at 573); *Gibbons v. Bristol-Myers Squibb Co.*, 919 F.3d 699, 708 (2d Cir. 2019); *Dolin v. GlaxoSmithKline LLC*, 901 F.3d 803, 814 (7th Cir. 2018), *cert. denied*, 139 S. Ct. 2636 (2019); *In re Celexa & Lexapro Mktg. & Sales Practices Litig.*, 779 F.3d 34, 41 (1st Cir. 2015). The Third Circuit departed from this settled preemption law when it held that GSK failed to "fully inform[]" the FDA when it did not submit information that was not even available to GSK at the time of the FDA's rejection letter and that the FDA says not to provide. The reason is simple: GSK could not have relied on either category of information to change Avandia's label.

As *Merck* recognized, the starting point of the preemption analysis is to determine exactly what the manufacturer *should* have told the FDA. 139 S. Ct. at 1680 (court assesses preemption "in light of the governing statutory and regulatory context"). Correctly framed in the context of the FDA's extensive labeling regime, the answer is straightforward: A brand manufacturer must have furnished all the

*material* information that it *possessed* at the time the FDA made its decision and which justified the label change that the plaintiff asserts was needed. *See, e.g.*, *Dolin*, 901 F.3d at 815; 21 C.F.R. § 201.57(c)(6)(i) (newly acquired information must provide "reasonable evidence of a causal association" of a "clinically significant adverse reaction linked" to a drug). The Third Circuit's conclusion to the contrary is based entirely on its inscrutable legal views that preemption is unavailable where potentially relevant information arises *after* the FDA's rejection, and that the materiality of information to the FDA's decision may be determined without considering the FDA regulations that establish what data a manufacturer must provide to change a label, or the FDA's actual (non)reliance on the information.

**1. Unavailable Information**

Intrinsic to the regulatory regime is the *explicit* recognition that label changes can only be based—and consequently that preemption can only be conditioned—on information already in the manufacturer's possession. To begin, a manufacturer may only change a drug's label when it has *obtained* "newly acquired information" that "reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. §§ 314.3; 314.70(c)(6)(iii). Assuming that threshold requirement is met, FDA regulations further dictate that manufacturers submit a "description and analysis of any other data or information . . . *obtained or otherwise received* by the applicant" that is "*relevant* to an evaluation of the safety and effectiveness of the drug." *Id.* § 314.50(d)(5)(iv) (emphasis added).

Information that does not exist has not been "obtained" or "received" by a manufacturer and so cannot be used to support a label change. Nor, to use *Merck*'s terminology, could such unavailable information have been one of the "justifications"—*e.g.*, a reason for seeking the change—that GSK could have provided to the FDA. *Merck*, 139 S. Ct. at 1678.

If, having been provided all the material information that the manufacturer could have relied upon to change the label, the FDA remains unconvinced of the wisdom of such a change, it cannot matter that the FDA sought additional unavailable information or acknowledged that relevant evidence might emerge in the future.[3] Such unknown information could not have formed the basis of the manufacturer's label change request when it was allegedly required. And the FDA's rejection of the application that *lacked* this unavailable information provides indisputable evidence that the manufacturer could not unilaterally have changed the label based on the material information *it did* have and that it had provided the FDA. *See, e.g.*, *Rheinfrank v. Abbott Labs., Inc.*, 680 F. App'x 369, 386 (6th Cir. 2017) (holding that preemption is available where "as of" the time when plaintiff asserts a warning was due, "the FDA would . . . have rejected" a label change); *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 395 (7th Cir. 2010) (explaining that data developed after the time that the manufacturer allegedly should have

[3] Specifically, two of the four categories of information that the FDA requested—the interim RECORD (and BARI-2D) data and the DREAM primary datasets—were not yet available to GSK at the time of the FDA's not approvable letter.

sought a label change "are not persuasive in determining whether there was clear evidence that the FDA would have rejected the proposed warning at" that time); *Goodell v. Bayer Healthcare Pharm. Inc.*, No. 18-CV-10694-IT, 2019 WL 4771136, at *4 (D. Mass. Sept. 30, 2019) ("Without factual allegations that Bayer had new information in th[e] time period [prior to when plaintiff alleges the warning was required] such that it could have or should have amended the label . . . the complaint is barred as preempted.") (collecting cases).

