No. 20-1069

In the Supreme Court of the United States

JANSSEN PHARMACEUTICALS, INC., JOHNSON & JOHNSON COMPANY, AND JANSSEN RESEARCH AND DEVELOPMENT, LLC,
Petitioners,

v.

A.Y., *et al.*,
Respondents.

On Petition for Writ of Certiorari to the Supreme Court of Pennsylvania

RESPONDENTS' BRIEF IN OPPOSITION

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QUESTION PRESENTED

Whether Pennsylvania's intermediate appellate court correctly concluded that, under the facts of this case, the petitioners failed to carry their burden of proving that federal law, as it existed in 2003, required them to conceal from doctors the serious risks associated with prescribing Risperdal, a brand-name antipsychotic drug, to children.

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INTRODUCTION

This Court has repeatedly recognized that "a central premise of federal drug regulation" is that a brand-name-drug manufacturer "bears responsibility for the content of its label at all times." *Wyeth v. Levine*, 555 U.S. 555, 570–71 (2009). The Court has also repeatedly recognized that federal law permits manufacturers to change their labels to add or strengthen safety information "without prior approval from the FDA." *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1679 (2019). As a result, in a case such as this one, involving a state-law failure-to-warn claim, "[i]mpossibility pre-emption is a demanding defense." *Wyeth*, 555 U.S. at 573. A "drug manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Merck*, 139 S. Ct. at 1679.

The court below applied these settled precedents and found that, based on the record in this case, the petitioners did not make such a showing. The trial focused on the petitioners' failure in 2003 to adequately warn about the risks of pediatric use of the antipsychotic drug Risperdal. The evidence revealed that the petitioners had conducted internal studies in 2001 and 2002 showing that Risperdal caused boys to grow permanent female breast tissue, a condition known as gynecomastia, at a significant rate. The petitioners did not change the drug's label to disclose this new information or otherwise act to inform doctors of the risk. Instead, the trial evidence revealed that the petitioners purposefully concealed the causal relationship between Risperdal and gynecomastia in boys to maximize sales of the drug, while aggressively marketing the drug for off-label pediatric use. The plaintiffs' expert, former FDA Commissioner David Kessler, testified that the

petitioners should have warned doctors about the risks of pediatric use of Risperdal, and that federal law would have permitted them to do so. Providing this information, Dr. Kessler added, would have allowed families and their doctors to make informed decisions about treatment options for vulnerable young children with mental-health conditions (many of whom, if they develop gynecomastia, are mercilessly teased and ineligible for mastectomies given their mental-health conditions). Further, the doctor who prescribed the drug to the patient in this case—who was four years old when he began taking Risperdal and developed gynecomastia—testified that she would not have done so had she known the risks. Crediting the plaintiffs' trial evidence, the jury found the petitioners liable under state law for failing to adequately warn, and the trial court entered judgment against them.

In affirming that judgment, the Superior Court of Pennsylvania rejected the petitioners' argument that they were powerless to warn about the causal relationship between Risperdal and gynecomastia because "only the FDA had the authority to warn about off-label uses" of Risperdal. App. 22. It found this argument to be "inconsistent with" FDA regulations, including a regulation on pediatric precautions. App. 22–23 (citing 21 C.F.R. § 201.57(f)(9) (2003) The court also found that the petitioners had not shown any conflict with the federal misbranding prohibition, and noted that "'the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning . . . is difficult to accept.'" App 23 (quoting *Wyeth*, 555 U.S. at 570). The court concluded that, on this record, the petitioners had not shown that federal law "would have 'clearly' prevented [them] from warning about the statistically significant increase in frequency and severity of gynecomastia in

boys taking Risperdal." App. 26. The Pennsylvania Supreme Court then denied review.

The Superior Court's case-specific holding does not satisfy this Court's certiorari criteria. The petitioners do not claim that it conflicts with any decision from any court, much less a state court of last resort or a federal circuit. The supposed legal error that they identify—based on their assertion that a 40-year-old regulation "prohibits manufacturers from adding off-label warnings" (at 19)—concerns a question that no other court has addressed. Indeed, the petitioners struggle to find any cases, beyond Risperdal cases, that even could be affected by the question that they say is presented. Nor is the question outcome-dispositive here given the regulation on pediatric precautions and the evidence that the petitioners could have communicated the risks of pediatric use of Risperdal in various ways. This case would also be a poor vehicle through which to explore any question about off-label warnings, in light of the evidence showing that the petitioners knowingly concealed Risperdal's risks while promoting the drug for off-label use to vulnerable kids.

Finally, the decision below is correct. The petitioners' argument to the contrary relies on a single sentence in an FDA regulation saying that a "specific warning" about an off-label use "may" be required by the FDA. 21 C.F.R. § 201.57(e) (2003). That sentence does not restrict what manufacturers may do when the FDA has not exercised its authority. And the sentence is immediately preceded by a clear command: that "labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard." *Id.* Moreover, other provisions in the same FDA regulation, and the FDA's statements when promulgating the regulation, confirm

that federal law did not prohibit the petitioners from adding a warning here. As the FDA explained, "there is no legitimate basis for limiting the labeling to hazards arising from the approved use of the drug, particularly when dangerous unapproved use of the drug has been found." *Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs*, 44 Fed. Reg. 37,434, 37,448 (June 26, 1979). Nor did the federal misbranding statute require the petitioners to hide the risks of pediatric use of Risperdal. Far from prohibiting warnings about off-label use of a drug, that statute requires such a warning in many instances. It proscribes labels that "fail[] to reveal" material facts of "consequences which may result" from "customary or usual" uses of the drug, including off-label uses. 21 U.S.C. § 321(n). There is no basis for certiorari.

