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 a Writ of Certiorari to the Supreme Court of Pennsylvania

BRIEF FOR THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA, AND AMERICAN TORT REFORM ASSOCIATION AS AMICI CURIAE IN SUPPORT OF CERTIORARI

James C. Stansel
Melissa B. Kimmel
Pharmaceutical Research and Manufacturers of America
950 F St., NW, Ste. 300
Washington, DC 20004
mkimmel@phrma.org
(202) 835-3400
Counsel for Pharmaceutical Research and Manufacturers of America

Michael X. Imbroscio
Counsel of Record
Paul W. Schmidt
Covington & Burling LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
mimbroscio@cov.com
(202) 662-6000
Counsel for Amici Curiae

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Additional Counsel Listed on Inside Cover

Continued from front cover…

Sherman Joyce
Lauren Sheets Jarrell
American Tort Reform Association
1101 Connecticut Ave., NW, Suite 400
Washington, DC 20036
lsheetsjarrell@atra.org
(202) 682-1168
Counsel for American Tort Reform Association

Tara S. Morrissey
Stephanie A. Maloney
U.S. Chamber Litigation Center
1615 H Street, NW
Washington, DC 20062
tmorrissey@uschamber.com
(202) 463-5337
Counsel for Chamber of Commerce of the United States of America

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INTERESTS OF *AMICI CURIAE*[1]

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association representing the nation's leading research-based pharmaceutical and biotechnology companies. PhRMA's members produce innovative medicines, treatments, and vaccines that save and improve the lives of countless individuals every day. Since 2000, PhRMA's members have invested more than $900 billion into discovering and developing new medicines, including an estimated $79.6 billion in 2018 alone. PhRMA, *About*, https://www.phrma.org/About (last visited Mar. 7, 2021). PhRMA's members are specifically leading the way in developing new vaccines and treatments for COVID-19, with nearly half of all such clinical trials using products invented by PhRMA's members. *See* PhRMA, *PhRMA COVID-19 Treatment Progress*, https://phrma.org/Coronavirus/Activity-Tracker (last updated July 20, 2020).

The Chamber of Commerce of the United States of America ("the Chamber") is the world's largest business federation. It represents approximately 300,000 direct members and indirectly represents the interests of more than 3 million companies and

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[1] In accordance with Rule 37.2(a), all counsel of record received timely notification of *amici curiae*'s intent to file this brief and have consented, in writing, to this filing. No party's counsel authored this brief in whole or in part. No party, counsel for a party, or person other than *amici curiae,* their members, and their counsel made any monetary contribution intended to fund the preparation or submission of this brief.

professional organizations of every size, in every industry sector, and from every region of the country. An important function of the Chamber is to represent the interests of its members in matters before Congress, the Executive Branch, and the courts. To that end, the Chamber regularly files *amicus curiae* briefs in cases that raise issues of concern to the nation's business community.

The American Tort Reform Association ("ATRA") is a broad-based coalition of businesses, corporations, municipalities, associations, and professional firms that have pooled their resources to promote reform of the civil justice system with the goal of ensuring fairness, balance, and predictability in civil litigation. ATRA is especially focused on pockets of the American judicial system where corporate defendants are subject to unfair and irrational treatment, as routinely occurs in the jurisdiction from which this case arises. For more than three decades, ATRA has filed amicus briefs highlighting these concerns.

SUMMARY OF ARGUMENT

Federal law vests the Food and Drug Administration with ultimate responsibility for determining which medicines can be marketed in the United States, the populations for which these medicines can be marketed (*i.e.*, the indicated uses as opposed to the "off-label" uses), and the warnings that must accompany these medicines. These unique responsibilities reflect the complex scientific issues involved in each of these decisions, as well as the expert judgment that these decisions require.

This Court's precedents dictate that the FDA regulatory structure preempts lawsuits like this one, where the FDA forbids companies from taking the unilateral action that state tort law purports to demand. Specifically, during the time covered by this lawsuit, the defendant warned of the exact condition at issue here. But the plaintiffs were nevertheless able to obtain a massive verdict by arguing that the defendant should have unilaterally added an additional warning about this condition in children—even though companies are not authorized to unilaterally add warnings related to the use of medicines in "off-label" populations and even though the FDA more broadly seeks to constrain affirmative company statements on off-label uses.

