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 OF *AMICUS CURIAE* PRODUCT LIABILITY ADVISORY COUNCIL, INC. IN SUPPORT OF PETITION FOR WRIT OF CERTIORARI

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BRIEF OF *AMICUS CURIAE* PRODUCT LIABILITY ADVISORY COUNCIL, INC. IN SUPPORT OF PETITION FOR WRIT OF CERTIORARI

INTEREST OF *AMICUS CURIAE*[1]

The Product Liability Advisory Council, Inc. ("PLAC") is a nonprofit professional association with scores of corporate members from a broad cross-section of American and international product manufacturers.[2] These companies seek to contribute to the improvement and reform of law in the United States and elsewhere, emphasizing the law governing the liability of product manufacturers and others in the supply chain. PLAC's perspective is derived from the experiences of a corporate membership that spans a diverse group of industries in various facets of the manufacturing sector. In addition, several hundred leading product litigation defense attorneys are sustaining (non-voting) members of PLAC.

PLAC's primary purpose is to file *amicus curiae* briefs in cases presenting issues that affect the development of product related litigation and impact

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[1] All parties were timely notified and consented to the filing of this brief. Pursuant to S. Ct. Rule 37.6, *amicus* states that no counsel for a party wrote this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than the *amicus curiae*, its members, or its counsel, has made a monetary contribution to this brief's preparation or submission.

[2] PLAC's current corporate membership is listed at <https://plac.com/PLAC/Membership/Corporate_Membership.aspx>.

PLAC's members. Since 1983, PLAC has filed more than 1,100 briefs as *amicus curiae* in both state and federal courts, including this Court, on behalf of its members, while presenting the broad perspective of product manufacturers seeking fairness and balance in the application and development of the law as it affects product risk management.

PLAC's interest in this action arises from the profound impact of state-law claims seeking to impose conflicting obligations on businesses regulated by the federal government. Many of PLAC's members, particularly FDA-regulated prescription medical product manufacturers, are subject to federally-imposed restrictions about what they can, and cannot, state in their product labeling. To avoid their being sitting ducks for product liability litigation, these manufacturers depend on federal supremacy to preclude state-law liability for their compliance with federal requirements – here, FDA's preclusion of statements in prescription drug labeling about "off-label" uses unless FDA itself requires them. Accordingly, this case presents an impossibility preemption situation under such cases as *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011).

PLAC's members cannot serve two masters imposing conflicting obligations. This case thus directly implicates another aspect of the "delicate balance" of FDA's regulatory scheme recognized in *Buckman Co. v. Plaintiffs Legal Committee*, 531 U.S. 341, 348 (2001). FDA's exclusive authority to require off-label statements is an issue that this Court has never addressed.

STATEMENT

As the petition argues, this appeal presents critical issues of first impression affecting the public health and the regime created by the federal Food & Drug Administration ("FDA") to protect it. The result below threatens both. It allows state law to punish, with massive liability, a regulated company's compliance with mandatory FDA labeling decisions. It does so in the context of "off-label" use – the one-third or so of all drug and medical device prescriptions for purposes FDA has not evaluated for safety and effectiveness. Such liability must be preempted, both to preserve FDA's power to regulate labeling, and to ensure the continued advance of medical science that is essential to the public health.

1. FDA Requires Pre-Approval of All Off-Label Warnings.

Off-label use is the necessary corollary of FDA regulation of prescription medical products. Advances in medical practice would be stymied if physicians could not treat patients with the most up-to-date therapies available, which off-label uses often are. Conversely, however, unlimited marketing of regulated products for any use, notwithstanding FDA oversight, would remove incentives to submit new potential product uses to FDA scrutiny.

While states regulate medical practice, the federal Food, Drug and Cosmetic Act ("FDCA"), Ch. 675, 52 Stat. 1040, *as amended*, 21 U.S.C. §§301, *et seq.*, limits

labeling of prescription medical products to uses FDA has reviewed and considers safe and effective. To ensure continued submission of new uses of drugs and devices, FDA has interpreted the FDCA to preclude "promotion" of off-label uses. Part and parcel of that prohibition is strict FDA control over any mention of off-label uses in approved product labeling. 21 C.F.R. §§201.57(c)(2) (drugs), 807.92(a)(5) (medical devices).

FDA did not require the warning at issue here, concerning what plaintiffs-respondents claim is an increased risk of gynecomastia associated with the then-off-label use of the prescription drug Risperdal for treating psychiatric conditions in minors, such as plaintiff/respondent A.Y. Therefore, defendants/petitioners were forbidden by federal law from adding the warning that plaintiffs have invoked state law to demand be added to an FDA regulated label.

