No. _____

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

PETITION FOR WRIT OF CERTIORARI

JAY P. LEFKOWITZ
Counsel of Record
GILAD BENDHEIM
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
(212) 446-4800
lefkowitz@kirkland.com

Counsel for Petitioners

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QUESTION PRESENTED

Off-label use of prescription drugs is an accepted and beneficial feature of medical practice, but federal law bars drug manufacturers from—and imposes significant civil and criminal penalties for—promoting their drugs for off-label use. 21 U.S.C. §§331(a), 333(a), 352(a) & (f). The FDA accordingly prohibits manufacturers from making unsolicited statements—including warnings in their FDA-approved labeling—about off-label uses, which impliedly promote such uses as safe and effective. By law, only the FDA may impose such a warning: a "specific warning relating to a use not provided for under the [product's labeling] *may be required by Food and Drug Administration*," but only after it determines the "drug is commonly prescribed" off-label and such "usage is associated with a clinically significant risk or hazard." 21 C.F.R. §201.57(e) (2003) (emphasis added).

Petitioner Janssen Pharmaceuticals markets Risperdal, a highly effective treatment for psychotic disorders that, until 2006, was approved only for adults but also prescribed off-label for children. The court below misapplied this Court's decision in *Wyeth v. Levine*, 555 U.S. 555 (2009)—which concerned warnings for *on-label* uses—to hold Petitioners liable under state tort laws for failing to unilaterally add warnings about Risperdal's *off-label* use in children. The decision below exposes Petitioners (and every drug manufacturer) to unendurable liability for failing to do precisely what federal law prohibits. This is the paradigm of impossibility preemption.

The question presented is:

Whether 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.

PARTIES TO THE PROCEEDING

Petitioners, the defendant-appellants below, are Johnson & Johnson, Janssen Pharmaceuticals, Inc., and Janssen Research and Development, LLC. Respondents, the plaintiffs-appellees below, are A.Y. and Billie Ann Yount.

STATEMENT OF RELATED PROCEEDINGS

This case arises from and is related to the following proceedings in the Philadelphia Court of Common Pleas; the Superior Court of Pennsylvania, Eastern District; and the Supreme Court of Pennsylvania:

- *A.Y. v. Janssen Pharms. Inc.*, No. 95 EAL 2020 (Supreme Court of Pennsylvania) (order denying petition for allowance of appeal issued Sept. 1, 2020).
- *A.Y. v. Janssen Pharms., Inc.*, No. 3058 EDA 2016 (Superior Court of Pennsylvania) (opinion filed Nov. 26, 2019).
- *A.Y. v. Janssen Pharms., Inc.*, No. 2094 (Philadelphia Court of Common Pleas) (opinion filed June 20, 2018).

The Superior Court's November 26, 2019 opinion remanded the case in part to the Philadelphia Court of Common Pleas for determination of potential punitive damages. 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).

CORPORATE DISCLOSURE STATEMENT

Petitioner Johnson & Johnson is a publicly held company and has no parent company. No publicly held corporation owns 10% or more of its stock. Johnson & Johnson is the parent company of Petitioner Janssen Pharmaceuticals, Inc., and owns 100% of its stock. Petitioner Janssen Research & Development, LLC is a wholly owned subsidiary of Johnson & Johnson. Its sole member is Centocor Research & Development, Inc.

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PETITION FOR WRIT OF CERTIORARI

The decision below upends the FDA's carefully calibrated approach to off-label warnings and exposes the pharmaceutical industry to massive state-law liability unless they violate the federal bar against unilaterally adding such warnings to their product labeling—and thereby impliedly promoting unapproved, off-label uses. That is the essence of impossibility preemption. *See PLIVA, Inc. v. Mensing*, 564 U.S. 604, 624 (2011). The decision and resultant $70 million verdict in this case—just one of nearly 10,000 similar cases pending against Petitioners—cries out for review.

Physicians' prescription of drugs for off-label use is widely accepted in the practice of medicine, but beyond the scope of federal regulation because the FDA regulates the manufacture, sale, and promotion of prescription medications (and not the independent decisions of healthcare professionals). 21 U.S.C. §396. Yet the Food, Drug, & Cosmetic Act ("FDCA") prohibits manufacturers from promoting a prescription drug for any uses not approved by the FDA and explicitly listed on the drug label. 21 U.S.C. §331(a). The FDA considers off-label promotion a form of misbranding—a felony, 21 U.S.C. §§331(a), 333(a)(2), 352(a) & (f)—and vigorously enforces the law against offending prescription drug manufacturers.

Consistent with those restrictions, prescription drug manufacturers may not unilaterally amend a drug's labeling to add a warning for an off-label use because doing so impliedly promotes the use of products for an off-label purpose that the FDA has not

determined is safe and effective. *See Regulations Regarding "Intended Uses"*, 85 Fed. Reg. 59,718, 59,724 (proposed Sept. 23, 2020) ("Any claim or statement made by or on behalf of a firm that implicitly represents a product for a particular use is also relevant to intended use."). Indeed, the very notion of an "off-label warning" is a contradiction in terms: Adding a warning about risks associated with an *off*-label use by definition puts that use *on*-label. The FDA reasonably concluded, therefore, that whether to add off-label warnings could not be left to a manufacturer's unilateral discretion.

The FDA instead reserved to itself the power to mandate off-label warnings where—and only where—the expert agency determines they are necessary. 21 C.F.R. §201.57(e) ("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.")[1] This is a sharp break from the regulatory paradigm for on-label uses, in which manufacturers are required to maintain the adequacy of their labels, and generally have the legal authority to update warnings regarding approved uses unilaterally (*i.e.*, without prior FDA review and approval). *See Wyeth v. Levine*, 555 U.S. 555, 568 (2009); 21 C.F.R. §314.70(c)(2)(i) (2003).

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[1] In June 2006, §201.57 was reorganized, and subsection (e) was recodified at §201.57(c)(6)(i), while other provisions in the section were incorporated into a new provision, §201.80. For consistency, this Petition refers to the off-label warning provision as 201.57(e) regardless of time period.

Notwithstanding the clear federal bar against manufacturer-initiated off-label warnings, the Pennsylvania state courts permitted this case to go to a Philadelphia jury that subsequently found that Tennessee law required Petitioners to provide pediatric warnings regarding Risperdal, even though the FDA never approved that product for use in children and never exercised its exclusive authority to mandate such off-label warnings.