The courts below erred in allowing this case to proceed in the face of federal law to the contrary. The impact of that error extends well beyond this litigation. The FDA's authority and expertise to address the labeling of medicines for unapproved uses or by

non-indicated populations, especially for pediatric users, will be undercut if state-law litigation can effectively second-guess the FDA's judgment. Allowing liability in this situation could impair innovation and investment in the development of new treatments by subjecting manufacturers to potentially massive liability for not unilaterally adding warnings about specific off-label risks, which they are not authorized to make without prior FDA consent and approval. This unfair and irrational basis for liability would ultimately harm the very patients that such expansive liability theories profess to benefit. At the same time, the FDA already has (and uses) the power to direct off-label and pediatric warnings where appropriate, *see* 21 U.S.C. § 355(o)(4), refuting any argument that public health will be further promoted by allowing the potentially conflicting judgments of individual juries in thousands of cases to dictate off-label safety warnings for prescription medicines.

ARGUMENT

I. THE DECISIONS BELOW IGNORE THAT THE FDA PRECLUDES COMPANIES FROM UNILATERALLY WARNING OF OFF-LABEL RISKS FOR GOOD POLICY REASONS.

1. The Supremacy Clause bars a state-law claim where it is "impossible for a private party to comply with both state and federal requirements." *English v. Gen. Elec. Co.*, 496 U.S. 72, 79 (1990). As the Court has held in addressing claims against the manufacturers of FDA-regulated medications, the "question for 'impossibility' analysis is whether the private party could independently do under federal law what

state law [supposedly] requires." *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 620 (2011). In other words, the manufacturer must have had the right under federal law to make the change at issue "unilaterally," without prior FDA approval. *Id.*; *see also Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472, 483–84 (2013); *Wyeth v. Levine*, 555 U.S. 555, 573 (2009).

When a manufacturer can unilaterally amend its labeling—as it can when the "changes being effected" ("CBE") regulation applies—there is no preemption unless the manufacturer can show that the FDA would have later rejected the unilateral labeling change. *Levine*, 555 U.S. at 571–73. But where a manufacturer lacks the right under federal law to unilaterally change its labeling in the first instance—for example, because the type of labeling change is not allowed by the CBE regulation or because the proposed change does not satisfy the standards set forth in the CBE regulation—then the claim is preempted. *See Mensing*, 564 U.S. at 624.

2. Warnings focused on off-label risk are preempted because they fit squarely into the category of labeling changes that a manufacturer cannot unilaterally implement. As specified in federal law, it is solely for the FDA to determine if warnings aboutoff-label risks *may be required*: "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 . . .*" 21 C.F.R. § 201.57(c)(6)(i) (emphasis added); *see also* 21 C.F.R. § 201.80(e). Thus, absent some form of prior agreement and approval from the FDA for an off-label

warning, companies cannot unilaterally add such warnings to their labeling.

The FDA's decision to limit a manufacturer from unilaterally warning about off-label risks is consistent with its broader policy decision to preclude manufacturers from unilaterally changing labeling where the FDA has decided that it alone should be the arbiter of specific types of labeling changes. Most relevant here, the FDA reserves for itself the authority to add a so-called boxed warning. It does so by employing the same verbiage it uses to preclude unilateral off-label warning changes: "Special problems, particularly those that may lead to death or serious injury, *may be required by the Food and Drug Administration* to be placed in a prominently displayed box." 21 C.F.R. § 201.80(e) (emphasis added); *see also* 21 C.F.R. § 201.57(c)(1) (same).[2]

When initially adopting the boxed warning regulation over 40 years ago, FDA was "asked whether a manufacturer may include a boxed warning without prior FDA approval." 44 Fed. Reg. 37,434, 37,448 (FDA Jun. 26, 1979). The FDA made clear that this language was intended to preclude manufacturers from making such a change without prior FDA endorsement: "[T]he decision as to whether a warning is legally required for the labeling of a drug must rest