2. *Wyeth v. Levine* and Its Progeny Mandate Preemption Where, as Here, A Label Change Requires FDA Preapproval.

In *Wyeth v. Levine*, 555 U.S. 555 (2009), the Court established that implied preemption, by reason of impossibility of simultaneous compliance with conflicting federal and state duties, does not exist when a manufacturer can "unilaterally" make a contested label change "before receiving" FDA approval. *Id.* at 571, 573 (relying on 21 C.F.R. §314.70(c)(6)(iii)(A)) ("*Levine*"). As explained in *PLIVA, Inc. v. Mensing*:

> [W]hen a party cannot satisfy its state duties without the Federal Government's special permission and assistance . . . , that party cannot independently satisfy those state duties for pre-emption purposes.

564 U.S. 604, 623-24 (2011) ("*Mensing*"). Most recently, in *Merck Sharp & Dohme Corp. v. Albrecht*, the Court again reiterated that "[t]he underlying question for this type of impossibility pre-emption defense is whether federal law (including appropriate FDA actions) prohibited the drug manufacturer from adding any and all warnings to the drug label that would satisfy state law." 139 S. Ct. 1668, 1678 (2019) ("*Albrecht*"). That inquiry is one of law for judges to decide. *Id.* at 1679-80.

Information about off-label risks of FDA-regulated products can only be added to an FDA-approved label when FDA itself requires it. This Court's consistent precedent since *Levine* therefore preempts state-law tort duties demanding off-label warnings. It is impossible to comply simultaneously with both state and federal requirements, since manufacturers such as petitioner cannot unilaterally add off-label information to FDA-regulated labeling to satisfy an asserted state-law duty.

3. The Decision Below.

As discussed more fully in the Petition, plaintiff/respondent A.Y. was prescribed the anti-psychotic drug Risperdal as a minor beginning in 2003. For three

years, until FDA approved a pediatric indication in 2006, this use was off-label. Plaintiffs claimed that Risperdal was defective during this period for not warning of the allegedly increased pediatric risk of gynecomastia (enlarged breasts in males).[3] After a trial judge in Philadelphia rejected petitioners' preemption defense based on compliance with FDA's restrictions on off-label warnings (RR.01451a-52a), a jury awarded $70 million based solely on these warning allegations. (App.56–57.)

Defendants/petitioners appealed, and the intermediate Pennsylvania Superior Court affirmed, mentioning FDA's regulation prohibiting off-label drug warnings only once, in passing. *A.Y. v. Janssen Pharmaceuticals, Inc.*, 224 A.3d 1, 14 (Pa. Super. 2019). The Superior Court was not always clear, but its key holding appears to be that, notwithstanding FDA preapproval requirements for off-label information, the general "Changes Being Effected" ("CBE") regulation, §314.70(c)(6)(iii)(A), applied equally to both on- and off-label uses, 224 A.3d at 15 – a conclusion without basis in law or fact. The Pennsylvania Supreme Court denied review, and petitioners timely sought review in this Court.

[3] Pursuant to 21 C.F.R. §201.57(f)(9)(vi), between 1993 and 2006, Risperdal's label stated that "[s]afety and effectiveness in children have not been established."

INTRODUCTION AND SUMMARY OF ARGUMENT

Without off-label use, the nation's health-care system would be hobbled. Uses not appearing in FDA-approved labeling comprise about one-third of all prescriptions for both drugs and medical devices. In many specialties, such as pediatrics, the rate of off-label use is much greater. The reason is simple: medical science advances faster than FDA regulation. Many standard-of-care medical treatments begin off label, and some remain that way. To use one current example, no on-label treatment for COVID-19 exists. It is simply too new for FDA regulation to have caught up with the present health emergency. To save lives, medical practice requires more agility.

Conversely, if FDA-regulated manufacturers could unilaterally add discussions of off-label uses to their products' approved labeling, incentives that encourage submission of products for FDA review could be undermined. FDA itself certainly thinks so. The investment of time, effort, and money to submit new "intended" product uses to FDA would be difficult to justify, were manufacturers free to add off-label information whenever they wanted.

FDA balanced these considerations and decided that information about off-label uses may appear on product labeling only if, and when, the Agency requires it. To ensure the continued submission of new uses to the Agency, FDA's regulatory scheme has for many years vested the Agency with sole authority to require

statements, such as warnings, pertaining to off-label uses. 21 C.F.R. §201.57(e) (only FDA "may" require inclusion of off-label information). As a prerequisite, FDA regulations require evaluation of both the seriousness of the off-label risk, and the prevalence of the off-label use before any off-label warning is required.