In allowing the jury to consider a claim that petitioners should have warned of off-label uses, the court below erroneously failed even to consider the statutory and regulatory provisions through which the FDA established the unique regulatory regime for off-label uses. Instead, the court relied almost exclusively on this Court's decisions in *Wyeth*, 555 U.S. 555, and *Merck Sharp & Dohme Corp. v. Albrecht*, 139 S.Ct. 1668 (2019), which involved warnings for approved *on-label* uses and *did not* address the FDA's express regulatory prohibitions against unilateral label changes for off-label uses. In doing so, the court reached the unfounded conclusion that Petitioners could have utilized the so-called Changes Being Effected ("CBE") process, 21 C.F.R. §314.70(c)(2)(i) (2003), to independently add warnings concerning risks allegedly associated with off-label uses of Risperdal. But the CBE process is reserved for changing warnings about approved (*i.e.*, on-label uses), not for warnings about unapproved off-label uses that the FDA expressly prohibits manufacturers from making themselves.

The Court in *Wyeth* explained that it "ha[d] no occasion in [*Wyeth*] to consider the pre-emptive effect

of a specific agency regulation bearing the force of law." 555 U.S. at 580. That is *precisely* the circumstance here. As Justice Breyer took care to "emphasize" in his concurrence, in specific circumstances "[t]he FDA may seek to determine whether and when state tort law acts as a help or a hindrance to achieving . . . safe drug-related medical care," and "may seek to embody those determinations in lawful specific regulations describing, for example, when labeling requirements serve as a ceiling as well as a floor," which might "have pre-emptive effect." *Id.* at 581–82 (Breyer, J., concurring). Ignoring this express reservation and the fact that *Wyeth* involved a situation where federal law permitted the manufacturer to act unilaterally to add a warning, lower courts—like the Superior Court in its decision below—have indiscriminately applied *Wyeth*'s discussions of the CBE regime to all manner of failure-to-warn claims, irrespective of the "specific regulations" that otherwise prohibit using CBE changes.

This case vividly illustrates the specific concerns raised in *Wyeth*. In 21 C.F.R. §201.57(e)—a "specific agency regulation bearing the force of law," 555 U.S. at 580—the FDA "embod[ied] [its] determination[]" that manufacturer-initiated off-label warnings would serve as a "a hindrance to achieving . . . safe drug-related medical care." *Id.* at 581–82 (Breyer, J., concurring). This agency mandate should rightly be accorded preemptive effect. At the very least, *Wyeth* itself demands that a preemption decision must grapple with the FDA's regulation on its terms. Instead, purporting to fly *Wyeth*'s banner, the court below disregarded the FDA's regulations prohibiting

manufacturer-initiated off-label warnings. In doing so, the court below committed two errors. *First*, it ignored that *Wyeth's* holding is limited to situations where, in stark contrast to this case, federal law authorizes manufacturers to effectuate the requested label change without FDA's prior approval. *Second,* it expanded the reach of the *procedural* CBE regulations to trump the FDA's *substantive* labeling regime in §201.57(e), and thereby usurped from the FDA its exclusive authority as the expert body charged with protecting public health to require—and, absent such action, to prohibit—off-label warnings. This is a consequential error that this Court should correct.

In addition to unsettling the federal regulatory scheme, the decision below has enormous adverse financial consequences. The court's erroneous view of the federal regulatory regime and the scope of federal preemption left Petitioners facing $70 million in compensatory liability to Plaintiffs in just the action below, which itself is just one of nearly 10,000 similar actions waiting in the wings. In fact, another Risperdal plaintiff subsequently obtained an *$8 billion* punitive damages award in the same court on the same theory of liability, before the trial court remitted it to a still significant $6.8 million. And because up to one-third of all United States prescriptions are prescribed off-label, the pharmaceutical industry as a whole is now exposed to astronomic liability as a result of off-label prescribing that they cannot redress through their product labeling.

This Court's intervention is thus needed to correct this significant and far-reaching distortion of federal

law and usurpation of the FDA's exclusive authority. The Court's decisions in *Wyeth* and *Mensing* make clear that state tort claims will be permitted when a manufacturer can independently modify a label and will be preempted when it cannot. This case falls squarely on the *Mensing* side of that divide. And because of how pervasive off-label use of drugs is in America, the question of whether off-label failure-to-warn claims are preempted is an exceedingly important one that this Court should resolve.

OPINIONS BELOW

The decision of the Supreme Court of Pennsylvania denying allowance of appeal is reported at 238 A.3d 341 (Pa. 2020) and reproduced at App.1. The opinion of the Pennsylvania Superior Court is reported at 2019 PA Super 348, 224 A.3d 1, 8 (2019) and reproduced at App.2. The opinion filed by the Philadelphia County Court of Common Pleas, as required by Pennsylvania Rule of Appellate Procedure 1925(b), is unreported, but is reproduced at App.60. The Order of the Philadelphia County Court of Common Pleas is unreported, but is available at 2016 WL 4131498 (Pa. Com. Pl. July 05, 2016) and is reproduced at App.205.

JURISDICTION

The Supreme Court of Pennsylvania denied Petitioners' petition for allowance of appeal on September 1, 2020. On March 19, 2020, this Court extended the deadline to file any petition for a writ of

certiorari due on or after that date to 150 days. This Court has jurisdiction under 28 U.S.C. §1257(a).[2]

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

21 C.F.R. §201.57 (eff. Apr. 1, 2003) is reproduced at App.208. 21 C.F.R. §314.70 (eff. Apr. 1, 2003) is reproduced at App.239.

STATEMENT OF THE CASE

A. The FDA's Review and Approval of Drug Labeling.

1. The FDA's statutory authority

The statutory regime under which the FDA regulates prescription drugs reflects a pervasive federal role in regulating the safety and effectiveness of their labeled uses. Congress enacted the original FDCA, Pub. L. No. 75-717, 52 Stat. 1040 (1938), to preclude interstate shipment of a new drug *unless* the

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[2] The Superior Court remanded in part to "consider conflict of-law-principles with respect to Tennessee and New Jersey and how they bear on Plaintiffs/Appellees' punitive damages claim." (App.58–59.) Petitioners did not seek allowance of appeal for this part of the Superior Court's order to the Pennsylvania Supreme Court. Nonetheless, this Court may treat the decision below as final, both because "the federal issue is conclusive" of the proceedings to come and because the "federal issue . . . will survive and require decision regardless of the outcome of future state-court proceedings." *Cox Broad. Corp. v. Cohn*, 420 U.S. 469, 479–80 (1975). If federal law preempts the state tort on which liability is founded here, there would be no punitive damages to assess. And regardless of the outcome of the punitive damages issue, this preemption question will remain unresolved and require this Court's decision.

FDA determined that the drug was "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," *id.* §505(a), (d), 52 Stat. at 1052, and it required that the labeling of all drugs provide "adequate directions for use" and "adequate warnings" against unsafe uses and methods of administration, *id.* §502(f), 52 Stat. at 1051.