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[2] The FDA similarly precludes manufacturers from unilaterally changing other labeling materials, including information in patient-focused Medication Guides, 21 C.F.R. §§ 208.1, 208.20(a)(6), and the "Highlights" Section of a prescription medicine label, 21 C.F.R. § 314.70(c)(6)(iii).

with the agency." *Id.* at 37447. And the FDA explained why it reserved this ability solely for itself: "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; *see also* 51 Fed. Reg. 43,900, 43,902 (FDA Dec. 5, 1986) (describing FDA's policy of "restraint in requiring warnings to be boxed because overuse of the box will ultimately lead to reducing its effect").

Similar considerations explain why the FDA employed the identical restrictive language to preclude unilateral off-label warnings. The FDA has asserted broad regulatory powers over off-label statements, and it further carefully regulates off-label pediatric use. As with boxed warnings, off-label warnings may only be "required by the Food and Drug Administration." 21 C.F.R. § 201.80(e).

3. Under the Federal Food, Drug, & Cosmetic Act ("FD&C Act"), a drug "shall be deemed to be misbranded . . . [i]f its labeling is false or misleading in any particular." 21 U.S.C. § 352(a)(1). As such, a manufacturer cannot modify the indicated uses or population for a medicine without prior FDA approval. Indeed, as the United States has confirmed to this Court, "a unilateral modification of the labeling, absent special circumstances, can open a manufacturer to liability for misbranding the drug." Br. of United States, *Wyeth v. Levine*, 2008 WL 2308908, at *21 (U.S. June 2, 2008) (citing 21 U.S.C. § 352(a); 21 U.S.C. § 352(f) (Supp. V 2005); 21 C.F.R. § 201.100(c)(1), (d); 21 U.S.C. § 355(a)).

For instance, the FDA prohibits labeling for prescription drugs from containing any clinical trial data for uses or populations that are not otherwise approved. *See, e.g.*, 21 C.F.R. § 201.57(b)(15)(i) ("any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in § 314.126(b) of this chapter and *must not imply or suggest indications or uses or dosing regimens not stated* in the 'Indications and Usage' or 'Dosage and Administration' section.") (emphasis added). The FDA has reinforced this restriction through express regulatory guidance. FDA, *Guidance for Industry: Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products—Content and Format*, at 2–3 (Jan. 2006), https://www.fda.gov/media/72140/download ("Studies Not To Include in the Clinical Studies Section . . . 1. Clinical studies with results that imply effectiveness for an unapproved indication, use, or dosing regimen.").

Beyond the labeling itself, the FDA generally disfavors even statements implying off-label uses, except in limited, specified circumstances and manners. *See, e.g.*, U.S. Dep't of Health & Human Services et al., *Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers* (June 2018), https://www.fda.gov/media/133620/download. Given the inherent balancing necessary whenever addressing an off-label use or non-indicated population, the FDA closely guards its authority in this crucial area, which explains why the FDA has reserved to itself the

decision about whether and if so how to provide warnings related to the off-label use of prescription medicines.

II. PERMITTING LIABILITY FOR FAILURE TO UNILATERALLY ADD OFF-LABEL WARNINGS WOULD DISRUPT FDA REGULATION AND THREATEN PATIENT SAFETY.

This Court's preemption cases properly recognize the critical responsibilities of the FDA and hold that manufacturers cannot be held liable for failing to take actions prohibited by federal law. Permitting liability for not unilaterally implementing off-label warnings would disrupt FDA regulation and impair manufacturer innovation and patient health.

In regulating prescription medicine labeling, the FDA must strike a delicate balance. Labeling conveys a wealth of information necessary for the safe and effective use of a medicine. But this information must be communicated in a manner that is useful to healthcare professionals. One way in which labeling achieves this balance is by providing information only when it is scientifically based and by focusing on the uses for which the medicine is intended.