This conclusion is doubly true here, where FDA made clear that its decision on Avandia's ischemic risk—and thus on the propriety of the label change—would have to await the "emerg[ence]" of the long-term RECORD data and the Advisory Committee's review of that information. CA3.SA.663. Plainly, GSK would have been unable to convince the FDA to change the label before the RECORD data was available, no matter what existing (and less persuasive) evidence GSK could muster. It is undisputed that this information was not available—and accordingly that the change could not have occurred—prior to the FDA's rejection letter.

Indeed, *most* preemption cases involve a risk that the manufacturer asserts was not sufficiently clear to justify a label change at the time plaintiffs assert the warning was due, but which by the time of plaintiffs' suit years later is more firmly established. And, in many such cases—like in this case—the FDA subsequently obtains more information supporting the requested change and so *later* orders or accepts a label change based on that new information. Post-

*Wyeth* and *Merck*, courts have repeatedly found impossibility preemption in such cases. *See, e.g.*, *Dolin*, 901 F.3d at 812 & n.2 (reversing district court's denial of preemption and, *inter alia*, rejecting district court's conclusion that the FDA's invitation to the manufacturer to request a meeting to discuss the label change that the FDA rejected—*i.e.*, suggesting the the FDA's position was not necessarily final—defeated preemption); *Rheinfrank*, 680 F. App'x at 386 (granting preemption where the FDA rejected requested developmental delay warnings in 2005, despite the FDA's subsequent 2011 approval of such warnings); *McGrath v. Bayer HealthCare Pharm. Inc.*, 393 F. Supp. 3d 161, 166 (E.D.N.Y. 2019) (granting preemption where plaintiff's evidence concerning the risks of gadolinium retention arose after the time plaintiff alleged that the warning was due); *In re Depakote*, 87 F. Supp. 3d 916, 922 (S.D. Ill. 2015) (granting preemption as of 1999 due to the FDA rejecting manufacturer's request to add a developmental delay warning in 2006, despite later approving such a warning in 2011); *Dobbs v. Wyeth Pharm.*, 797 F. Supp. 2d 1264, 1277 (W.D. Okla. 2011) (same as of 2002 due to the FDA's conclusion that a warning for adult suicide risk for SSRI users was unsupported, despite the FDA's subsequent determining in 2007 that such warnings were warranted); *Roberto v. Boehringer Ingelheim Pharm., Inc.*, 2019 WL 5068452, at *21 (Conn. Super. Ct. Sept. 11, 2019) (explaining that information that "postdate[s] the plaintiff's [injury] obviously could not have provided the basis for a label change that might have prevented that [injury]" and so cannot be the basis for denying preemption).

Taken on its face, the Third Circuit's holding below would deny preemption in every one of the cases described in the preceding paragraph on the grounds that, by neglecting prophetically to furnish the later-developed data, the manufacturer failed to fully inform the FDA of all the information needed "to accept or reject" a label change. App.33. Because *Merck* did not purport to overrule or change *Wyeth*, *see Merck*, 139 S. Ct. at 1676; *Dolin v. GlaxoSmithKline LLC*, 951 F.3d 882, 891 (7th Cir. 2020) ("[Merck] did not adopt a new rule of preemption law."), such a complete schism reifies the magnitude of the Third Circuit's error. The Third Circuit has articulated a rule of law that puts it at odds with the decisions of every other court to consider the impact of after-developed evidence on preemption.

**2. Available Information**

The Third Circuit's view of the impact of *unavailable* information on a manufacturer's entitlement to preemption is reason enough to reverse, but it magnified that error with its treatment of *available* information. As *Merck* made clear, a manufacturer meets the "fully informed" prong if it has "submitted all material information to the FDA." 139 S. Ct. at 1680. But relying solely on the *fact* that the FDA requested the information in its not approvable letter, the Third Circuit rejected GSK's position that the few pieces of data that were available at the time of the FDA's rejection were immaterial to the FDA's ultimate labeling decision. App.16. This is clear legal error. The result of the Third Circuit's view of materiality is that *any* request by an FDA official for more information will sound the death knell for

preemption in *every* failure-to-warn case because the information is thus automatically deemed "material" and so defeats the manufacturer's ability to show that it fully informed the FDA of all material information.