STATEMENT

I. Statutory and regulatory background

The contents of a prescription-drug label. When a manufacturer applies for FDA approval of a new drug, the manufacturer is responsible for proposing the drug's label and crafting its contents. 21 U.S.C. § 355(b). The drug's "label," in this context, refers to both "the written material that is sent to the physician who prescribes the drug and the written material that comes with the prescription bottle." *Merck*, 139 S. Ct. at 1672; *see* 21 U.S.C. § 321(m).

To comply with FDA regulations, the manufacturer must include on the label certain categories of information warning of the drug's risks, set forth in specific sections. These sections include: (1) "boxed" warnings for risks that could cause death or grave injury; (2) "contraindications" listing the circumstances in which the drug should not be used; (3) "warnings and precautions" about other potential

safety hazards; and (4) "adverse reactions" that could be caused by using the drug. 21 C.F.R. § 201.57(c). The label must also list, in a section called "indications and usage," the drug's approved uses. *Id.* At the time period relevant to this case, the "warnings and precautions" section of the label was divided into two separate sections, "warnings" and "precautions." 21 C.F.R. § 201.57(e) & (f) (2003).

The manufacturer's post-approval duty to maintain the label. Once a drug is approved, federal law does not regulate how the drug may be prescribed by doctors. It does, however, require the manufacturer to maintain responsibility for "ensuring that its warnings remain adequate as long as the drug is on the market." *Wyeth*, 555 U.S. at 571. That is true not only for risk information communicated specifically under the "warnings" section of the label, but also for risk information communicated in other sections.

With respect to the "warnings" section, the FDA has long required that the "labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." 21 C.F.R. § 201.57(c)(6)(i); *see id.* § 201.80(e); *see also* 21 C.F.R. § 201.57(e) (2003). As the agency noted when promulgating that regulation in 1979, the FDA did "not agree that physicians [would] be misled by clear and concise statements" about significant risks, but would "welcome such information so that they can make their best informed medical judgments." 44 Fed. Reg. at 37,447. Moreover, because many drugs are commonly prescribed for off-label uses, the FDA made clear that "there is no legitimate basis for limiting the labeling to hazards arising from the approved use of the drug." *Id.* at 37,448.

The FDA reached the same conclusion with respect to the "precautions" section, particularly with reference to off-label uses affecting children. During the relevant period, FDA regulations provided that, if a drug had not been approved for pediatric use, the precautions section of the label must include the following disclaimer: "Safety and effectiveness in pediatric patients have not been established." 21 C.F.R. § 201.57(f)(9)(vi) (2003). FDA regulations also mandated that the precautions section "shall" describe any "specific hazard" "associated with" any off-label pediatric use. *Id.* The hazard "shall" also be included, if appropriate, in the "Contraindications" or "Warnings" sections. *Id.* When the FDA imposed these requirements, it rejected a request that the agency require "precautions regarding pediatric use" only for on-label uses. 44 Fed. Reg. at 37,453. The FDA did so "because many drugs not specifically indicated for pediatric patients are commonly prescribed for them." *Id.*

The FDA's approach to "adverse reactions" reflects a similar understanding. For the relevant period, the FDA required that this section "shall list the adverse reactions that occur with the drug,'" which it defined to mean any "undesirable effect[s] reasonably associated with the use of the drug." 21 C.F.R. § 201.57(g) (2003). The FDA determined that this disclosure must be "based on all the information available to the manufacturer concerning the drug," because "it is essential to the safe use of a drug for the physician to know all adverse reactions that are likely to occur with it." 44 Fed. Reg. at 37,443, 37,453.

In addition to these regulatory requirements, several statutory provisions require the manufacturer to maintain the adequacy of its label. The provisions on misbranded drugs, for example, require the manufacturer to ensure

that the label warns of material consequences associated with a common off-label use of the drug. These provisions forbid labels that "fail[] to reveal" material facts about "consequences which may result" from using a drug "under the conditions of use prescribed in the labeling or advertising thereof or under such conditions of use as are customary or usual." 21 U.S.C. §§ 321(n), 352(a).

The process for changing a label. Although most label changes must be approved by the FDA before being implemented, a regulation called "changes being effected" (or CBE) "permits drug manufacturers to change a label without prior FDA approval" for safety reasons. *Merck*, 139 S. Ct. at 1673. The CBE regulation authorizes a manufacturer to make unilateral changes to a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction for which [there is] evidence of a causal association." 21 C.F.R. § 314.70(c)(6)(iii). The current version of the CBE regulation limits these changes to those involving "newly acquired information," *id.*, but that language did not exist in the version at issue here.[1]

By its terms, the CBE rule applies only to the sections on contraindications, warnings, precautions, and adverse reactions. *Id.* It does not apply to boxed warnings. The FDA has drawn that distinction since 1979, when it advised manufacturers that, "to ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by FDA." 44 Fed.

[1] Although the CBE rule in effect in 2003 was not limited to newly acquired information, in this case, the petitioners' decision to conceal the causal relationship between Risperdal and gynecomastia closely followed their discovery of that relationship through internal studies.

Reg. at 37,448. A manufacturer, however, can add this information to the other sections without FDA approval.

When the FDA promulgated its labeling regulations, it specifically mentioned the CBE rule. It explained that "these labeling regulations do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered." *Id.* at 37,447. The FDA went out of its way to state that "[t]he addition to labeling and advertising of additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters" to such professionals, is "not prohibited by these regulations." *Id.*

If a manufacturer uses the CBE process to update its label, "the FDA retains authority to reject labeling changes made pursuant to the CBE regulation." *Wyeth*, 555 U.S. at 571. The FDA may also require a "specific warning" about an off-label use if certain circumstances are met. 21 C.F.R. § 201.57(c)(6)(i). But prior to 2007, the relevant time period in this case, "the FDA lacked the authority to order manufacturers to revise their labels." *Wyeth*, 555 U.S. at 571. Thus, unless a manufacturer submitted a supplemental application, the FDA had little practical ability to force a label change.