To enforce those requirements, the statute prohibited manufacturers from distributing a new drug until the drug obtained FDA approval, and it required manufacturers to submit "specimens of the labeling proposed to be used for such drug" to the FDA as a central component of such approval. *See id.* §505(a), (b), 52 Stat. at 1052. Thus, if a manufacturer alters a drug's labeling without submitting the proposed changes to the FDA, the drug would be "misbranded" because it would no longer be one for which approval was obtained, and interstate distribution of the drug would be unlawful and subject to criminal and civil penalties. *See id.* §§301(a), (d), 303(a), 304, 505(a), (d)(1), 52 Stat. at 1041–46, 1052.

In 1962, Congress amended the FDCA to require the FDA to determine that a drug is not only safe, but also that it is *effective* "under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." Drug Amendments of 1962, Pub. L. No. 87-781, §102(b), (c), 76 Stat. 780, 781 (1962). After the amendment, the determination of a drug's safety is "inseparable from consideration of the drug's effectiveness." S. Rep. No. 87-1744, at 15 (1962). The addition of the "effectiveness" requirement reflects the central pillar of the FDA's modern regulatory authority. Since 1962, the FDA's

risk-benefit calculus for approving a drug is whether or not its intended uses—as set-out in the "labeling thereof"—outweigh its safety risks.

2. The FDA's regulatory approval and labeling regime

Consistent with the 1962 amendment, the FDA's drug approval regime expressly ties the right to market a drug with the adequacy of its labeling *for the particular use(s) or indication(s) proposed on the label*. It does so by requiring proof of safety and efficacy of a drug for *those labeled uses*, and by forcing the FDA to conduct a risk-benefit balancing *concerning those uses* prior to approval—*i.e.*, to determine whether the product's benefits for the specified use outweigh its risks for that use, under the conditions of use and warnings set forth in the labeling. *See* 21 U.S.C. §355(d); 21 C.F.R. §314.50(d)(5)(viii) (requiring new drug applications to include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks *under the conditions stated in the labeling*" (emphasis added)).

Under FDA regulations, a drug's labeling must describe the drug, its indications and usage, contraindications, warnings, precautions, and instructions on dosage. 21 C.F.R. §201.56(d)(1). Throughout the relevant period (and still today), FDA regulations also describe the "[s]pecific requirements on content and format of labeling for human prescription drugs," including by specifying the circumstances in which a manufacturer must warn of risks associated to the uses indicated on the FDA-approved label. *Id.* §201.57. To ensure that these requirements are met, the FDA reviews the drug's

proposed labeling as part of the approval process. Once the FDA approves a drug, it requires the manufacturer to distribute the drug only under the precise FDA-approved labeling. *Id.* §314.105(b).

Because the FDCA permits manufacturers to distribute only those drugs that the FDA has certified to be safe and effective *under labeled conditions of use*, a manufacturer generally may not change a drug's FDA-approved labeling without obtaining the FDA's prior approval of a supplemental application (a "PAS" filing). *See* 21 U.S.C. §355(a), (b)(1)(F), (c)(1)(A), (d); *see also* 21 C.F.R. §314.70(b)(3). A narrow exception to this rule in the FDA regulations permits a manufacturer to file a CBE supplement to implement a labeling change before the FDA has acted on the application. But a CBE supplement is allowed only if the change is, *inter alia*, intended "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction." 21 C.F.R. §314.70(c)(2)(i); *Wyeth*, 555 U.S. at 568. Of course, the CBE regulation does not permit a manufacturer to impose *any* strengthened warning it desires; in all circumstances, the content of the label must conform to §201.57's substantive requirements delineating what sorts of warnings may appear on a label in the first place. *See, e.g.*, *Wyeth*, 555 U.S. at 570 (explaining that the FDCA's "misbranding provision focuses on the substance of the label," not the means by which the label was altered). No matter how it is implemented, a label change precluded by §201.57 would render the label "false or misleading" and subject the manufacturer to enforcement action for misbranding. 21 C.F.R. §201.56(b).

3. The FDA's Off-Label Warning Regulatory Regime

Although medical practitioners may prescribe drugs off-label, manufacturers may not *promote* the off-label use of their drugs. The FDCA prohibits "misbranding," 21 U.S.C. §331(a), and provides that a drug is misbranded if its labeling fails to bear "adequate directions for use," *id.* §352(f). Adequate directions for use, in turn, may be included on the label only with respect to a product's "intended use." 21 C.F.R. §§201.5, 801.5. And if a product is "offered and used" for a use other than the "intended use," such promotion can establish a different "intended use" that lacks the required "adequate directions for use." *Id.* §§201.128, 801.4.[3] In short, a manufacturer who makes any unsolicited statement regarding an off-label use for their drug—or amends the label of their drug in a manner inconsistent with the FDA's label-content regulations—may be found to be promoting a new intended use, and faces a serious risk of civil and criminal prosecution. *See* 21 U.S.C. §333(a)(2); 21 C.F.R. §§1.3, 202.1(l); 85 Fed. Reg. at 59,724–25 (explaining that statements "that implicitly

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[3] Although under this definition mere knowledge of an off-label use could create a change in intended use, the FDA has long rejected this interpretation and "would not regard a firm as intending an unapproved new use for an approved or cleared drug or device based solely on that firm's knowledge that its product was being prescribed or used by doctors for such use." *Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs*, 82 Fed. Reg. 14,319, 14,320 (March 20, 2017).

represent[] a product for a particular use" may establish an intended use).

B. Facts and Procedural History

This Petition arises from one of more than 7,000 cases in the Philadelphia Court of Common Pleas, most of which allege that Janssen failed to warn about a risk of gynecomastia in children who used Risperdal (Risperidone) off-label, even though federal law prohibited Janssen from making such warning because the product was not approved for pediatric use at that time.[4]

The FDA approved Risperdal in 1993 for the treatment of psychotic disorders in adults. Risperidone is included on the World Health Organization's list of essential medicines,[5] and the FDA itself has noted that Risperdal is "an important and beneficial therapeutic option for many children and adolescents." (RR.00149a.)[6]

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[4] *See* Court of Common Pleas Trial Division - Civil Complex Litigation Center Mass Tort Program Case list, https://www.courts.phila.gov/apps/cvclc/caselist/default.aspx?search=Risperdal (last visited Jan. 29, 2021). There are thousands more such cases pending in other jurisdictions, most of which allege failure to warn about pediatric risks. As of December 30, 2018, there were an estimated 13,400 Risperdal cases pending in the U.S. Johnson & Johnson Co., Annual Report (Form 10-K) 84–85 (Feb. 20, 2019).

[5] *Model List of Essential Medicines*, WHO (2019) https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?sequence=1&isAllowed=y.