This conundrum: (1) the necessity of off-label use for the advancement of medical treatment, and thus the public health; versus (2) the potential for unilateral off-label statements to reduce incentives to obtain FDA approval of new indicated product uses, has never been addressed by this Court. It is another aspect of the "delicate balance of statutory objectives" that this Court recognized in *Buckman* as characteristic of FDA regulatory efforts in this area.

Review is critical. Preemption of the state-law claim here, because of that claim's inherent conflict with FDA's pre-approval requirement, is essential to prevent overwhelming mass-tort liability. Petitioners were held liable for complying with supreme federal law. Given the ubiquity of off-label use, every FDA-regulated product manufacturer will sooner or later face the same prospect of massive liability.

REASONS FOR GRANTING *CERTIORARI*

I. The Interference with FDA Regulation of Off-Label Use That Occurred in This Case Threatens Both the Federal Regulatory Scheme and the Public Health.

Under the FDCA, before a prescription medical product may be marketed in the United States, it must have FDA approval or clearance to be labeled for at least one "intended use." 21 C.F.R. §§201.57(c)(2), 807.92(a)(5). FDA review of drugs and medical devices is based entirely on the intended use(s) submitted by regulated manufacturers. 21 U.S.C. §§355(d) (drugs); 360c(i)(1)(E)(i) (devices). "[D]uring the approval process, the agency can look solely to [the applicant's] labeling claims to determine the intended use of its drug." *Spectrum Pharmaceuticals, Inc. v. Burwell*, 824 F.3d 1062, 1068 (D.C. Cir. 2016).

This Court first addressed off-label use in *Buckman*, defining it as "use of a device [or drug] for some other purpose than that for which it has been approved by the FDA." 531 U.S. at 350. Off-label use includes "prescriptions of the [product] for a condition not indicated on the label, treating an indicated condition at a different dose or frequency than specified on the label, or treating a different patient population than approved by the FDA." *Ironworkers Local Union 68 v. AstraZeneca Pharmaceuticals, LP*, 634 F.3d 1352, 1356 n.4 (11th Cir. 2011).

Buckman recognized that "off-label use is generally accepted" under the law as a "necessary corollary

of the FDA's mission to regulate in this area without directly interfering with the practice of medicine." 531 U.S. at 350 (citation omitted). Thus, "[p]hysicians may prescribe drugs and devices for off-label uses." *Id.* at 351 & n.5. FDA agrees:

> [H]ealth care professionals are generally permitted to prescribe or use approved/cleared medical products for unapproved uses when they judge that the unapproved use is medically appropriate for their individual patients, and relevant, truthful, and non-misleading scientific or medical information regarding unapproved uses of approved medical products may help health care professionals make better individual patient decisions.

"Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Public Hearing; Request for Comments," 81 Fed. Reg. 60299, 60300 (FDA Sept. 1, 2016) (footnote omitted).

Given that medical science advances far more quickly than regulatory oversight, off-label use is essential.

> *New uses for drugs are often discovered after FDA approves the package inserts that explain a drug's approved uses*. Congress would have created havoc in the practice of medicine had it required physicians to follow the expensive and time-consuming procedure of obtaining FDA approval before putting drugs to new uses.

United States v. Algon Chemical, Inc., 879 F.2d 1154, 1163 (3d Cir. 1989) (citation and quotation marks omitted) (emphasis original). "In clinical practice, new uses or dosing regimens often become widespread and well accepted long before they are reflected in the labeling."[4]

Indeed, the current COVID-19 crisis is too recent for there to be *any* FDA "intended use" for *any* drug or medical device intended to treat the pandemic. All COVID-19 treatments, including vaccines, are available by way of FDA "emergency use authorizations," which may involve "unapproved uses of approved drugs" – off-label use. 21 U.S.C. §§360bbb-3(a)(1), 360bbb-3(a).

For these reasons, off-label use is "commonplace in modern medical practice and ubiquitous in certain specialties." *Washington Legal Foundation v. Henney*, 202 F.3d 331, 333 (D.C. Cir. 2000) (citation omitted). Recent estimates indicate the rate of off-label use remains "notoriously high among some patient populations." Rodney Adams & Leslie Crudele, "The Eroding Off-Label

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[4] Am. Acad. Pediatrics, Committee on Drugs, "Uses of Drugs Not Described in the Package Insert (Off-Label Uses)," 110 PEDIATRICS 181, 182 (2002); *see* "Promotion of Drugs & Medical Devices for Unapproved Uses": Hearing Before the Human Resources & Intergovernmental Relations Subcomm. of the House Comm. on Gov't Operations, 102d Cong., 1st Sess. 103 (1991) ("There are too many variations in clinical circumstances and too much time delay in regulations to allow the government to impede the physician's ability to practice . . . when it is medically appropriate.") (statement of George Lundberg, M.D., editor of the Journal of the American Medical Association).