II. Factual and procedural background

A.Y. develops gynecomastia from taking Risperdal at age four, without any warning about the risk on the label. Respondent A.Y. was four years old when he was diagnosed, in 2003, with attention deficit hyperactivity disorder and oppositional defiant disorder. He was soon prescribed Risperdal. Within a few months of taking the drug, A.Y. began to develop noticeable breasts, which became increasingly visible over the years. He has since

been diagnosed with gynecomastia, an endocrine disorder caused by elevated levels of prolactin, the protein that leads to the growth of permanent breast tissue. Today, in his early twenties, A.Y. has a breast size of 40D or 42C. He will have breasts of this size for the rest of his life.

A.Y.'s reaction came as a surprise to the doctor who prescribed him the drug. The drug's label contained no specific warnings about gynecomastia and stated that endocrine disorders such as gynecomastia were a "rare" side effect "occurring in fewer than 1/1000 patients." App. 31; *see also* Pa. Sup. Ct. Record 282a–89a, 478a. The label did not disclose that the petitioners had previously discovered a causal relationship between Risperdal and gynecomastia in children at rates that qualified as "frequent" under the label's definitions. App. 31–32.

Despite being aware of the risks of pediatric use of Risperdal, the petitioners did not warn of those risks. Unbeknownst to A.Y.'s doctor and family, the petitioners had conducted clinical studies of Risperdal's effects on children, including studies paying special attention to the problem of gynecomastia. In 2002, the year before A.Y. was prescribed Risperdal, one study performed by the petitioners revealed that the gynecomastia rate among participating boys was actually 5.5% and far higher than the rate for similar-use drugs. App. 31–32; A follow-up study showed that the true incidence of gynecomastia in boys taking Risperdal could be as high as 12.5%. *Id.* The study also demonstrated that, for many of these patients, the condition took time to reveal itself and was permanent. Pa. Sup. Ct. Record 166a–72a. The petitioners' own statistical analysis of the study data showed that boys who experienced elevated prolactin levels 8–12 weeks after ingesting Risperdal were three times more likely to

develop gynecomastia, and that there was a 98.5% likelihood that this relationship was causal. *Id.* at 199a.

Despite having exclusive access to these findings, the petitioners did not avail themselves of the CBE procedure to warn doctors that analysis of the petitioners' study data had established a causal relationship between Risperdal and gynecomastia in boys. Instead, the petitioners chose to manipulate and obscure this information from doctors, the scientific community, and the FDA, while aggressively promoting Risperdal for off-label pediatric use through sales representatives and marketing literature. *Id.* at 246a–62a. A.Y.'s doctor testified that, had she been informed that Risperdal caused boys to grow female breast tissue, she would have had a different conversation with A.Y.'s mother about the risks of the drug and would not have prescribed Risperdal to A.Y. *Id.* at 480a–82a.

A.Y. files suit, and a jury finds that the petitioners violated their state-law duty to adequately warn. In 2013, A.Y. and his family brought this case against the petitioners in the Philadelphia Court of Common Pleas. They asserted that the petitioners had violated their duty, under Tennessee law (where A.Y. lives), to adequately warn about the risks of Risperdal in pediatric patients.

Before trial, the petitioners moved for summary judgment on preemption grounds. Among the evidence considered was deposition testimony from Dr. Kessler, the plaintiffs' standard-of-care expert and former FDA commissioner. Dr. Kessler testified that, in his opinion, the petitioners "could have and should have warned pediatric practitioners prescribing this drug off-label to children." *Id.* at 270a. He discussed the relevant statutory and regulatory background and explained that, when there is a "red flag" such as the one in this case, there are

"multiple avenues" though which "a company can warn," because "a company can always warn about safety." *Id.* at 262a. These avenues include not just making changes to the label using the CBE rule, but also warning through the company's "sales force," through "medical education," and through other communications. *Id.* at 270a–73a. Dr. Kessler further testified that there was "no doubt in [his] mind" that the petitioners were targeting the pediatric market and promoting the drug for pediatric use from 2001 to 2006. *Id.* at 246a–62a. He testified that the petitioners were "promoting, marketing, [and] certainly doing outreach" for Risperdal for "indications in children that [were] off-label," and "if you're engaged in that kind of promotion, [] you have to warn." *Id.* at 289a–90a. The trial court denied summary judgment.

A two-week trial was held. The jury returned a verdict for A.Y., finding that the petitioners were "negligent by failing to provide an adequate warning to [his] healthcare providers about the risk of gynecomastia from taking Risperdal." *Id.* at 2136a. The jury also found that the petitioners "intentionally falsif[ied], destroy[ed], or conceal[ed] records containing material evidence in this case." *Id.* The petitioners moved to have the verdict set aside, arguing (among other things) that it was preempted by federal law. The trial court denied the post-trial motion and entered judgment. App. 60–204.

The judgment is upheld on appeal, and the court finds that the petitioners had not shown impossibility preemption. The Superior Court affirmed the trial court's determination that federal law did not preempt the jury's liability finding. Quoting this Court's cases, the Superior Court began its analysis by noting that "impossibility preemption [is] 'a demanding defense,'" App. 17, and that

a "manufacturer will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." App. 26 (quoting *Merck*, 139 S. Ct. at 1679). "[A]s the United States Supreme Court has recently reiterated, the CBE regulation contemplates that drug manufacturers bear ultimate responsibility to provide adequate descriptions of a drug's newly discovered risks to ensure consumer safety," and allows manufacturers to change their drug labeling without waiting for FDA approval. App. 23. Thus, "[t]he underlying question for this type of impossibility pre-emption defense is whether"—despite the existence of this pathway—"federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." App. 24 (quoting *Merck*, 139 S. Ct. at 1678).