[6] References to the Superior Court Reproduced Record will be denoted RR.####.

As with many antipsychotics, Risperdal is reported to be associated with elevated levels of the hormone prolactin (a condition known as "hyperprolactinemia"). Most individuals with hyperprolactinemia do not exhibit side effects. But some individuals with hyperprolactinemia have exhibited gynecomastia, which is the growth of breast tissue in males. Since the initial approval, Risperdal's label has always contained warnings about reports of hyperprolactinemia and gynecomastia. But because Risperdal was approved only for adults, the FDA-approved labeling did not include a pediatric warning with reporting rates of possible adverse events in pediatric populations until the FDA approved the product for pediatric uses in 2006. Instead, between 1993 and 2006, the Risperdal label stated that "[s]afety and effectiveness in children have not been established"—as required by 21 C.F.R. §201.57(f)(9)(vi). After the FDA approved Risperdal for pediatric use in 2006, the label was revised to describe that, based on aggregate data, 2.3% of the subjects in 18 pediatric studies involving Risperdal developed gynecomastia at some point during their clinical trial participation. (RR.03081a.)

Plaintiff A.Y.'s doctor first prescribed him Risperdal in 2003, when A.Y. was four years old, to treat his behavior associated with oppositional defiant disorder. (App.9.) That prescribed use, commencing three years before the FDA approved any pediatric indication, was "off-label." (App.8.) A.Y. developed gynecomastia, and—consistent with the existing warnings—his doctor discontinued the Risperdal treatment. (App.9.) But A.Y.'s mother specifically requested that Risperdal treatment be resumed,

because it was the only medication that had successfully treated him. (RR.01707a, 02537a.)

Nonetheless, A.Y. and his mother brought suit against Janssen, asserting that he would not have used Risperdal had he known of the risk of gynecomastia from the pediatric use of Risperdal. Even after that filing, A.Y.'s mother insisted that he continue to receive Risperdal. (RR.2430–31a, 2633a.) The trial court, however, prevented Janssen from presenting to the jury this evidence of A.Y.'s continued Risperdal use. (App.78–79.)

After trial, the jury found Janssen liable for failing to warn about the risk of gynecomastia in pediatric users before the 2003 initial prescription of Risperdal. Although Plaintiffs put forth no evidence of medical costs, lost wages, or any other compensable loss—indeed, although A.Y. was then an adult, neither he nor his mother testified—the jury awarded A.Y. $70 million in compensatory damages for his alleged embarrassment and emotional distress. (App.56–57.) That award was based solely on a state-law failure-to-warn claim that the trial court allowed over Janssen's objections. (RR.02140a.)

Both before the trial court and on appeal, Janssen argued that the federal regulatory regime preempted A.Y.'s claims. (App.12, 69.) Janssen explained, as set forth below, that 21 C.F.R. §201.57(e) makes clear that warnings pertaining to off-label use can be added to product labeling only by the FDA, and thus that application holders like Janssen cannot unilaterally add off-label warnings through a CBE revision under 21 C.F.R. §314.70, which is reserved for changes that do not require FDA pre-approval.

The trial court denied this portion of Janssen's summary judgment motion (RR.01451a–52a), passingly asserting in its post-trial opinion that this Court's holding in *Wyeth* made Janssen responsible for the contents of Risperdal's label (App.98). The trial court otherwise failed to mention §201.57(e) or its express reservation of the FDA's exclusive authority to address off-label use in labeling. (App.103–04.)

Janssen appealed, and, in its briefs and application for reargument *en banc*, again argued that §201.57(e) precluded Janssen from effectuating the label change Plaintiffs demanded. (App.17.) The Superior Court, too, rejected this argument, and likewise failed to grapple with §201.57(e), noting this dispositive regulation just once in passing. (App.21.) Instead, relying on a series of block quotations from this Court's decisions in *Wyeth* and *Merck*, the Superior Court held that manufacturers' general responsibility "to provide adequate descriptions of a drug's newly discovered risks to ensure consumer safety" meant that Janssen could have used the CBE procedure to implement Plaintiffs' requested off-label warning. (App.23–24.) Absent from its analysis was any recognition that in §201.57(e) the FDA prohibited manufacturers from utilizing the CBE procedure to implement off-label warnings. Likewise unaddressed was that *Wyeth* expressly disclaimed the application of its holding to such circumstances where an on-point regulation put a CBE change out of the manufacturer's reach. Nevertheless, the Superior Court deemed *Wyeth* "controlling." (App.23.) On top of this clear error, the court turned *Wyeth*'s discussion of a manufacturer's labeling obligations into a supra-regulatory edifice that, at pain of crippling state-law

tort judgments, obligates manufacturers to utilize the CBE procedure to add warnings about any "heightened risks of injury associated with the drug," despite federal law that prohibits the addition of such a warning for off-label uses absent FDA approval. (App.23.) After the Superior Court denied Janssen's request for rehearing, Janssen sought allowance of appeal from the Pennsylvania Supreme Court, which that court denied.

REASONS FOR GRANTING THE PETITION

This Petition asks the Court to make clear that courts may not hold drug manufacturers liable under state law for failing to do precisely what federal law prohibits them from doing. Given the widespread use of off-label prescription drugs, and the thousands of pending cases in which pharmaceutical companies face potentially crushing liability, manufacturers face literally billions of dollars in exposure if such state-law claims are allowed to proceed.

Each of the lower court's errors can be traced back to this Court's seminal decision in *Wyeth*, which held that brand-name prescription drug manufacturers may be liable under state tort laws for failing to provide adequate warnings regarding *on-label* uses because such manufacturers generally have both the responsibility and power unilaterally to alter *on-label* warnings under the CBE regulation. But the Court in *Wyeth* was careful to limit its holding to situations in which FDA regulations did not expressly prohibit manufacturers from using the CBE regulations to impose the allegedly required warning.

Because lower courts overread that ruling as foreclosing any federal preemption of state tort claims

against any drug manufacturers, this Court took *Mensing*— which also concerned warnings for *on-label* use—to clarify that federal law preempts claims against generic manufacturers. That is so because generic manufacturers are prohibited from using the CBE regulation to deviate from the branded drug's labeling. *See Mensing*, 564 U.S. at 614–15. In *Mensing*, this Court reiterated that where FDA regulations *prohibit* manufacturers from unilaterally implementing label changes via the CBE provision, *Wyeth*'s preemption rationale does not control, irrespective of whether, as a general matter, manufacturers are responsible for maintaining the adequacy of their labels.

