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

REPLY BRIEF FOR PETITIONERS

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REPLY BRIEF FOR PETITIONERS

Respondents' opposition only affirms that the decision below undermines the FDA's off-label warning regime and exposes the pharmaceutical industry to billions of dollars in state-law liability unless manufacturers violate federal law. Unremedied, the Superior Court's ruling will hold manufacturers responsible for the consequences of off-label uses that they are powerless either to prevent or warn against. Beyond that industry-wide result, the potential impact on Petitioners from the thousands of Risperdal cases pending in the Pennsylvania courts is so significant that this Court's intervention is warranted.

Respondents refuse to engage with the plain text of the regulatory provision through which the FDA prohibits manufacturers from unilaterally warning of off-label risks. 21 C.F.R. §201.57(e) (2003). Instead, Respondents advance an interpretation of §201.57(e) that renders key language superfluous and is supported only by Respondents' hypothetical policy arguments.

Respondents reiterate the lower court's erroneous conclusion that Petitioners could have utilized the Changes Being Effected ("CBE") process, 21 C.F.R. §314.70(c)(2)(i) (2003), to add warnings concerning risks allegedly associated with off-label uses of Risperdal. As Petitioners explained, the CBE process is limited to changes for approved—not unapproved or off-label—uses.

Respondents similarly insist that Petitioners could unilaterally have warned of Risperdal's supposed off-label risks via the pediatric use

exception, 21 C.F.R. §201.57(f)(9)(vi), "Dear Doctor" letters, or the "adverse reactions" regulations. But these avenues are unavailable for off-label uses, so to utilize them without FDA pre-approval would violate federal law.

Finally, Respondents argue that the question presented is unimportant and that this case is an inapt vehicle. These contentions are belied by the diverse Amici supporting Petitioners, the many off-label warning cases brought in recent years, and the straightforward legal question presented.

At bottom, the decision below contravenes the Supremacy Clause by holding manufacturers liable for *not doing* precisely what federal law *prohibits* them from doing. Given the stakes of this question, the Petition should be granted. If, however, this Court has any doubts about the meaning of §201.57(e) or the FDA's prohibition on off-label warnings, it should solicit the views of the FDA itself.

I. Manufacturers Cannot Unilaterally Impose Off-Label Warnings.

1. 21 C.F.R. §201.57(e) provides 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 [FDA]." This means manufacturers cannot unilaterally add off-label warnings. Indeed, §201.57(e) already requires a drug's label to "include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug." The only reason to specify thereafter that the FDA—which of course may enforce its own regulations—*may require* off-label warnings is to establish that off-label

warnings otherwise are prohibited. *See* Petition for Certiorari ("Petition") 20–21.

2. Respondents run from the language of §201.57(e), offering no interpretation tied to the regulation's text. Instead, Respondents' interpretation renders the "may be required" language superfluous.

Under Respondents' view, even without the "may be required" provision, §201.57(e) requires manufacturers to impose warnings for on- and off-label uses. Brief in Opposition ("BIO") 5, 27–28. This interpretation renders the "may be required" language meaningless—it creates no additional obligations, confers no additional rights, and serves no purpose.[1]

Undeterred, Respondents offer two arguments to support their view; neither withstands scrutiny.

First, Respondents rely on the final sentence of 21 U.S.C. §321(n) to suggest that a drug is misbranded if its label does not reveal material facts concerning the "'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)." BIO 28. This is wrong.

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[1] Given Respondents' erroneous contention that, at the time, the FDA could not compel manufacturers to change their labels, BIO 8; *but see* Petition 20–21, not only is the "may be required" language meaningless, but it is *ultra vires* because it empowers the FDA to "require" a change when such power was lacking. Because Respondents' interpretation implicitly challenges §201.57(e)'s validity, if the Court is inclined to entertain this position, it should seek the views of the FDA.

Section 321(n) governs only approved (on-label) uses. It provides that failure to reveal information that is "material with respect to consequences which may result *from the use of the article to which the labeling or advertising relates* … under such conditions of use as are customary or usual" may constitute misbranding. 21 U.S.C. §321(n) (emphasis added). Because the "consequences" must flow from uses to which the "labeling or advertising relates," those uses are by definition *not* off-label. Thus, the failure to discuss the consequences of off-label use is not misbranding under §321(n).[2]