Drug Use Promotion Prohibition," 12 J. HEALTH & LIFE SCI. L. 1, 5 (2019) ("twenty to sixty percent of all drug prescriptions are written for off-label uses") (footnote omitted).[5]

Pediatrics – the field implicated by this case – is one specialty where off-label use is particularly prevalent. Some "80% of drugs prescribed for children are being prescribed for off-label uses." Wendy Teo, "FDA & the Practice of Medicine: Looking at Off-Label Drugs," 41 SETON HALL LEGIS. J. 305, 322 (2017) (footnote omitted). A large study determined that "78.9% of children discharged from pediatric hospitals were taking at least 1 off-label medication." Christopher Wittich, Christopher Burkle, & William Lanier, "Ten Common Questions (& Their Answers) about Off-Label Drug Use," 87(10) MAYO CLIN. PROC. 982, 983 (2012) (citation omitted). Off-label prescribing in certain pediatric subspecialties is higher still, with off-label use rates of 96% in cardiovascular/renal, 86% for pain treatment, and 80% of gastrointestinal care. Alicia Bazzano, *et al.*, "Off-Label Prescribing to Children in the United States Outpatient Setting," 9 ACAD.

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[5] *Amarin Pharma, Inc. v. FDA*, 119 F.Supp.3d 196, 200-01 (S.D.N.Y. 2015) ("in certain fields, off label prescription is the norm rather than the exception") (collecting research); Shane M. Ward, "WLF & the Two-Click Rule: The First Amendment Inequity of the Food & Drug Administration's Regulation of Off-Label Drug Use Information on the Internet," 56 FOOD & DRUG L.J. 41, 45-46 (2001) (over 30% for cancer patients, 40% for AIDS patients, 80% for children, and 90% for rare disease sufferers).

PEDIATRICS 81, 81 (2009). This case implicates state-of-the-art medicine.

As FDA recognizes, the medical "[s]tandard of care," *i.e.*, sufficient care to avoid malpractice liability, "may include uses or treatment regimens that are not included in a product's approved labeling." FDA, "Informed Consent Information Sheet, Guidance for IRBs, Clinical Investigators, and Sponsors," at 9 (Draft Guidance, July 2014). Thus, off-label use represents not only "the best available intervention for a patient," but in some areas "the only treatment option." Rebecca Dresser & Joel Frader, "Off-Label Prescribing: A Call for Heightened Professional & Government Oversight," 37 J. L. MED. & ETHICS 476, 481 (2009). This ubiquity of off-label use explains why "FDA's drug approval process generally contemplates that approved drugs will be used in off-label ways." *United States v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012). FDA has the difficult job of maintaining "a somewhat delicate balance of statutory objectives" concerning off-label use. *Buckman*, 531 U.S. at 348.

Off-label use by physicians and other health-care providers is "medical practice" traditionally regulated by the states, rather than FDA. "[A] state has broad power to establish and enforce standards of conduct" for "all professions concerned with health." *Barsky v. Board of Regents*, 347 U.S. 442, 449 (1954). Drug labeling, however, is regulated by FDA. *E.g.*, *Kordel v. United States*, 335 U.S. 345, 349-50 (1948).

To pursue its "difficult task of regulating [off-label] marketing and distribution . . . without intruding upon decisions statutorily committed to the discretion of health care professionals," *Buckman*, 531 U.S. at 350, FDA maintains strict control over any information in drug or medical device labeling that concerns off-label use.[6] FDA has "long taken the position" that any "promotion" of off-label use "violates the FDCA" and is thus illegal. *Amarin Pharma, Inc. v. FDA*, 119 F.Supp.3d 196, 203 (S.D.N.Y. 2015). Thus, courts have frequently held that "[t]he FDCA creates both civil and criminal penalties for drug manufacturers that promote the use of approved drugs for unapproved uses (referred to here as 'off-label' uses." *In re Celexa & Lexapro Marketing & Sales Practices Litigation*, 915 F.3d 1, 5 (1st Cir. 2019) (citations omitted).[7]

FDA closely regulates off-label information because it considers allowing unilateral dissemination of such information – envisioned by the decision below – to "implicate several substantial government interests related to health and safety," "all" of which "relate to FDA's larger substantial interest in protecting and promoting public health." Memorandum, "Public Health

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[6] *E.g.*, 21 C.F.R. §202.1(e)(4)(i)(a) (advertisements "shall not recommend or suggest any use that is not in the [approved] labeling").