This case arises at the intersection of *Wyeth* and *Mensing*, and reflects the same problems that led this Court to limit *Wyeth*'s scope in *Mensing*. Like *Wyeth*, it involves a brand manufacturer. But like *Mensing*, it involves a regulatory prohibition that bars manufacturers from using a CBE to change a label. Unlike either prior case, however, this one (and the thousands of pending cases just like it) involves the unique (and oxymoronic) context of *off-label* warnings. The Pennsylvania Superior Court, however, ignored that distinction because it misread and misapplied *Wyeth*'s assertion that brand manufacturers bear responsibility for the content of their labeling at all times. (App.23 (explaining that "as 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").)

That decision is contrary to *Wyeth*'s actual holding, and directly in conflict with federal law addressing the wholly distinct context of off-label uses. Today in Pennsylvania as a result of the Superior Court's gross misapprehension of *Wyeth*, a pharmaceutical manufacturer bears an evergreen obligation to use the CBE rule to unilaterally change its drug's label to warn of potential hazards for off-label uses, even though the FDA expressly prohibits a manufacturer from doing so.

This error has serious consequences for the interplay between state and federal law, and for the FDA's ability to exercise its statutory obligation to ensure the safety of drug products. It also has untenable implications for Petitioners, as it imposes a standard that is impossible to meet in a mass tort litigation with potentially billions of dollars of exposure, and which has already yielded a $70 million verdict here (with potential punitive damages to follow), and a (later-remitted) multi-*billion* dollar punitive damages verdict to a single plaintiff in an analogous subsequent action. And the error similarly has draconian financial implications for all prescription drug manufacturers, as up to one-third of all drug prescriptions are for unapproved uses. In short, the decision below puts the entire pharmaceutical industry to an impossible Hobson's Choice: modify your label and risk federal prosecution for misbranding, or face untold billions of dollars in state-tort judgments for failing to do so. This Court's intervention is needed.

I. The Decision Below Wrongly Decides an Important Issue of Federal Preemption Law.

The essence of the Supremacy Clause is that state law may not require what federal law prohibits. Here, the Pennsylvania courts permitted a state tort lawsuit for failure-to-warn to proceed despite the fact that 21 C.F.R §201.57(e) and longstanding FDA policies in the realm of off-label promotion and drug warning labeling make crystal clear that a manufacturer may not independently warn the public about risks associated with off-label uses of their drugs. Rather, the FDA has reserved for itself the careful balancing required to determine whether to impart such a suggestive warning. The instant lawsuit should have been preempted by federal law.

A. FDA Regulations Control How a Manufacturer May Alter a Drug's Label and Prohibit Manufacturers from Independently Warning of Off-Label Risks.

1. 21 C.F.R. §201.57(e) prohibits manufacturers from adding off-label warnings

When A.Y. began taking Risperdal in 2003, the FDA's regulations dictating when manufacturers could include a warning for risks associated with the use of a drug—and the permissible content of such a warning—was codified in §201.57(e). That regulation generally provided that a drug's "labeling shall describe serious adverse reactions and potential safety hazards" associated with the drug, but clarified that such warnings necessarily are limited to *approved* uses unless the FDA specifically orders otherwise:

> 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.

21 C.F.R. §201.57(e) (emphasis added).

That language makes clear that the FDA alone has the authority to add off-label warnings. And it preempts A.Y.'s claims here because Janssen could have not complied with any state-imposed duty to add such warnings on its own without violating federal law. Both the plain text of §201.57(e) and its regulatory context confirm this conclusion.

1. By its terms, §201.57(e) is an exclusive grant of authority to the FDA. By law, everything that appears on a product's label is "required" by the FDA: the FDA can only approve a drug if it finds that the drug's labeling adequately discloses risks and contains sufficient warnings. *See* 21 U.S.C. §355(d) ("If the Secretary finds . . . such labeling is false or misleading in any particular[,] he shall issue an order refusing to approve the application."). And inherent in the FDA's authority to regulate drug labeling is its authority to "require" that a manufacturer adequately describe the drug's risks on its label. *Id.* §352(a)(1) ("A drug or device shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular."); *see also* FDA, SAFETY LABELING CHANGES — IMPLEMENTATION OF SECTION 505(O)(4) OF THE FD&C

ACT (July 2013) at 2–3 (listing the FDA's prior means of enforcing requested labeling changes).

Against this backdrop, the only reason to specify that the FDA can require off-label warnings is to establish that off-label warnings otherwise are prohibited. It therefore serves a restrictive purpose—to reserve to the FDA the sole authority to implement off-label warnings—not simply to reiterate the non-exclusive authority that the FDA *always* has in the context of drug labeling. To hold otherwise would fail to provide independent meaning to a unique and striking turn of phrase whose inclusion cannot be anything but intentional. And because reading "may be required" by the FDA as an exclusive reservation of labeling authority also serves to give independent meaning to every other prescriptive phrase in subsection (e), the canon against surplusage works with particular force here. *See, e.g.*, *Marx v. Gen. Revenue Corp.*, 568 U.S. 371, 385 (2013).

If the FDA intended "may be required by" the FDA to mean that, whether or not the FDA *required* the off-label warning, manufacturers *also* had an obligation to impose one, it easily could (and should) have said just that. The regulation would simply have said that "[t]he labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug"—precisely the language that §201.57(e) *already* employs for warnings for on-label uses in its second sentence. That the regulation uses different language to describe when warnings for *off-label* uses are required than for when warnings for *on-label* uses are required indicates that the regulatory mandate is different for

the two situations. *See, e.g.*, *Henson v. Santander Consumer USA Inc.*, 137 S. Ct. 1718, 1723 (2017) ("[W]hen we're engaged in the business of interpreting statutes we presume differences in language . . . convey differences in meaning."). Namely, whereas manufacturers "shall" revise their labels to account for risks associated with on-label uses, manufacturers have no independent regulatory authority to institute such a change for off-label warnings. Only the FDA "may" require such warnings.

Finally, the FDA elsewhere used the same phrase to signify that the FDA has exclusive authority to allow the use of certain labeling—and courts typically give the same language in the same law the same meaning. *See, e.g.*, *Fourth Estate Pub. Benefit Corp. v. Wall-Street.com, LLC*, 139 S. Ct. 881, 889 (2019) (rejecting the "implausible assumption that" the same word could have "different meanings in consecutive, related sentences within a single statutory provision"). In particular, the sentence that immediately follows the off-label warning provision uses the same "may be required by" the FDA formulation to describe "black box warnings," which the FDA explained "are permitted in labeling only when specifically required by FDA." *Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs*, 44 Fed. Reg. 37,434, 37,448 (June 26, 1979); *see In re Depakote*, 87 F. Supp. 3d 916, 924 (S.D. Ill. 2015) (holding that black box cannot be changed by a CBE). Notably, the sentence discussing the black-box warning in the proposed rule merely said that such "labeling may be required," *Labeling for Prescription Drugs Used in Man*, 40 Fed. Reg. 15,392, 15,397 (Apr.