Second, Respondents fashion a hypothetical to suggest that the "may be required" language under Petitioners' view would be "senseless." BIO 28–29. But their hypothetical proves Petitioners' argument. Respondents imagine a drug that is dangerous when used off-label but nevertheless "effective for that off-label use." BIO 28. Respondents muse that, given §201.57(e)'s wording, neither manufacturers *nor* the FDA could warn of that risk. BIO 28. Respondents' hypothetical is a contradiction in terms: Until the FDA determines that a drug is both "safe *and* effective" for a given use—*i.e.*, approves it on-label—the drug cannot be "effective" for that use. S. Rep. No. 87-1744, at 15 (1962). There is no circumstance where the FDA

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[2] Were Respondents correct, the misbranding regulations would both *prohibit* manufacturers from warning of risks associated with unapproved uses (because it would implicitly promote unapproved uses) and *require* that same warning. *See Scialabba v. Cuellar de Osorio*, 573 U.S. 41, 87 (2014) (Alito, J., dissenting) (courts interpret statutes "'as a … coherent regulatory scheme' rather than an internally inconsistent muddle, at war with itself").

has found a drug "effective" and yet the drug remains governed by §201.57(e)'s off-label provision. Respondents' sole example supporting their argument is illusory, reaffirming that Petitioners are correct that manufacturers cannot unilaterally add warnings regarding off-label uses.

3. The subsequent provision of §201.57(e) confirms as much. Respondents concede that in the sentence following the off-label warning clause, §201.57(e) again uses the "may be required by" the FDA locution to grant the FDA *exclusive* authority over black-box warnings. BIO 29. Respondents argue, however, that "may be required" does not confer exclusive authority when used in the preceding sentence regarding off-label warnings. In support, they note that a *later-enacted* version of a *different* regulation—21 C.F.R. §314.70(c)(6)(iii) (2016)—reiterates that CBE changes cannot be used to alter black-box warnings, from which they infer that a CBE *can* be used for off-label warnings. BIO 29. But §314.70(c)(6)(iii)—a different regulation written at a different time—cannot change the meaning of the "may be required" language in §201.57(e). *Bostock v. Clayton Cty.*, 140 S. Ct. 1731, 1738 (2020) (interpreting laws "in accord with the ordinary public meaning of its terms at the time of its enactment").

Respondents seemingly rely on the *expressio unius* canon, but that principle has no force where, as here, "language suggesting exclusiveness is missing." *Chevron U.S.A. Inc. v. Echazabal*, 536 U.S. 73, 81 (2002). Indeed, it is unsurprising that the FDA would "repeat themselves" in §314.70(c)(6)(iii) out of "a sense of belt-and-suspenders caution" regarding the black-

box warning. *King v. Burwell*, 576 U.S. 473, 502 (2015) (Scalia, J., dissenting). What would be surprising is if the FDA intentionally utilized the "may be required" language in §201.57(e) understanding that it would "have no operation at all." *Id.*

"May be required by" the FDA has a specific and undisputed meaning in the black-box context and Respondents offer no support for their position that the FDA intended a different meaning for the identical language—in abutting sentences—in the off-label context. *Fourth Estate Pub. Benefit Corp. v. Wall-Street.com*, 139 S. Ct. 881, 889 (2019).[3]

4. Because Respondents cannot rebut the plain text of §201.57(e), they contend that notwithstanding the prohibition on off-label warnings, Petitioners "had multiple ways to inform doctors about" Risperdal's off-label risks, via (1) the pediatric exception, 21 C.F.R. §201.57(f)(9)(vi); (2) "Dear Doctor" letters; or (3) the "adverse reaction" section. BIO 22–25. These arguments, too, conflict with the plain text of FDA regulations.

The pediatric exception in §201.57(f)(9)(vi) does not apply, and even if it did, does not permit a manufacturer unilaterally to warn of off-label risks.[4]

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[3] Respondents assert that Petitioners made "no argument about how (or why)" the "broadly worded grant of authority" in the CBE regulations would prohibit manufacturers from unilaterally warning of off-label uses. BIO 26. To the contrary, Petitioners explained that the procedural CBE regulations are subsidiary—and must yield—to §201.57(e). Petition 27–30.

[4] The existence of the pediatric exception allowing manufacturers to seek—by a Prior Approval Supplement ("PAS")—the specified off-label warnings confirms that

When A.Y. began taking Risperdal as a four-year-old in 2003, Risperdal was not approved for any pediatric uses. As required, Risperdal's label stated that "[s]afety and effectiveness in children have not been established." (RR.02573a); 21 C.F.R. §201.57(f)(9)(vi). Nevertheless, Respondents say that §201.57(f)(9)(vi) "required" Janssen to add a special gynecomastia warning.