Striking this proper balance is critically important. Patients may be harmed when labeling communicates safety information in a manner that leads prescribers to downplay or disregard risks. Physicians may disregard lengthy labeling that is replete with speculative or less relevant warnings, and thus overlook more germane and scientifically sound safety information. *See, e.g.*, *Robinson v. McNeil Consumer*

Healthcare, 615 F.3d 861, 869 (7th Cir. 2010) ("The resulting information overload [from describing every remote risk] would make label warnings worthless to consumers."); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 816 n.40 (5th Cir. 1992) (noting that if manufacturers were required to clutter their warnings with "every possible risk," then "physicians [would] begin to ignore or discount the warnings"); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 49,603, 49,605–06 (unjustified statements in FDA labeling may cause "more important warnings" to be "overshadow[ed]").

Moreover, unfounded or inapplicable warnings can discourage the beneficial use of medicines. *See, e.g.*, *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010) ("[O]verwarning can deter potentially beneficial uses of the drug by making it seem riskier than warranted . . . ."); *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P.3d 1, 14 (Cal. 2004) ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision."); Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. at 49,605–06 ("[O]verwarning . . . may deter appropriate use of medical products . . . ."). All medicines have risks, and all prescribing decisions are based on balancing those risks against the potential benefits to the patients for whom the medicine is intended. Distorting that balance, by overstating unfounded or speculative risks, or by focusing on risks in populations for whom the

medicine is not approved, may inhibit medical professionals from making optimal prescribing decisions.

Additionally, the decision to add an off-label warning is not simply a binary '*yes*' or '*no*' as the verdict in this case seems to imply. The content, positioning, length, tone, and other aspects of the warning all need to be carefully considered by FDA. *See* Br. of United States, *Albrecht*, 2018 WL 4562163 at *6 (U.S. 2018). Precision for labeling addressing off-label pediatric uses is particularly important and requires extensive dialogue with FDA. *Id.* Suggesting that a sponsor can bypass this interactive process with the FDA and unilaterally implement compliant labeling would undermine FDA regulation. Moreover, *sua sponte* action by the sponsor in this situation would create its own form of liability if or when the sponsor did not get it just right.

The consequences of getting this critical balance wrong are serious, which is exactly why the FDA tightly regulates labeling to ensure it appropriately and accurately conveys the risks and benefits associated with all medicines, with a focus on the risks to be expected from the approved uses of the medicines. Through its regulatory oversight, the FDA brings to bear its expert judgment about whether a risk should appear in a medicine's labeling and, if so, how best to convey that information without diluting the labeling by including speculative or scientifically-unfounded warnings.

The verdict in this case particularly runs roughshod over the FDA's expertise, by punishing a company for not unilaterally making a labeling

change that the FDA has determined lies in such an important area that it has reserved changes in that area for itself. Juries that are generally not well-versed in the complex duties and responsibilities of the FDA—including its determinations regarding off-label use generally and pediatric use specifically—cannot provide the same assurances for patient safety as the FDA. Having a series of lay juries specifically reach their own disparate views on how a company should warn about off-label risks threatens to seriously disrupt the FDA's efforts to regulate how and when off-label information is conveyed by manufacturers.[3] The potential patient safety harm from that disruption is clear.

At the same time, allowing liability because a company does not take unilateral action that the FDA forbids may harm innovation and thus harm patient health. Developing new medicines is an expensive endeavor, requiring massive investments of resources.

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[3] For example, this Court has recognized in another context the risk to patient safety that would arise from encouraging companies to submit information to the FDA not because it has been required by the FDA, but simply to avoid liability claims. *See Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 351 (2001) (preempting fraud-on-FDA claims in part because of concern that allowing such claims would encourage manufacturers "to submit a deluge of information that the [FDA] neither wants nor needs" out of "fear that their disclosures . . . will later be judged insufficient in state court"). The same concerns could apply to a liability regime that encourages manufacturers to request off-label or pediatric warnings on topics that are already addressed in labeling and that the FDA has determined do not require additional off-label-specific or pediatric-specific verbiage.