7, 1975), but in response to comments asking "whether a manufacturer may include a boxed warning without prior FDA approval" the final rule added "by the" FDA to clarify that *only* the FDA may implement such a label, 44 Fed. Reg. at 37,448, 37,463.

Consistent with settled rules of statutory interpretation, the same interpretation applies to warnings regarding off-label uses. Just as the FDA has explained that the same "may be required" language is an exclusive reservation of authority to the Agency in the black-box content, the "may be required" language in §201.57(e) functions as an exclusive reservation of authority to FDA in the off-label warnings context. Indeed, the fact that the FDA added "by the" FDA to the off-label warning sentence at the same time that it added it to the black-box warning sentence *for the purpose of* prohibiting manufacturers from unilaterally adding such labeling, makes clear that a similar prohibition applies to off-label warnings. *See* 40 Fed. Reg. at 15,397; 44 Fed. Reg. at 37,463.

2. The FDA's regulatory and policy statements further reinforce that §201.57(e) vests the FDA with exclusive authority to decide whether to impose an off-label warning.

As noted, in the proposed rule, subsection (e) read merely that off-label warnings "may be required if the drug is commonly prescribed." 40 Fed. Reg. at 15,397. The FDA's final rule, by contrast, clarified that the warning "may be required *by the Food and Drug Administration*," making clear that implementing an off-label warning is not simply something that may be required of a manufacturer, but rather is something

that *the FDA* may require a manufacturer to do, but which is not otherwise permitted under the regulations. 44 Fed. Reg. at 37,463.

The FDA reaffirmed this position in the preamble to its 2006 amendments to §201.57—which renumbered subsection (e) to subsection (c)(6)—where it explained that "the final rule (§201.57(c)(6)(i)) states that FDA may require labeling to include a specific warning relating to a use that is not provided for under the 'Indications and Usage' section" and "clarified that its authority under this provision must be exercised in accordance with sections 201(n) and 502(a) of the act." *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3,922, 3,947 (Jan. 24, 2006). Sections 201(n) and 502(a) of the FDCA are the FDA's misbranding regulations, which make clear that manufacturers generally are not permitted to make *any* representations about off-label uses. The FDA's caution that this provision *should not* be construed as changing the misbranding rules would be nonsensical if §201.57(e) in fact broke dramatically from the rest of the FDA's misbranding proscriptions and somehow allowed manufacturers to add off-label warnings unilaterally. The decision below that *requires* manufacturers to warn about off-label risks is completely at odds with the FDA's strenuous insistence—in the face of significant First Amendment concerns—that manufacturers generally are *not* permitted to share even truthful information related to off-label uses of their drugs. *See U.S. v. Caronia*, 703 F.3d 149, 154, 166–69 (2d Cir. 2012).

The FDA's most recent statements concerning §201.57(e) leave no doubt that a manufacturer may not itself impose off-label warnings. In its 2018 guidance on the Indications and Usage section, the Agency explains that:

> 'Indications or uses must not be implied or suggested in other sections of the labeling if not included' in the INDICATIONS AND USAGE section (§201.57(c)(2)(iv) and (v)). *However, FDA may require* a specific warning relating to an unapproved use in the WARNINGS AND PRECAUTIONS section of the labeling if the drug is commonly prescribed for a disease or condition and if such usage is associated with a clinically significant risk or hazard (§201.57(c)(6)(i)).

FDA, INDICATIONS AND USAGE SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS — CONTENT AND FORMAT GUIDANCE FOR INDUSTRY (July 2018) (emphasis added). The meaning here is plain. Manufacturers, in the exercise of their obligation to maintain the adequacy of their labels, must take care not to imply that an off-label use is possible, such as by including a warning related to an off-label use. "*However*," whereas a manufacturer may not do so on their own, the "*FDA may require*" such a specific warning in a narrow set of circumstances, and the prohibition on off-label warnings does not preclude a manufacturer from complying with that order. *See* However, *Webster's New World College Dictionary* (4th ed. 2006) (meaning "nevertheless; yet; in spite of that").

The Superior Court simply failed to contend with §201.57(e), or to explain why its clear text did not compel a finding that Plaintiffs' off-label failure-to-warn claim was preempted. Instead, the court addressed this controlling regulation just once, where, in the context of describing Janssen's preemption argument, the court noted that Janssen argued that §201.57(e) "provides that only the Food and Drug Administration ('FDA') may require a warning concerning a risk of an off-label or non-approved use." (App.21.) The court never considered the text of §201.57(e) and, after this passing mention, never returned to the subject.

Having ignored the key language in the regulation, the court then pivoted to a series of block quotes from this Court's decisions in *Wyeth* and *Merck* that—despite *Wyeth's* express indication to the contrary—the court below claimed was the "controlling jurisprudence" on prescription drug manufacturer's labeling obligations. (App.23.) Relying exclusively on *Wyeth's* comment that the "manufacturer bears responsibility for the content of its label" and its discussion of the manufacturer's ability to utilize the CBE regulation to effectuate label changes *where there is no express FDA regulation prohibiting such a change*—but without so much as addressing that precise prohibition in §201.57(e)—the court held that Janssen could have implemented the warning that Plaintiffs sought by a CBE.[7] (App.23–24.) That conclusion is dangerously wrong.

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[7] The Superior Court briefly noted that a different provision—§201.57(f)(9)(vi)—supposedly "provided that any

2. The CBE procedure does not permit label changes for off-label uses

The totality of the Superior Court's analysis of the preemption issue rested on its view that *Wyeth* interpreted the CBE regulation as a substantive rule requiring manufacturers to "provide adequate descriptions of a drug's newly discovered risks to ensure consumer safety" irrespective of the drug's approved uses. (App.23.) This reflects a gross overreading of a single line in *Wyeth*, which explained only that the "CBE regulation . . . both *reflects* the manufacturer's ultimate responsibility for its label and provides a mechanism for adding safety information to the label prior to FDA approval." *Wyeth*, 555 U.S. at 571 (emphasis added). As *Wyeth* recognized, the CBE rules—which generally permit a manufacturer unilaterally to "add or strengthen a contraindication, warning, precaution, or adverse reaction," 21 C.F.R. §314.70(c)(2)(i),—are merely procedural; they describe the circumstances in which a manufacturer may satisfy its obligations under the

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'specific hazard' associated with an unapproved pediatric use 'shall be described in this subsection of the labeling.'" (App.22.) But this passing comment did not form the basis of the court's holding that the "authority" of *Wyeth* and *Merck* precluded finding preemption. More importantly, §201.57(f)(9)(vi) does not apply to a risk like gynecomastia that is not specific to particular pediatric subgroups, and, furthermore, warnings under §201.57(f)(9)(vi) *must be made by a Prior Approval Supplement*, so cannot be added by the manufacturer unilaterally, *see 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).

substantive provisions of §201.57 by independently initiating a label change, rather than having to wait for FDA pre-approval of a PAS.