Respondents mischaracterize the regulatory language to assert that §201.57(f)(9)(vi)'s "mandate applies to any 'use of the drug' that is associated with any specific hazard in ***any*** 'pediatric subgroup.'" BIO 23 (emphasis added). Section 201.57(f)(9)(vi) does *not* refer to "any" pediatric subgroup. It is a narrow exception to §201.57(e) that requires warnings only where the "hazards" are "specific" to "premature or neonatal infants, or other pediatric subgroups," *i.e.*, to particular pediatric subgroups, not all children. *See Epic Sys. Crop. v. Lewis*, 138 S. Ct. 1612, 1625 (2018) ("[W]here … a more general term follows more specific terms in a list, the general term is … understood to embrace only objects similar in nature to those objects enumerated by the preceding specific words." (cleaned up)). Had the FDA wanted to institute the broad requirement Respondents advance, §201.57(f)(9)(vi) would have obligated warnings associated with "any subgroup" (as Respondents pretend it does), "any pediatric population" (the term used elsewhere in

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manufacturers may not impose any other off-label warning. If, as Respondents contend, § 201.57(e) requires manufacturers to warn of *any* "serious risk or hazard," the FDA would not have enacted a specific pediatric-focused obligation already encompassed by the general warning obligation.

§201.57(f)(9)(vi)), or "the pediatric population" (the term used in subsections (ii) and (iii) to describe all pediatric subgroups). It did not, and such "differences in language … convey differences in meaning." *Henson v. Santander Consumer USA Inc.*, 137 S. Ct. 1718, 1723 (2017). Because the alleged risk of gynecomastia from off-label use of Risperdal applies to *all* pediatric users, §201.57(f)(9)(vi) does not require (or permit) a manufacturer to warn of that risk.

Respondents fall back that §201.57(f)(9)(vi) applies because "boys" is a pediatric subgroup. BIO 23. Not so. The FDA has defined the four subgroups, and they are age-based: "neonates," "infants," "children," and "adolescents." *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, 64,242 (Dec. 13, 1994); *see also* 21 U.S.C. §201.57(f)(9)(i).

Regardless, Respondents are wrong that §201.57(f)(9)(vi)'s warning could be implemented by a CBE. The FDA fully catalogued the subsections of §201.57(f)(9) that *could* be amended by CBE, 59 Fed. Reg. at 64,248, and—as Respondents concede—subsection (f)(9)(vi) is not among them. *Barnhart v. Peabody Coal Co.*, 537 U.S. 149, 168 (2003) (where "items expressed are members of an 'associated group or series'" the *expressio unius* canon "justif[ies] the inference that items not mentioned were excluded by deliberate choice"). Where §201.57(f)(9)(vi) applies, a manufacturer must implement a warning through a PAS, *not* a CBE. Because a manufacturer cannot independently warn of a risk that can only be communicated *after* the FDA accepts a PAS, *PLIVA,*

Inc. v. Mensing, 564 U.S. 604, 623–24 (2011), §201.57(f)(9)(vi) cannot vitiate Petitioners' preemption defense.

Respondents are likewise incorrect that Petitioners could have disclosed the alleged off-label risk via "Dear Doctor" letters. BIO 25. The FDA considers any written communication—including "Dear Doctor" letters—to be "labeling" and requires them to "be 'consistent with and not contrary to [the drug's] approved … labeling.'" *Mensing*, 564 U.S. at 615 (quoting 21 C.F.R. §201.100(d)(1)). "A Dear Doctor letter that contained substantial new warning information"—like an off-label warning—"would not be consistent with the drug's approved labeling." *Id.*; *see Hahn v. Richter*, 628 A.2d 860, 863 (Pa. Super. Ct. 1993), *aff'd*, 673 A.2d 888 (1996) ("[F]ormer head of the F.D.A., Dr. Herbert Ley … testified that the F.D.A. would not have allowed Upjohn to contact physicians or send a 'Dear Doctor' letter regarding the intrathecal use of Depo-Medrol *because it was not an approved use for the drug*." (emphasis added)). Just as a state law requiring manufactures to impose an off-label warning would be preempted, so too would any state law requiring manufacturers to issue "Dear Doctor" letters for off-label uses, because it would be inconsistent with the approved label and the misbranding rules.