The court then addressed the petitioners' arguments for why federal law prohibited them from "adding any all warnings" that would have satisfied Tennessee law. *Id.* First, the court addressed the petitioners' argument that federal law prohibited them from telling doctors that Risperdal caused gynecomastia in children because "only the FDA had the authority to warn about off-label uses." App. 22. The court explained that this argument lacks any authority and is "inconsistent with" the statutory and regulatory framework, including 21 C.F.R. § 201.57(f)(9), which "was in effect in 2003 and provided that any 'specific hazard' associated with an unapproved pediatric use 'shall be described'" on the label. App. 23–24. Second, the court rejected the petitioners' suggestion that the federal misbranding statute made it unlawful for the petitioners to tell doctors about the causal relationship, agreeing with this Court that the argument was "difficult to accept." App 23 (quoting *Wyeth*, 555 U.S. at 570). Third, the court

concluded that the petitioners did not make "a showing of full disclosure to the FDA during the relevant time." App. 25. Finally, the Court cited Dr. Kessler's trial testimony that, "by the year 2000 or 2001, Janssen was marketing Risperdal for children and adolescents, and was, thus, obligated to share their studies at this time." App. 22.

The Pennsylvania Supreme Court denied review.

REASONS FOR DENYING THE WRIT

I. The petitioners' question is not presented.

The petitioners ask this Court to grant certiorari to decide "[w]hether federal law preempts state-law claims that a manufacturer failed to provide adequate warnings relating to the off-label use of their products, where federal law bars the manufacturer from unilaterally altering its labeling to provide such warnings." Pet. i–ii.

The court below did not address this question, and it is not presented here. The court below did not accept the premise that federal law barred the petitioners from unilaterally altering their labeling to provide appropriate risk information. To the contrary, the Superior Court "disagree[d] that the regulatory scheme would have 'clearly' prevented [them] from warning about the statistically significant increase in frequency and severity of gynecomastia in boys taking Risperdal." App. 26. The Superior Court also rejected the argument that "only the FDA had the authority to warn about off-label uses." App. 22–23. The Court of Common Pleas likewise concluded that "it was possible for [the petitioners] to comply with both their state law duty to adequately warn foreseeable users of Risperdal and their federal labeling duties." App. 103.

What the petitioners are really asking the Court to decide, then, is whether they have shown that federal law in fact barred them from telling doctors that Risperdal caused gynecomastia in children. Or put in this Court's words: whether federal law prohibited the petitioners "from adding any and all warnings to the drug label that would satisfy state law." *Merck*, 139 S. Ct. at 1678.

II. The antecedent question is not certworthy.

The petitioners acknowledge (at 34) that the actual question on which they seek certiorari is whether 21 C.F.R. § 201.57(e) "categorically precludes manufacturers from independently implementing off-label warnings." This question does not meet the Court's certiorari criteria. Nor is it outcome-determinative here.

A. There is no split of authority on the meaning of the 2003 version of 21 C.F.R. § 201.57(e).

To begin, the petitioners do not claim that the decision of the Pennsylvania Superior Court conflicts with any "decision of another state court of last resort or of a United States court of appeals." Sup. Ct. R. 10(b). They do not claim that the decision conflicts with *any* decision on the question of whether 21 C.F.R. § 201.57(e) "precludes manufacturers from independently implementing off-label warnings." Pet. 34. Nor do they point to any decision of any other court that has ever addressed that question. The petition thus fails to satisfy the criteria of Rule 10(b).

B. The absence of cases addressing this question makes clear that it is not sufficiently important to require this Court's review.

Because no conflict exists in the lower courts, the petitioners rely on Rule 10(c) and contend that "this issue presents an important question of federal law that has not

been, but should be, settled by this Court." Pet. 35. But their inability to cite a single case even addressing the meaning of 21 C.F.R. § 201.57(e) demonstrates that this is not one of those rare issues that is so important that it cries out for immediate resolution by this Court in the absence of any conflict below. Indeed, if the issue were as important as the petitioners profess, one would expect to see at least one other case (and likely dozens) addressing the issue—especially given that the language on which the petitioners rely has been in the regulation since 1979. The petitioners cite none.

Nevertheless, the petitioners assert (at 34) that the question is "exceptionally important"—primarily, because it is important to them. They lament the number of cases that have been brought against them by boys who grew permanent breast tissue after their doctors prescribed Risperdal to them without knowing that the drug causes gynecomastia in children. Pet. 35. But even within the universe of pediatric Risperdal cases, the question is of limited import because most plaintiffs in these cases used the drug after it had been approved for limited pediatric use in 2006. *See, e.g.*, *Risperdal & Invega Cases*, 49 Cal.App.5th 942, 952–60 (Cal. Ct. App. 2020) (finding no preemption of the state-law claims of "plaintiffs who took risperidone after the 2006 label change"). A question that affects only cases involving the use of a single drug more than 15 years ago is nowhere near important enough to warrant this Court's intervention, particularly in the absence of any split.

Beyond pediatric Risperdal cases, the petitioners are able to muster just four cases that involve failure-to-warn claims and off-label uses. *See* Pet. 36. Two of those cases were resolved years ago and neither involved 21 C.F.R.

§ 201.57(e). As for the remaining two, the petitioners do not contend that either presents this question. They do not cite any opinion from either case, but only the filing of the cases. That is it. Thus, far from demonstrating "massive state-law liability," Pet. 1, the petitioners' own discussion of importance actually reveals the opposite.

The petitioners' inability to cite any cases illustrates the hollowness of their claim of being put to a "Hobson's Choice" (or "Catch-22") between "federal prosecution for misbranding" and "untold billions of dollars in state-tort judgments" for failing to warn. Pet. 18, 36. The petitioners cite no examples of the FDA prosecuting a manufacturer for informing doctors about safety risks associated with a drug commonly prescribed for off-label uses where, as here, the manufacturer has exclusive knowledge of those risks. "And the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept." *Wyeth*, 555 U.S. at 570. When this kind of Hobson's Choice argument was made to the Court in *Wyeth*, no one "identified a case in which the FDA ha[d] done so." *Id.* The petitioners add none to the list.