The problem here is obvious: §201.57(e) expressly *prohibits* manufacturers from using the CBE procedure to violate the FDA's substantive proscription against manufacturer-initiated off-label warnings. By applying its distorted conception of the CBE regulations to this regulatory context, the Superior Court thus further deviated from *Wyeth*'s express qualification that the decision *was not* meant to apply where the FDA's substantive proscriptions bar access to the CBE procedure.

The Superior Court thus misapplied *Wyeth* twice over: *first*, by ignoring *Wyeth*'s admonition that courts *not* apply its ruling to the precise circumstance at issue here, and *second*, by converting the CBE "mechanism" that *Wyeth* explained only "reflects" the FDA's substantive labeling regime into a substantive requirement of its own. In so doing, the decision below creates a standalone rule for warnings that would supersede the entirety of the FDA's regulatory regime and usurp the FDA's exclusive authority to regulate labeling in general (and off-label warnings in particular). Indeed, that is the same error that this Court sought to remedy in *Mensing*, where it rejected plaintiffs' theory that generic manufacturers could use the CBE procedure to add warnings that have not been approved for the equivalent brand drug. There, the Court explained that permitting plaintiffs' proposed use of the CBE process to impose new warnings would "violate the statutes and regulations requiring a generic drug's label to match its brand-

name counterpart's." *Mensing*, 564 U.S. at 614. Unchastened, Plaintiffs and the court below again seek to run roughshod over *Wyeth*'s express limits—here, by using the CBE procedure to do what the plain text of §201.57(e) prohibits. Plainly, the Court's intervention is still needed.

The FDA has clearly stated, moreover, that the CBE regulations are subordinate to the substantive requirements of §201.57. In its 2008 final rule amending the CBE regulations, the FDA explained that:

> [i]f new information about a drug comes to light, a sponsor must make a decision as to whether the requirements of §201.57 are met, and whether to submit a CBE supplement or other type of supplemental application. Failure to update labeling as required could result in regulatory actions or criminal penalties.

Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 46,905 (Aug. 22, 2008). That makes clear that consideration of potentially using the CBE or PAS procedures comes into play only after determining whether the substantive requirements set forth in §201.57 authorize the use of those procedures.

The lower court's decision inverts that framework: It gives primacy to *Wyeth*'s broad language concerning the CBE procedure, and altogether ignores both the strict limits that §201.57(e) imposes on off-label warnings and *Wyeth* and *Mensing*'s repeated warnings that the CBE procedure's availability is constrained

by the substantive requirements set forth elsewhere in the statute and the FDA implementing regulations. In Pennsylvania today, *how* a manufacturer may make a label change carries more weight than *whether* the change may be made to begin with. If accepted, the Superior Court's view of a manufacturer's duty to update its label by way of the CBE process would swallow much of the FDA's carefully crafted limitations in §201.57 and would undermine the FDA's expectation that CBE changes should be used in only "limited" circumstances. *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2,848, 2,849–50 (Jan. 16, 2008).

B. The Decision Below Undermines Congress and the FDA's Carefully Calibrated Balance in Regulating Off-Label Promotion.

The FDA's election to maintain sole authority to decide whether to implement an off-label warning is consistent with its approach to the two broader regulatory issues at the crossroads of which off-label warnings sit: off-label promotion and drug warnings. In both areas—consistent with the FDCA—the Agency has mandated extreme care and caution to avoid implying uses for which a drug is not indicated or risks which are not adequately supported. An off-label warning implicates both these concerns, and the FDA has reasonably concluded that such fraught decisions may be made only by the Agency charged with making these difficult public safety determinations. The decision below threatens to undermine the careful balance that the FDA has

reached to regulate off-label promotion, avoid the risk of overwarning, and still protect the public health. This is precisely the task that Congress expressly delegated to the FDA's expert judgment, *see* 21 U.S.C. §393(b), and (at least in the context of unapproved uses) its judgments should not be subject to second-guessing by manufacturers, plaintiffs' attorneys, or even the courts. *See, e.g.*, *Mobil Oil Expl. & Producing Se. Inc. v. United Distrib. Cos.*, 498 U.S. 211, 214–15 (1991); *United States v. Article of Drug . . . Bacto-Unidisk . . .*, 394 U.S. 784, 791–92 (1969).

As explained above, the FDA has long interpreted the FDCA to forbid manufacturers or distributors of drugs from promoting "off-label" uses of approved drugs. Misbranding is a felony, 21 U.S.C. §333(a)(2), and the FDA and DOJ have successfully prosecuted many enterprises for "off-label" promotions. *See generally Caronia*, 703 F.3d at 154 (collecting cases). And the FDA has taken the position before this Court that even for *on-label* uses, warnings that differ from those included on the FDA-approval label can give rise to misbranding liability. *See Mensing*, 564 U.S. at 615. The FDA takes the same position for *any unsolicited* statements by a manufacturer—even truthful ones—about off-label uses, whether or not included on the actual label. 21 C.F.R. §202.1(l).

On top of its apprehensions regarding off-label promotion and misbranding, the FDA is generally concerned with manufacturers distributing even warnings that relate to *approved* uses of drugs without prior FDA approval or a compelling reason to act quickly. As the FDA has explained, and as this Court has recognized, "[t]he hierarchy of label

information is designed to 'prevent overwarning'" and "is also designed to exclude '[e]xaggeration of risk, or inclusion of speculative or hypothetical risks,' that 'could discourage appropriate use of a beneficial drug.'" *Merck*, 139 S. Ct. at 1673 (quoting 73 Fed. Reg. 49,605–49,606 (Aug. 22, 2008)). For this reason, the FDA has warned that "additional disclosures of risk information can expose a manufacturer to liability under the [FDCA] if the additional statement is unsubstantiated or otherwise false or misleading." 71 Fed. Reg. at 3,935. Accordingly, the FDA's position is that prior approval is usually necessary to avoid disruption of "FDA's careful balancing of how the risks and benefits of the product should be communicated," and that, even where available, "the CBE supplement procedures are narrow exceptions to this general rule." 73 Fed. Reg. at 2,849.

It should come as no surprise, then, that where off-label promotion meets warning labeling, the risk of manufacturer misstep is so significant that the FDA has concluded that manufacturers are not be permitted to make such difficult policy-laden decisions on their own.