a. This lip-service materiality analysis cannot be right. Materiality defies absolute treatment, and must, at a minimum, be assessed in the context of the applicable regulatory requirements and established Agency practice. *See, e.g.*, *Universal Health Servs., Inc. v. U.S. ex rel. Escobar*, 136 S. Ct. 1989, 2001 (2016) ("[M]ateriality cannot rest on 'a single fact or occurrence as always determinative.'" (quoting *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 39 (2011))); *Matrixx*, 563 U.S. at 39 (explaining that categorical materiality rules "must necessarily be overinclusive or underinclusive" (quoting *Basic Inc. v. Levinson*, 485 U.S. 224, 236 (1988))); *In re Donald J. Trump Casino Sec. Litig.-Taj Mahal Litig.*, 7 F.3d 357, 369 (3d Cir. 1993) ("[M]ateriality is a relative concept . . . ."). Contrary to this Court's and its own precedent, the Third Circuit's categorical treatment below ignores the FDA's regulatory expectations altogether. Instead of contending with the unmistakable federal constraints on what kinds of information GSK could include in its application to the FDA, the Third Circuit's materiality analysis applies a milquetoast—if superficially appealing—rule that information is material if the FDA wants to consider for some purpose. But this standard cannot withstand scrutiny, either in the abstract or as applied to this case.

The FDA could ask for a lot of different kinds of information for a lot of different reasons. Surely, *some*

inquiry into the nexus between the requested information, the regulatory regime, and the purpose of the request is required before reaching a determination that the information is material to a decision made pursuant to that regime. The Third Circuit's categorical materiality rule mirrors the First Circuit's approach that this Court rejected in *Escobar*, in favor of the more nuanced assessment that "the Government's decision to expressly identify" some information as important "is relevant, but not automatically dispositive" to that information's materiality. 136 S. Ct. at 2003–04. The determination must *also* be based on evidence of the Government's usual practices "in the mine run of cases" with respect to that information and what the Government ultimately did with the information *in that case*. *Id.* at 2003.

The Third Circuit performed no such analysis when purporting to assess the materiality of the information the FDA requested. It did not consider whether FDA regulations called for or even permitted a manufacturer to provide this data in the first instance or whether the kind of data that the FDA requested is usually relied upon in label change determinations. And despite its zealous defense of the FDA's exclusive prerogative to determine materiality, the panel failed entirely to assess whether the FDA *itself* believed that any of the DREAM, ADOPT, or Nissen information was material, or whether the FDA actually relied on the requested data in making its ultimate labeling decision.

But the record makes clear that the FDA *did not* rely on the information.[4] In fact, the FDA would have rejected GSK's PAS in June 2007 even had GSK included this information because the FDA was unwilling to make *any* decision on Avandia's ischemic risk until it could convene an Advisory Committee to review the "newly emerging" RECORD results *that didn't yet exist*. CA3.SA.663. Information that has no impact on the outcome of Agency's determination is, by definition, immaterial. *C.f. Santa Fe Indus., Inc. v. Green*, 430 U.S. 462, 474 n.14 (1977) (undisclosed information is immaterial where recipient would not "have acted differently had they" received it); *In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1425 (3d Cir. 1997) (Alito, J.) (holding that information that "had no effect on [a stock] price . . . was immaterial as a matter of law"); *United States v. Ippolito*, 774 F.2d 1482, 1486 (9th Cir. 1985) ("If it would have no effect, then the misstatement would not be material."). Moreover, aside from the bare fact of the information request, nothing in the record supports the view that GSK improperly withheld material information from the FDA, and there is no indication that the FDA *or even the Third Circuit* ever reached such a conclusion. *See* App.15–18. Indeed,

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[4] The data from the few omitted studies from Dr. Nissen's analysis did not appear in the Avandia label that the FDA approved in November 2007, and the FDA concluded that ADOPT and DREAM did not show Avandia to increase ischemic risks. CA3.JA.743. And, of course, given the FDA's final conclusion in 2013 that the cumulative evidence did *not* support the warning GSK had proposed in its May 2007 PAS, it is clear that the requested data proved to be ultimately immaterial to the FDA's decision.

the contemporaneous record shows just the opposite. *After* the FDA sent its not approvable letter and requested the additional information, the FDA told GSK that if GSK at that point tried unilaterally to change the label via the CBE regulations, *that conduct* would "make people think that GSK must have other information" that it withheld from the FDA. App.5. But the FDA did not at that point harbor such suspicions, even though it knew that GSK had not initially furnished the additional information FDA requested. This is unsurprising, as GSK provided all the material information that FDA regulations seek, and more.

b. Had the Third Circuit engaged in the analysis of FDA regulations and practices that this Court's materiality precedent demands, it, too, would have reached this conclusion. Although one wouldn't know it from reading the Third Circuit's one-paragraph treatment of materiality, *see* App.16, FDA regulations clearly prescribe the content of label change applications, *see supra* pp. 5–6. When it comes to submitting "safety information," in particular, the data must be presented through an "integrated summary." 21 C.F.R. § 314.50(d)(5)(vi). If FDA regulations are to have any meaning at all, a manufacturer who—consistent with the applicable regulations—submits an application that contains such an "integrated summary" of all the "relevant" safety data that it possesses has provided the FDA with all the "material information" needed to fully inform the FDA of the justification for the label change. *Merck*, 139 S. Ct. at 1680.