The reason for this is no mystery. Federal law "does not provide that a drug is misbranded simply because the manufacturer has altered an FDA-approved label" or has included a warning or precaution about off-label use. *Id.* The federal misbranding statute instead focuses on the "substance of the label and, among other things, proscribes labels that fail to include 'adequate warnings.'" *Id.* (quoting 21 U.S.C. § 352(f)). It proscribes labels that "fail[] to reveal" material facts about "consequences which may result from . . . customary or usual" use of the drug—including common off-label uses. 21 U.S.C. §§ 321(n) &

352(a). In other words, the federal misbranding provision does not bar manufacturers from providing critical information about known risks. It encourages, even requires, disclosure instead.

The petitioners' misbranding argument is not helped by the fact that the FDA's labeling regulations prohibit statements that "imply or suggest" off-label uses. 21 C.F.R. § 201.57(c)(15)(i); *id.* § 201.80(c)(2)(i) ("Indications or uses must not be implied or suggested in other sections of labeling if not included in this section."). The petitioners have not shown (and cannot show) that it was impossible for them to craft a warning or precaution about the risks caused by pediatric Risperdal use without suggesting that the drug has been approved for that use. Indeed, in 2002, the year before the conduct at issue here occurred, courts had made clear that, when the label for a drug approved only for adult use "specifically disclaims the product's effectiveness for pediatric populations," and pediatric use is "nowhere indicated by the label," that use is "not 'suggested' by that label." *Ass'n of Am. Physicians & Surgeons, Inc. v. U.S. Food & Drug Admin.*, 226 F. Supp. 2d 204, 215–17 (D.D.C. 2002).

So there is no Hobson's Choice here. Longstanding federal law permitted pharmaceutical manufacturers to independently provide physicians with risk information about off-label uses in the circumstances of this case. The complete lack of case law even debating this proposition underscores that certiorari is unwarranted here.

C. The decision below is fully consistent with this Court's cases.

The petitioners claim that the Pennsylvania Superior Court's decision is contrary to this Court's cases in *Wyeth* and *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011), which

"make clear that state tort claims will be permitted when a manufacturer can independently modify a label and will be preempted when it cannot." Pet. 6. They contend that "[t]his case falls squarely on the *Mensing* side of that divide." *Id.* The petitioners are correct that *Wyeth* and *Mensing* establish the governing framework for this case, and that the Superior Court's decision below entails an application of that framework to particular facts. But the petitioners are incorrect that the Superior Court's decision contravenes those cases. To the contrary, the decision reflects the conventional application of settled law to case-specific circumstances.

Like this case, *Wyeth* involved a state-law failure-to-warn claim against a brand-name drug manufacturer. The Court held that the claim was not preempted even though the FDA had approved the drug's label. Explaining that "[i]mpossibility pre-emption is a demanding defense," the Court rejected Wyeth's argument that "it would have violated" the federal misbranding prohibition "if it had unilaterally added such a warning." *Id.* at 570-73. As the Court explained, "Wyeth's cramped reading of the CBE regulation and its broad reading of the [federal] misbranding" provision not only contradicted the text, structure, and purpose of those provisions, but were also "premised on a more fundamental misunderstanding"—the notion that "the FDA, rather than the manufacturer, bears primary responsibility for drug labeling." *Id.* at 570. The Court explained that a "central premise of federal drug regulation" is that the brand-name manufacturer "bears responsibility for the content of its label at all times." *Id.* at 570–71. As a result, "Wyeth had a duty to provide a warning that adequately described that risk, and the CBE regulation permitted it to provide such a warning before receiving the FDA's approval." *Id.* at 571. Thus,

"absent clear evidence that the FDA would not have approved a change to [the] label," *id.*, Wyeth could not show that it was impossible to comply with both federal and state law.

The Court concluded that "[o]n the record before [it], Wyeth ha[d] failed to demonstrate that it was impossible for it to comply with both federal and state requirements." *Id.* at 573. The Court reached this conclusion because the CBE regulation affirmatively permits manufacturers of brand-name drugs to change a drug's label without prior FDA approval "to 'add or strengthen a contraindication, warning, precaution, or adverse reaction' or to 'add or strengthen an instruction . . . that is intended to increase the safe use of the drug.'" *Id.* at 568 (quoting 21 C.F.R. § 314.70(c)(iii)).

Merck reaffirmed these principles. The Court in that case reiterated that a brand-name manufacturer "'bears responsibility for the content of its label at all times,'" and is under a continuing obligation to "'ensur[e] that its warnings remain adequate as long as the drug is on the market.'" 139 S. Ct. at 1677 (quoting *Wyeth*, 555 U.S. at 570–71). When a risk of a particular drug becomes apparent, the manufacturer has "'a duty to provide a warning that adequately describe[s] that risk.'" *Id.* (quoting *Wyeth*, 555 U.S. at 571). As in *Wyeth*, the Court in *Merck* observed that this duty was especially important to the regulatory design prior to 2007 (which is also the relevant period in this case). Before then, "'the FDA lacked the authority to order manufacturers to revise their labels.'" *Id.* (quoting *Wyeth*, 555 U.S. at 571).

Wyeth and *Merck* make clear that brand-name drug manufacturers have the ability to ensure the adequacy of their labels under federal law. Because the CBE rule

permits such manufacturers to provide updated risk information, they "will not ordinarily be able to show that there is an actual conflict between state and federal law such that it was impossible to comply with both." *Merck*, 139 S. Ct. at 1679.