See, e.g., J.A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New 23 Estimates of R&D Costs*, at 5 (Nov. 18, 2014) (estimated average industry cost of new prescription drug approval, inclusive of failures and capital costs, is $2.59 billion). As the Tenth Circuit observed in the context of medical devices, "[r]equiring manufacturers to comply with fifty states' warning requirements . . . on top of existing federal . . . requirements, might introduce sufficient uncertainty and cost that manufacturers would delay or abandon at least some number of lifesaving innovations." *Caplinger v. Medtronic, Inc.*, 784 F.3d 1335, 1346 (10th Cir. 2015) (Gorsuch, J.).

More broadly, allowing an "overly aggressive tort environment" can lead to "increased costs and risks of doing business in an area," "disincentives for innovations which promote consumer welfare," and "deterrence of economic development and job creation initiatives," among other effects. The Perryman Group, *Economic Benefits of Tort Reform* at 4 (Nov. 2019), https://www.perrymangroup.com/media/uploads/report/perryman-economic-benefits-of-tort-reform-in-louisiana-11-04-19.pdf. Excessive tort costs impact more than just companies' development decisions—for example, aggregate tort costs are estimated to have cost an average of more than 240,000 jobs annually in California. *See id.* at 10.

The context of this case highlights the very real risks of expensive, protracted litigation. For the past two years, the court before which this case was tried has been ranked as the least fair jurisdiction in the country by the American Tort Reform Foundation.

ATRA, *Philadelphia Court of Common Pleas & the Supreme Court of Pennsylvania*, https://www.judicialhellholes.org/hellhole/2020-2021/philadelphia-court-of-common-pleas-the-supreme-court-of-pennsylvania/ (last visited Feb. 25, 2021); *see also* ATRA, *2020-2021 Executive Summary*, https://www.judicialhellholes.org/reports/2020-2021-executive-summary (last visited Mar. 2, 2021). This ranking flows from the fact that this court has earned a "reputation for excessive verdicts" that are unhinged from actual legal standards and factual records. *Id*. Indeed, this report specifically highlights the verdicts in this litigation as especially egregious examples of lawsuits gone awry. *See id.*

Allowing this type of liability system to proceed unchecked, even in circumstances where the manufacturer has warned about the relevant injury and is prohibited from making the specific off-label warning on which the lawsuit is predicated, will only magnify the social harm from this type of litigation.

III. THE FDA HAS THE POWER AND THE STATUTORY OBLIGATION TO ENSURE THAT PRESCRIPTION MEDICINE LABELS APPROPRIATELY COMMUNICATE RISKS FROM OFF-LABEL USES.

Not only does the FDA reserve to itself the responsibility for dictating the presence and content of warnings for off-label uses and populations, but it possesses the full range of tools necessary to effectively exercise that responsibility. In this sense, there is no credible suggestion that state tort law is a necessary

complement to the federal regulation of off-label warnings for prescription medicines.

1. Companies have the obligation to report all safety information to the FDA, including information relating to off-label uses of their medicines. This obligation includes the duty to report "serious and unexpected" adverse events that a company learns about to the FDA within 15 days of receipt and to periodically report all other adverse events. 21 C.F.R. § 314.80. The FDA also receives adverse event reports from doctors, patients, and other individuals through its voluntary reporting system. *See* FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program* (Aug. 29, 2018), https://www.fda.gov/Safety/MedWatch/default.htm.

The FDA not only approves labeling before a medicine can be marketed, but the agency continues to scrutinize safety information and adjust labeling as necessary for as long as the medicine remains on the market. FDA carefully monitors this safety information from usage of the medicine in the marketplace and works collaboratively with sponsors to identify any off-label risk information that might warrant inclusion in the labeling so that "the public get[s] the accurate, science-based information they need." FDA, *What We Do* (Mar. 28, 2018), https://www.fda.gov/aboutfda/whatwedo.