Applying the regulatory scheme to the specific sub-population data from DREAM and ADOPT, and the handful of studies from Dr. Nissen's meta-analysis that the FDA sought, it is clear that the data is immaterial, both as a matter of FDA regulations and the law of preemption. *No* manufacturer's label change request would *ever* have included that sort of granular information because FDA regulations specifically ask for "integrated summaries," not every scrap of data. Especially considering that GSK had already provided the FDA with the results from ADOPT and DREAM, Nissen's study, and "reviewed the totality of the evidence available to [GSK] about myocardial ischemic events in studies with [Avandia] and other comparator agents," CA3.SA.610–17, the absence from GSK's submission of additional, statutorily proscribed, information cannot be the basis for denying preemption.

In any event, this additional data about particularly at-risk subpopulations that the FDA requested could not have supported the broad *universal* label that GSK sought, the FDA rejected, and Respondents assert GSK *should have* imposed. Such data indicating that only particular subgroups of Avandia users might face increased risks would not have "justified a change in the label" that Respondents say GSK should have imposed—a warning of ischemic risks *for all* Avandia users. GSK could not have justified a request to impose a universal warning with this subgroup data that tended to undermine the need for that

warning. *Dolin*, 901 F.3d at 815.[5] That the FDA thereafter requested this information to determine whether a *different* and *narrower* label might be appropriate does not undermine that such information was immaterial to the actual label change request that was pending before the Agency—the only label Respondents claim was required under state law.

Instead of conducting this analysis, the Third Circuit concluded that information *must* be material *whenever* an FDA official, for *whatever* reason, indicates an interest in it, *whether or not* the Agency actually relies on the information in reaching its ultimate decision. This Court has already rejected such a blinkered treatment of materiality and the "extraordinarily expansive view of liability" that would result from its adoption. *Escobar*, 136 S. Ct. at 2004. Coupled with its already unreasonable obligation to provide non-existent information to the FDA, the Third Circuit's materiality analysis will force manufacturers—contrary to FDA regulations—to bury the FDA in every shred of data remotely related to the subject of an application in the hopes of avoiding any follow-up communications that would torpedo a preemption defense. Even then, there is no guarantee that the FDA might not ask for something

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[5] Relatedly, the ADOPT and DREAM studies, and the data underlying them, could not have been a basis for a CBE to add a warning about ischemic risks because the data did not show that Avandia increases those risks, and so did not meet the definition of "newly acquired evidence" that could support a CBE change. *See* 21 C.F.R. § 314.3. Where, as here, a manufacturer cannot utilize a CBE change at the time that it allegedly should have changed a drug's label, state law tort claims are preempted. *See Mensing*, 564 U.S. at 620 (citing *Wyeth*, 555 U.S. at 573).

else entirely. Practically speaking because manufacturers cannot reach so deep into the future or their archives, preemption in the Third Circuit is a dead letter.

* * *

At the time the FDA rejected GSK's request to add a universal ischemic risk warning to Avandia's label as inadequately supported by the existing material data before the Agency, GSK either did not have, or FDA regulations instructed GSK not to provide, the additional data that the FDA sought in its rejection letter. This is clear evidence, *a fortiori*, that GSK would not have succeeded in changing the label at the earlier time—with the benefit of even *less* evidence—that Respondents assert GSK should have implemented this change. Preemption should have followed easily. The Third Circuit's contrary conclusion relies on an amalgam of ill-conceived holdings, each of which alone cannot withstand the slightest scrutiny, and which together would sound the death knell of impossibility preemption. *Merck* made clear that it "would be difficult" to meet *Wyeth*'s "clear evidence" standard, not hopeless. 139 S. Ct. at 1678. It is untenable to condition preemption on a manufacturer's ability to do the impossible, be it to reach into the future and supply data that does not yet exist, or clairvoyantly to predict the particular data points that, while not presently material under governing FDA regulations, might someday be of interest to an Agency official. The Third Circuit's irrational holdings do just that, and cannot stand.

## CONCLUSION

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

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