That judgment is well founded. It is hard to imagine a good faith warning in this case that *would not* run afoul of the FDA's off-label promotion rules. For example, Plaintiffs insisted below that Janssen should have warned that use of Risperdal in pediatric populations causes gynecomastia more frequently than when used in adult applications. (App.21–22.) Such a warning, however, would imply that the drug *can* be used in pediatric populations (promotion) even though Risperdal's labeling truthfully stated that the

product was not evaluated or approved for pediatric use. In light of its documented efficacy (*e.g.*, RR.00149a), an accurate warning about the limited risks of using Risperdal off-label in pediatric populations would have had the effect of disclosing that its benefit outweighs its potential side effects. Indeed, it is this reality that supported the FDA's ultimate approval of Risperdal to treat children. Imposing such a warning prior to Risperdal's pediatric approval would have been implicit off-label promotion.

Because off-label warnings inherently promote off-label *use*, they raise fundamentally different risks than the ones which arise from over-warning about indicated uses (and as to which *Wyeth* expressed skepticism). 555 U.S. at 570 (noting that the "very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning . . . is difficult to accept."); *but see Mensing*, 564 U.S. at 615 (deferring to the FDA's position that a drug is misbranded if its labeling "contained substantial new warning information" because such a warning "would not be consistent with the drug's approved labeling"). In this case, it is not primarily the warning itself that carries the risk of misbranding, but the implication from the warning that the drug is safe and effective for the *off-label* use for which the warning was imposed. FDA regulations explicitly prohibit including on a drug's label 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.").

Consistent with those regulations, the FDA repeatedly has brought misbranding enforcement actions against manufacturers who have engaged in off-label promotion (as opposed to overwarning about approved uses). *Caronia*, 703 F.3d at 154 (collecting cases). Simply stated, the decision whether to implement an off-label warning is not for a manufacturer to make; the FDA has proactively reserved to itself this weighty decision of how best to protect public safety. This Court should defer to the Agency's reasoned expert judgement, grant this Petition, and hold that state-law failure-to-warn claims that would require manufacturers to act otherwise are preempted.

II. The Question Presented Is Exceptionally Important and This Case Is an Ideal Vehicle to Resolve It.

Whether §201.57(e) categorically precludes manufacturers from independently implementing off-label warnings, and accordingly whether state-law failure-to-warn claims based on allegedly missing off-label warnings are preempted, is an exceptionally important and purely legal question that this Court should resolve. Aside from its doctrinal importance in resolving the lower courts' widespread overreading of *Wyeth*, even after *Mensing*, resolving this issue has enormous financial implications both for Janssen and the pharmaceutical industry writ large. And because the vast scope of potential liability in these cases usually incentivizes manufacturers to settle, cases like this one that cleanly raise this issue only rarely will reach this Court. The Court should take this

opportunity to inject clarity and predictability into this area of law.

On its face, this issue presents an important question of federal law that has not been, but should be, settled by this Court. The Court has already determined that federal law preempts state tort claims regarding on-label uses unless the defendant could have made the sought-after change unilaterally (*Wyeth*). As a result, state failure-to-warn claims against *generic* manufacturers—whom the FDA prohibits from using the CBE rules to implement label changes that differ from the brand's label—are preempted (*Mensing*). This case presents a similarly far-reaching question that can cleanly delineate the scope of the preemption defense: may brand manufacturers assert a preemption defense in state failure-to-warn claims involving off-label uses where FDA regulations prohibit them from imposing warnings concerning risks of off-label uses?

Given the enormous financial implications, both for Janssen and pharmaceutical companies more broadly, the Court's intervention is all the more necessary. Approximately 10,000 additional pediatric Risperdal cases remain pending across the country. In this case, the jury awarded $70 million in compensatory damages alone for A.Y.'s emotional distress; another Pennsylvania jury had awarded a different individual Risperdal plaintiff *$8 billion* in punitive damages, which the trial court ultimately remitted to $6.8 million. *See Murray v. Janssen Pharm., Inc.*, No. 1990, 2020 WL 372419 (Pa. Com. Pl. Jan. 16, 2020). Plaintiffs here are likewise returning to the Philadelphia trial court in a bid to obtain punitive damages. (App.59.) Absent this Court's

intervention, Janssen faces literally billions of dollars in liability for cases that all should be dismissed as a matter of law on preemption grounds.

Janssen is not alone. As many as a third of all prescriptions in the United States are prescribed off-label. *See* Congressional Research Service, *Off-Label Use of Prescription Drugs* (July 1, 2019), https://fas.org/sgp/crs/misc/R45792.pdf. If manufacturers can be held liable for failure-to-warn risks that the FDA prohibits them from disclosing, the liability could be—as it is in this case—devastating. Indeed, numerous other manufacturers currently have or recently have had actions pending against them asserting failure-to-warn claims for off-label uses. *See, e.g.*, Allergan, *Drake v. Allergan, Inc.*, 63 F.Supp.3d 382 (D. Vt. 2014); Pfizer, *Allen v. Pfizer, Inc.*, No. 155496/2019 (N.Y. Sup. Ct. complaint filed May 31, 2019); AstraZeneca, *id.*; Merck, *id.*; Bristol-Myers Squibb, *Rogers-Gatlin v. Bristol-Myers Squibb Co.*, No. 152534/2015 (N.Y. Sup. Ct. dismissed Dec. 3, 2015); and Teva, *Bennett v. Teva Pharm. USA, Inc.*, 1:19-cv-02126 (D. Del. complaint filed Nov. 12, 2019). This is but a partial count of the many lawsuits that assert failure-to-warn theories for off label use, and the copycat impact of the Risperdal verdicts cannot be lightly ignored, as it will not be difficult for enterprising attorneys to identify a drug whose off-label use might be associated with a particular risk and whose label—by definition and by regulation—does not disclose that risk.

The Superior Court's ruling binds manufacturers in a Catch-22 between misbranding and failure-to-warn liability that they cannot escape, especially

because neither they nor the FDA can prevent medical professionals from prescribing off-label. When a manufacturer's only means of protecting itself from potentially business-ending liability is to get out of the business, something has gone terribly awry. *See Mut. Pharm. Co. v. Bartlett*, 570 U.S. 472, 488 (2013) ("[A]n actor seeking to satisfy both his federal- and state-law obligations is not required to cease acting altogether in order to avoid liability."). This Court's intervention is urgently needed to set it straight.

CONCLUSION

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

Respectfully submitted,

JAY P. LEFKOWITZ
Counsel of Record
GILAD BENDHEIM
KIRKLAND & ELLIS LLP
601 Lexington Avenue
New York, NY 10022
(212) 446-4800
lefkowitz@kirkland.com

Counsel for Petitioners

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