The decision below adheres to the principles laid out in *Wyeth* and *Merck*. It quotes extensively from both cases and concludes that the petitioners, as manufacturers of a brand drug, did not establish that the "regulatory scheme would have 'clearly' prevented [them] from warning about the statistically significant increase in frequency and severity of gynecomastia in boys taking Risperdal." App. 26. "[A]s the United States Supreme Court has recently reiterated, the CBE regulation contemplates that [brand-name] drug manufacturers bear ultimate responsibility to provide adequate descriptions of a drug's newly discovered risks to ensure consumer safety." App. 23. More, "[t]his was particularly so prior to 2007—the relevant period in the case *sub judice*—when the FDA lacked authority to order manufacturers to revise their labels." *Id.* The Superior Court rightly regarded the petitioners' attempt "to justify [their] withholding of additional warnings," on the ground that this was necessary to avoid misbranding, "to be of the type effectively rejected in *Wyeth*." App. 26; *see* App. 25.

The decision below is also consistent with *Mensing*, which involved a state failure-to-warn claim against the manufacturer of a generic drug. Although the Court found that the claim was preempted, it did so based on a key difference between generic manufacturers like Mensing and brand-name manufacturers like the petitioners: "brand-name and generic drug manufacturers have different federal drug labeling duties." 564 U.S. at 613. "A

brand-name manufacturer"—like the petitioners—"is responsible for the accuracy and adequacy of its label," whereas a generic manufacturer is primarily "responsible for ensuring that its warning label is the same as the brand name's." *Id.*

Mensing confirms the correctness of the decision below. The petitioners assert that *Mensing* "concerned warnings for on-label use," while this case "involves the unique (and oxymoronic) context of off-label warnings." Pet. 17. But *Mensing* actually concerned off-label use. It involved the generic version of a drug that was not approved for use over twelve weeks and included a limitation on its label: "[T]herapy longer than 12 weeks has not been evaluated and cannot be recommended." 564 U.S. at 609. Despite this limitation on the label, the plaintiffs had been prescribed the drug "for several years" and then developed tardive dyskinesia. *Id.* at 610. Their failure-to-warn claims were therefore predicated on unindicated off-label use of the drug. *See also, e.g.*, *McNeil v. Wyeth*, 462 F.3d 364, 369–71 (5th Cir. 2006) (rejecting the argument made by Reglan's brand manufacture that it had no duty to warn about the risks of "use longer than twelve weeks," finding that the manufacturer knew about the risks of such "off-label use," which is what "create[d] [its] duty to physicians not to be misleading about the risk of long-term use").

Even though *Mensing* involved off-label rather than on-label use, no one involved in the proceedings before this Court—not the parties, not the federal government, not even the Court itself—believed that the character of the use had any bearing on whether a manufacturer had the ability to update risk information on its label through the CBE process. Quite the contrary: The majority

acknowledged that had the plaintiffs taken the brand-name version of the drug, "*Wyeth* would control and their lawsuits would not be pre-empted." 564 U.S. at 625. The decision below did not run afoul of this Court's cases by reaching the same conclusion.

D. The meaning of 21 C.F.R. § 201.57(e) is not outcome-determinative here.

In any event, whether the 2003 version of 21 C.F.R. § 201.57(e) precluded a brand manufacturer from adding a safety warning about an off-label use does not control this case's outcome. By its plain text, this provision applied only to the part of the label called "warnings." But the preemption question in this case turns on whether there was *any* way that the petitioners could have informed doctors of the significant risks of prescribing Risperdal to children without bringing themselves into violation of federal law. The petitioners assume that they could inform doctors only by changing the "warning" section of the label. But the trial record below and the regulatory regime in effect at the time show the opposite: The petitioners in fact had multiple ways to inform doctors about the serious risks to children associated with Risperdal, and therefore to comply with their state-law duty.

1. For starters, as the Superior Court recognized, the petitioners could have added this information to the part of the label entitled "precautions." Given the unique facts of this case (involving off-label pediatric use), the relevant precautions regulation is 21 C.F.R. § 201.57(f)(9)(vi). The Superior Court correctly observed that this provision was "in effect in 2003 and provided that any 'specific hazard' associated with an unapproved pediatric use 'shall be described in this subsection of the labeling.'" App. 22–23.

This provision not only permitted the petitioners to add such information to the label; it required them to do so.

The petitioners try to minimize the significance of this provision by burying it in a footnote, claiming incorrectly that (1) the court below did not rely on it, (2) the provision "does not apply to a risk like gynecomastia that is not specific to particular pediatric subgroups," and (3) any "warnings under § 201.57(f)(9)(vi) *must be made by a Prior Approval Supplement*, so cannot be added by the manufacturer unilaterally." Pet. 26–27 n.7 (emphasis in original). Each of these statements is wrong.

First, the court below did not ignore this provision. It explicitly cited the provision as the primary basis for the plaintiffs' argument opposing the petitioners' "'off-label use' defense." App. 22–23. The court then credited that argument when it held that the petitioners had failed to show that the FDA's "regulatory scheme"—including 21 C.F.R § 201.57(f)(9)(vi) (2003)—"would have 'clearly' prevented [them] from warning about the statistically significant increase in frequency and severity of gynecomastia in boys taking Risperdal." App. 26.

Second, the plain text and purpose of the provision on pediatric precautions make clear that its mandate applies to any "use of the drug" that is associated with any specific hazard in any "pediatric subgroup"—even if the hazard is associated with every pediatric subgroup. 21 C.F.R. § 201.57(f)(9)(vi). Contrary to the petitioners' reading, a manufacturer is not absolved of its obligation to provide information about a hazard that affects children simply because the hazard affects all children, and not just some. Even if that were the rule, this case does involve a hazard to a particular pediatric subgroup—boys. And regardless of whether this provision required a pediatric precaution

under these circumstances, nothing in the provision even purports to prohibit such a precaution, which is the relevant question for impossibility preemption.