Respondents' claim that Petitioners could have implemented the prohibited off-label warning via "the 'adverse reactions' section of the label" fails, too. BIO 24. Risperdal's label already reflected that gynecomastia is a potential adverse reaction. (RR.02578a.) What Respondents *actually* seek is a

warning that this reaction is amplified when used off-label for boys. This is not an "adverse reaction" warning. It is a warning governed by §201.57(e) or (f)(9)(vi), neither of which permits unilateral off-label warnings. The "adverse reactions" section cannot support Respondents' end-run of §201.57(e).[5]

II. The Question Presented Is Exceptionally Important And Worthy Of Certiorari.

Whether §201.57(e) precludes manufacturers from unilaterally 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 question that this Court should resolve. Although there is no split of authority, there also was no split of authority in *Mensing*, and this case is important for the same reason. It implicates the normal operation of the Supremacy Clause. In *Mensing*, the Court recognized that the dramatic expansion of state-law failure-to-warn liability in the face of a federal law prohibiting such warnings presented an exceptionally important issue of federal law. So, too, here.

Although Respondents assert that the question presented is only "important to [Petitioners]," BIO 15, the multiple Amici representing a diverse array of interests supporting Petitioners demonstrate the

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[5] Even were these arguments viable, they were not the basis of the Superior Court's holding. Apart from describing that Petitioners raise the pediatric exception (App.22–23), the Superior Court does not mention any of these regulations, and this Court should decline to consider them in the first instance, *CRST Van Expedited, Inc. v. E.E.O.C.*, 136 S. Ct. 1642, 1654 (2016).

opposite: If adopted, the Superior Court's dramatic expansion of failure-to-warn liability would establish a form of "absolute liability that would prove disastrous" across the industry, Brief of *Amicus Curiae* Product Liability Advisory Council, Inc. at 19, which will "harm innovation and thus harm patient health," Brief for the Pharmaceutical Research & Manufacturers of America et al. as *Amici Curiae* at 12; Brief of Washington Legal Foundation as *Amicus Curiae* at 16–18.[6]

Even were Respondents correct that this issue related only to Janssen, this issue is cert-worthy given the Superior Court's misconstrual of *Wyeth* and the magnitude of liability facing Petitioners because of the decision below. Currently pending in just the Pennsylvania courts are another 7,000 Risperdal cases; in one (later-remitted) case, the jury awarded a plaintiff $8 billion in punitive damages. Iterated thousands more times, the liability could cripple Petitioners, and would force settlement of claims that should be constitutionally preempted, because no manufacturer can afford to incur such damages while awaiting this Court's case-by-case intervention. Respondents' contention that intervening to rectify a state court's misunderstanding of federal law that, at a minimum, jeopardizes *the world's largest* healthcare

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[6] Respondents wrongly imply that off-label failure-to-warn cases are rare. BIO 15. In recent years, scores have been filed. *See, e.g.*, *Polt v. Sandoz, Inc.*, 462 F.Supp.3d 557 (E.D. Pa. 2020); *Blackburn v. Shire*, 2020 WL 2840089 (N.D. Ala.); *Galinis v. Bayer Corp.*, 2019 WL 2716480 (N.D. Cal.); *In re Zofran (Ondansetron) Products Liab. Litig.*, 2019 WL 4980310 (D. Mass.); *Kelley v. Insys Therapeutics*, 2019 WL 329600 (N.D. Ohio).

company—with the associated public health repercussions—is "nowhere near important enough to warrant this Court's intervention," BIO 15, is unpersuasive.

III. This Case Is An Ideal Vehicle To Resolve The Pure Legal Question Presented.

Despite Respondents' efforts to muddy the issue with alleged factual issues—which played no role in the Superior Court's decision and which are irrelevant to the question presented—this case presents a clean legal issue: Does §201.57(e) prohibit manufacturers from unilaterally warning of off-label risks and, if so, does it preempt state failure-to-warn laws that would obligate manufacturers to implement such a warning?

Because the issue presented is a legal one, it does not matter whether—as Respondents allege, BIO 31—Janssen was promoting Risperdal for off-label use. If true, the FDA could pursue Janssen for those violations; Respondents cannot. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001); 21 U.S.C. §337(a). Regardless, Petitioners' alleged regulatory violations have no bearing on the question presented; notwithstanding a manufacturer's conduct, state law cannot compel an entity to violate federal law.

Respondents also argue that the "regulatory regime … has since been revised," BIO 31, but fail to say what changed or why it matters. The relevant language in §201.57(e) and (f)(9)(vi) is virtually identical despite being recodified. And, although the CBE regulation has changed a fraction (now, unlike in 2003, it requires that information be "newly discovered" to permit a CBE change), this makes CBE

changes *less available* (and thus preemption *more* available). It does not impact the pure legal question before the Court.

CONCLUSION

This Court should grant certiorari.

Respectfully submitted,

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