While the manufacturer bears responsibility for its labeling, the FDA is the final authority on its contents. In exercising that authority, the FDA frequently communicates with drug manufacturers regarding new and amended labeling. The United

States has described the development of labeling as "an iterative process between the applicant and FDA" with respect to any "scientific, medical, and procedural issues that arise." Br. of United States, *Merck Sharp & Dohme Corp. v. Albrecht*, 2018 WL 4562163, at *5–6 (U.S. Sept. 20, 2018). The dynamics of the FDA-manufacturer relationship thus involve frequent communications throughout the tightly-regulated labeling process. *See, e.g.*, 21 C.F.R. § 314.102(b) (if FDA reviewers identify "easily correctable deficiencies" in a supplement, they will "make every reasonable effort to communicate [them] promptly to applicants"). It is thus the norm that, should a safety issue arise with respect to an off-label use or population, the manufacturer will engage with FDA to address whether, and if so how, to reflect that safety concern in a medicine's labeling. For the reasons discussed above, FDA keeps tight control over that process and acts as the gatekeeper for all such labeling decisions.

2. Even in the absence of a specific labeling request from a manufacturer, FDA retains the tools to direct a manufacturer to enhance its warnings in the face of a potential safety concern. That power was expressly codified with the adoption of Section 505(o)(4) of the Food and Drug Administration Amendments Act ("FDAAA") in 2007, which requires the FDA to regularly evaluate safety information and mandate a warning if the FDA learns of a safety issue from any source. *See* 21 U.S.C. § 355(o)(4); *see also* FDA, *Guidance for Industry: Safety Labeling Changes—Implementation of Section 505(o)(4) of the FD&C Act* at 16 (July 2013), https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformatio

n/guidances/ucm250783.pdf (compiling non-exhaustive list of sources of new safety information). Under this current statutory regime, which codified the prior de facto practice of FDA, once the FDA "becomes aware of new safety information that [it] believes should be included in the labeling of the drug," Section 505(o)(4) requires the FDA to "promptly" engage the drug's sponsor to amend the drug's labeling. 21 U.S.C. § 355(o)(4)(A). If the sponsor and FDA cannot agree to the content of the labeling, Section 505(o)(4) expressly grants the FDA authority to "issue an order directing the [manufacturer] to make such a labeling change as the [FDA] deems appropriate to address the new safety . . . information." *Id.* § 355(o)(4)(E).

The FDAAA thus confirmed the FDA's authority and responsibility to ensure a medicine's labeling remains scientifically accurate during its marketing. The legislative record surrounding the FDAAA reflects Congress's intent to clarify the FDA's authority and responsibilities in order to better protect public health. *See, e.g.*, 153 Cong. Rec. S10136–37 (daily ed. July 26, 2007) (statement of Sen. Grassley); *see also* 153 Cong. Rec. S11839–40 (daily ed. Sept. 20, 2007) (statement of Sen. Coburn) ("there is an overriding Federal interest in ensuring that the FDA, as the public health body charged with making these complex and difficult scientific judgments, be the final arbiter of how safety information is conveyed.").

Given this historic power over labeling, the FDA had and continues to have ample authority over safety labeling, including when a potential safety issue implicates an off-label use or non-indicated population. Indeed, the fact that the FDA was well aware of the

applicable safety risks here—as reflected in the approved Risperdal labeling at the time—only confirms that the FDA made an affirmative policy judgment that additional information about this risk in pediatric patients was not warranted. *Cf. Merck Sharp & Dohme Corp. v. Albrecht*, 139 S. Ct. 1668, 1686 (2019) (Alito, J. concurring) (citing 21 U.S.C. § 355(o)(4)(A); Br. of United States, *Albrecht*, 2018 WL 4562163, at *30, *33–34.

This extensive authority rebuts any claim that verdicts like this one are necessary to ensure patient safety. To the contrary, for the reasons expressed above, verdicts like this one threaten to disrupt the FDA's ability to regulate in a way that can only impair patient safety.

3. Finally, it is crucial to understand here how the FDA dedicates unique care in regulating what prescription labeling says about the specific off-label use of medicines by children. The FDA has developed an extensive array of programs and guidance in conjunction with federal legislation to generate sound scientific data and promote science-based pediatric labeling. The FDA's careful regulatory control over pediatric labeling bears special deference.