Third, the petitioners are simply mistaken when they say that updating risk information under the precautions provision may not be done unilaterally. The authority that the petitioners cite for this claim refers only to subsections (f)(9)(ii) through (f)(9)(iv) when discussing the availability of the unilateral CBE process. Pet. at 27 (citing *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection In the Labeling*, 59 Fed. Reg. 64,240, 64,248 (Dec. 13, 1994)). It does not mention (f)(9)(v) or (f)(9)(vi), which is in keeping with the FDA's position that changes to add or strengthen warnings about safety "could be put into effect at the time a supplement covering the change is submitted to FDA." *See* 59 Fed. Reg. at 64,248.

2. Nor is the precautions provision the only other route that the petitioners could have taken to comply with their state-law duty to adequately warn. The provision covering the "adverse reactions" section of the label stated in 2003 that this section "shall list the adverse reactions that occur with the drug." 21 C.F.R. § 201.57(g). And the CBE regulation permits changes "[t]o add or strengthen" an "adverse reaction." *Id.* § 314.70(c)(6)(iii)(A). Under these provisions, the petitioners could have unilaterally changed this section of the label to inform doctors of the causal relationship between Risperdal and gynecomastia.

3. Finally, the plaintiffs presented evidence at trial, including expert testimony from Dr. Kessler, the former FDA Commissioner, recounting the many other ways in which the petitioners "could have and should have warned pediatric practitioners prescribing [Risperdal] off-label to

children." Pa. Sup. Ct. Record 270a. Dr. Kessler testified that they could have done so through "their sales force," "medical education," and other communications. *Id.* 270a–73a. Dr. Kessler further testified that, as the court below noted, "[i]n his expert opinion, by the year 2000 or 2001," the petitioners were "marketing Risperdal for children and adolescents" and were thus "obligated to share their studies at this time." App. 22. As Dr. Kessler explained, the petitioners were "promoting, marketing, [and] certainly doing outreach" for Risperdal for "indications in children that [were] off-label." Pa. Sup. Ct. Record 289a–90a. "[I]f you're engaged in that kind of promotion" in particular, he explained, "you have to warn" doctors about the risks so they can make informed recommendations. *Id.*

So, on this record, the problem for the petitioners is insurmountable. Preemption authorizes a court to nullify the jury's verdict only if federal law bars all ways that the petitioners could have adequately warned A.Y.'s doctors of the risks of Risperdal. But even if the petitioners' construction of 21 C.F.R. § 201.57(e) were correct, they still had multiple other ways to warn A.Y.'s doctors under federal law. Thus, the proper interpretation of the 2003 version of 21 C.F.R § 201.57(e) does not affect the outcome here and has no bearing on the correctness of the decision below. For this reason, too, certiorari is unwarranted.

III. The decision below is correct.

Certiorari is also unwarranted because the Superior Court got it right. The court held that, under the facts of this case, the petitioners have not carried their burden of showing that federal law required them to withhold evidence of a "causal association between Risperdal and more frequent and severe gynecomastia in juvenile boys than had been observed in the adult male population."

App. 22, 26. The petitioners' argument to the contrary was that "Risperdal was not approved for pediatric use" in 2003, and "only the FDA had the authority to warn about off-label uses." App. 22. The court properly rejected that argument as "inconsistent with governing" law, and as "out of step with controlling jurisprudence on drug manufacturers' responsibilities to act on their unique access to product information by adequately warning consumers of newly discovered heightened risks of injury associated with the drug." App. 22–23.

In their petition, the petitioners maintain that "[t]he CBE procedure does not permit label changes for off-label uses." Pet. 27. But the CBE regulation contains no such prohibition. It expressly permits a brand manufacturer to unilaterally change a label "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. § 314.70(c)(6)(iii)(A). The petitioners make no argument about how (or why) this broadly worded grant of authority would be unavailable to add or strengthen a contraindication, precaution, or adverse reaction (three of the four categories listed in the CBE rule) for an off-label use.

The regulations themselves leave no doubt that these sections may refer to off-label uses—particularly off-label pediatric uses. As already noted, the relevant precautions regulation specifically applies to drugs that have not been approved for use in the pediatric population. 21 C.F.R. § 201.57(f)(9)(vi) (2003). It says that "[i]f use of the drug in" any "pediatric subgroup[]" is "associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the 'Contraindications' or 'Warnings' section of the labeling and this subsection shall refer to it."

Id. By using the word "shall," the rule affirmatively requires a manufacturer to add warnings about off-label use to the precautions section (and, in certain instances, the contraindications and warnings sections too). Plainly, the petitioners could not be barred from providing increased risk information when federal law required them to do so.

The sole authority that the petitioners cite in support of their claim that they could not have used the CBE process to provide updated safety information relating to off-label uses is 21 C.F.R. § 201.57(e), which covered only the "warnings" section. The petitioners acknowledge that, in 2003, this provision obligated brand manufacturers to revise their labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." 21 C.F.R. § 201.57(e). They claim, however, that an implicit exception was carved out by the next sentence, which stated that a "specific warning relating to a use not provided for under the 'Indications and Usage' section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard." *Id.* The petitioners contend that this sentence "expressly *prohibits* . . . manufacturer-initiated off-label warnings." Pet. 28. This novel reading of the regulation—which no court has ever adopted—cannot be reconciled with the text, context, structure, or purpose of the FDA's scheme.

The text is unambiguous. Brand manufacturers must change their labels "to include a warning as soon as there is reasonable evidence of an association of a serious hazard

with a drug; a causal relationship need not have been proved." That rule contains no language limiting it to on-label uses. To construe the rule as containing such an implicit limitation, moreover, would contradict the federal misbranding statutes, which require manufacturers to warn of any material consequences associated with a common off-label use of a drug. These statutes expressly forbid labels that "fail[] to reveal" material facts about "consequences which may result" from using a drug not only "under the conditions of use prescribed in the labeling or advertising thereof" (*i.e.*, on-label uses), but also "under such conditions of use as are customary or usual" (*i.e.*, common off-label uses). 21 U.S.C. §§ 321(n) & 352(a). The petitioners' reading is thus contrary to this explicit statutory and regulatory text.