To increase and spur investment in pediatric studies and labeling, Congress passed the Best Pharmaceuticals for Children Act ("BPCA") in 2002, Pub. L. 107-109 (2002), codified at 21 U.S.C. § 355a, and the Pediatric Research Equity Act ("PREA") in 2003, Pub. L. 108-155 (2003), codified 21 U.S.C. § 355c. Both were reauthorized in 2007 and made permanent in 2012 with the passage of the Food and

Drug Administration Safety and Innovation Act (Public Law 112-144). These pediatric initiatives have resulted in hundreds of pediatric label changes. Susan Thaul, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective*, Congressional Research Service, RL33986 at 17 (June 25, 2012), https://crsreports.congress.gov/product/pdf/RL/RL33986/14.

BPCA and PREA operate as complementary tools. "BPCA (often called the 'carrot'), provides a financial incentive (pediatric exclusivity) to pharmaceutical companies" that engage in pediatric studies that are requested and approved by the FDA, while "PREA (the 'stick') requires pediatric assessments of new drug and biologic licensing applications for all new active ingredients, indications, dosage forms, dosing regimens, and routes of administration." Patrick E. Clarke, *FDA Encourages Pediatric Information on Drug Labeling*, FDA (Dec. 31, 2015), rb.gy/phlmsc. PREA also authorizes the FDA to require the manufacturer of an approved drug to submit a pediatric assessment under a range of circumstances, including (1) when it "is used for a substantial number of pediatric patients for the labeled indications [and] adequate pediatric labeling could confer a benefit on pediatric patients," and (2) when "the absence of adequate pediatric labeling could pose a risk to pediatric patients." 21 U.S.C. § 355c(b)(1).

As a result of this elaborate statutory regime, the FDA already requires by law that pediatric-specific labeling be included if the manufacturer has successfully applied for approval to list a pediatric indication, if the manufacturer has received pediatric

exclusivity after conducting appropriate studies, or if the manufacturer has submitted the safety and effectiveness findings from pediatric assessments required under PREA. *See* Thaul, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective* at 14–15. Further exemplifying the primary role of the FDA in determining pediatric use warnings, the PREA and BPCA reauthorizations dictate that "[w]hen the Secretary determines that a pediatric assessment or study does or does not demonstrate that the subject drug is safe and effective in pediatric populations or subpopulations, the *Secretary must order the label to include information about those results* and a statement of the Secretary's determination," "even if the study results were inconclusive." *Id.* at 15 (emphasis added).

Again, this close regulation of pediatric labeling reinforces why the FDA reserved to itself the authority to direct off-label warnings, and how using state law to compel such warnings from manufacturers would interfere with FDA regulation. The Court should agree to hear this important case to confirm that juries adjudicating state tort suits are not the right bodies to be deciding these complicated scientific and policy questions.

CONCLUSION

The petition for a writ of certiorari should be granted.

Date: March 8, 2021

Respectfully submitted,

/s Michael X. Imbroscio

James C. Stansel
Melissa B. Kimmel
Pharmaceutical Research and Manufacturers of America
950 F St., NW, Ste. 300
Washington, DC 20004
mkimmel@phrma.org
(202) 835-3400
Counsel for Pharmaceutical Research and Manufacturers of America

Sherman Joyce
Lauren Sheets Jarrell
American Tort Reform Association
1101 Connecticut Ave. NW, Suite 4001
Washington, DC 20036
lsheetsjarrell@atra.org
(202) 682-1168
Counsel for American Tort Reform Association

Michael X. Imbroscio
Counsel of Record
Paul W. Schmidt
Covington & Burling LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001
mimbroscio@cov.com
(202) 662-6000
Counsel for Amici Curiae

Tara S. Morrissey
Stephanie A. Maloney
U.S. Chamber Litigation Center
615 H Street, NW
Washington, DC 20062
tmorrissey@uschamber.com
(202) 463-5337
Counsel for Chamber of Commerce of the United States of America