The sentence in the regulation granting the FDA limited authority to require a "specific warning" about off-label use does not change this result. 21 C.F.R. § 201.57(e) (2003). Saying that the FDA "may" require a specific warning in some circumstances is not the same as forbidding a manufacturer from providing a warning of any kind on its own. If that were the case, bizarre results would follow. For example, in 2003—in language that has since been removed—section 201.57(e) authorized the FDA to require a specific off-label warning only if there was also a "lack of substantial evidence of effectiveness for [a] disease or condition" for which the drug is commonly prescribed. *Id.* Because, "prior to 2007, the FDA lacked the authority to order manufacturers to revise their labels," *Wyeth*, 555 U.S. at 571, the petitioners' reading of the 2003 regulation would mean that *no one* could have warned about even very serious risks associated with common off-label uses of a drug as long as the drug was effective for that off-label use. The petitioners' offer no

reason why the FDA would have created a senseless regime—one that considers only a drug's potential benefits and not its potential costs, even when lives are at stake.

Nor does it matter that the 2003 rule had a sentence saying that "[s]pecial problems, particularly those that may lead to death or serious injury, may be required by the [FDA] to be placed in a prominently displayed box." 21 C.F.R. § 201.57(e). The petitioners rely on this language (at 22), which has since been relocated, and point to the fact that "black box [warnings] cannot be changed by a CBE." The reason for that, however, is that the FDA has always treated black-box warnings as different from the other sections of the label. Indeed, the current version of the labeling regulations requires the "[b]oxed warning" to be listed in a separate section of the label. 21 C.F.R. § 201.57(c)(1) (2015). The CBE rule allows manufacturers to unilaterally change only the "contraindication, warning, precaution, or adverse reaction" sections of the label—not the boxed warning section. *Id.* §314.70(c)(6)(iii). That the CBE rule draws a distinction between black-box warnings and other warnings and precautions about off-label use, even though both use the same "may be required by the FDA" language, 21 C.F.R. § 201.57(c)(1) (2015), confirms that this language does not by itself eliminate the availability of the unilateral CBE process.

The current regulatory regime is also consistent with the FDA's longstanding approach. When the FDA created boxed warnings in 1979, it stated during the notice-and-comment period that it was "advis[ing]" manufacturers "that, to ensure the significance of boxed warnings in drug labeling, they are permitted in labeling only when specifically required by [the] FDA." 44 Fed. Reg. at

37,448. The FDA did not say the same of warnings outside the black box, including those about off-label use. In fact, it said the opposite: The FDA concluded that "there is no legitimate basis for limiting the labeling to hazards arising from the approved use of the drug, particularly when dangerous unapproved use of the drug has been found." *Id.*

The FDA also advised that "these labeling regulations do not prohibit a manufacturer . . . from warning health care professionals whenever possibly harmful adverse effects associated with the use of the drug are discovered." *Id.* at 37,447. The FDA expressly stated that "additional warnings, as well as contraindications, adverse reactions, and precautions regarding the drug, or the issuance of letters directed to health care professionals (*e.g.*, 'Dear Doctor' letters containing such information) is not prohibited by these regulations." *Id.* The FDA's only limitation on unilateral changes concerned the placement of the warning—it could not be unilaterally put in the black box; the limitation was not about substance. *See In re Avandia Mktg., Sales & Prods. Liab. Litig.*, 945 F.3d 749, 761 (3d Cir. 2019), *cert. denied*, No. 19-1444 (finding no preemption because the plaintiffs "are not arguing that GSK should have added the black box *itself* through the CBE process, but rather that GSK should have added the *content* of the black-box warning *anywhere* on the label"). Certiorari is unwarranted for these reasons as well.

IV. This case would be an unsuitable vehicle through which to address off-label warnings.

Finally, this case would be a bad vehicle for the Court to address the ability of drug manufacturers to warn about hazards associated with common off-label uses of a drug, even assuming that this were a certworthy question.

For one thing, the case presents the question in the context of a regulatory regime that has since been revised in significant respects. Many of the arguments made by the petitioners seek to direct attention to (or away from) language that was moved, modified, deleted, or added in the years since 2003. If the Court were inclined to confront the question of whether, and to what extent, federal law preempts a state failure-to-warn claim based on off-label use of a drug, it should wait for a case that more closely resembles the federal law that is currently in effect.

For another thing, the petitioners criticize the court below for failing to undertake (in their view) a sufficiently rigorous examination of the question presented. Even if there were something to that criticism, it would mean that no court, not even the court below, has grappled with the question presented to the petitioners' liking. This Court should not be the first court to do so.

Further, the record here shows that the petitioners withheld critical risk information that A.Y.'s doctor would have needed to properly assess the risks that Risperdal posed to a young child, even as the petitioners were aggressively marketing Risperdal for pediatric off-label use. In this unique setting—involving not just off-label use but off-label promotion—a brand-name manufacturer's professed concerns about being caught between a regulatory rock and a state-law hard place ring hollow. Warning doctors about the risks of the off-label use would not have violated federal law. It would have helped doctors care for vulnerable children and prevent further harm.

At the end of the day, the petitioners ask this Court to intervene to grant them immunity for failing to warn of the risks of a drug's off-label uses when the pertinent FDA regulations did not prohibit them from providing updated

safety information. The petitioners make this request, moreover, through a vehicle in which the evidence shows that they actively promoted the drug for off-label use while deliberately concealing important risk information from doctors, the scientific community, and the FDA—thereby depriving families of the ability to make informed decisions about medical treatment options for children experiencing difficult mental and behavioral challenges. This Court should decline the invitation.

CONCLUSION

The petition for certiorari should be denied.

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