[7] The same is true for medical devices. *E.g.*, *Coleman v. Medtronic, Inc.*, 167 Cal. Rptr.3d 300, 307 (Cal. App. 2014) (the FDCA "prohibit[s] a device manufacturer from promoting the use of a device in a manner inconsistent with premarket approval") (citations omitted).

Interests . . . Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products," at 3 (FDA Jan. 2017).[8] These interests include:

- motivating development of robust scientific data on safety and efficacy;
- maintaining FDA's premarket review process for safety and efficacy of each intended use in order to prevent harm and to prevent diversion of health care resources to ineffective treatments;
- ensuring that FDA-required labeling is accurate and informative;
- ensuring integrity and reliability of promotional information regarding uses of medical products;
- ensuring patient informed consent;
- supporting informed medical decision-making; and
- furthering scientific understanding and research.

Id.

As manufacturers may not discuss the benefits of off-label use, allowing plaintiffs to demand unilateral

[8] This sixty-page document detailing FDA's rationale for maintaining control over off-label information is available at <https://downloads.regulations.gov/FDA-2016-N-1149-0040/attachment_1.pdf.> *See also* 82 Fed. Reg. 6367 (FDA Jan. 19, 2017) (announcing memorandum's availability).

addition only of risk information would bias labeling against off-label use. This Court recognized in *Albrecht* that FDA maintains a "hierarchy of label information" in order to avoid "exaggeration of risk, or inclusion of speculative or hypothetical risks, that could discourage appropriate use of a beneficial drug." 139 S. Ct. at 1673 (citation and quotation marks omitted). Unconstrained state-law demands for off-label risk information, together with FDA restrictions on countervailing information about off-label benefits, would create exactly the same "overwarning" pressure that *Albrecht* cautioned against.

FDA control over off-label information begins with "intended use" – as measured by the "objective" intent of the product's suppliers. 21 C.F.R. §§201.5 (drugs), 801.5 (devices). Manufacturers must include "adequate directions for use" for all intended uses of FDA-regulated products. *Id.*, *see also* 21 U.S.C. §352(f). FDA will not approve a new drug application with labeling that discusses uses other than those the Agency has concluded are safe and effective. 21 U.S.C. §355(d)(1, 4-5). The regulations require prior FDA review and approval of warnings pertaining to off-label uses of drugs, and limit such off-label warnings to "commonly prescribed" uses.

> A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA . . . if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

21 C.F.R. §201.57(c)(6)(i).[9] *See* 21 C.F.R. §201.80(e) (similar language pertaining to certain older drugs). FDA regulations further prohibit drug labeling from citing clinical studies that "imply or suggest" off-label uses. 21 C.F.R. §§201.57(c)(9)(15)(i); 201.80(m)(1)(i).

Based on these regulations, "FDA may . . . require changes to the product's labeling or promotional materials designed to discourage potential off-label use of the product that might cause harm to consumers." *Church & Dwight Co. v. SPD Swiss Precision Diagnostics, GmBH*, 843 F.3d 48, 56 (2d Cir. 2016) (citation omitted). When off-label use is "widespread," FDA "may require the manufacturer to include statements in the drug's labeling." *Richardson v. Miller*, 44 S.W.3d 1, 11-12 (Tenn. App. 2000). For instance, to combat a "common belief" in the effectiveness of an off-label drug use, FDA may require a contrary statement when a "preponderance of the evidence . . . shows the drug is ineffective." 21 C.F.R. §§201.57(c)(2)(ii); 201.80(c)(3)(iv). "In addition to warning about risks from approved uses, the FDA has authority to impose warnings about off-label or unapproved uses when there is evidence of a clinically significant risk." *Bailey v. Wyeth, Inc.*, 37 A.3d 549, 556 (N.J. Super. Law Div. 2008) (citation and footnote omitted), *aff'd*, 28 A.3d 1245 (N.J. Super. App. Div. 2011) (on basis of trial court opinion).

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[9] In 2003, the relevant time period for this case, identical language appeared at 21 C.F.R. §201.57(e).

FDA's control over off-label statements is equally firm with respect to medical devices. As to devices, FDA,

> may require the . . . person(s) responsible for the labeling or advertising of the device to include . . . a statement, notice, or warning. Such statement, notice, or warning shall be in the manner and form prescribed by the Commissioner. . . .

21 C.F.R. §895.25(b). As to off-label use specifically, FDA,

> may require a statement in labeling . . . regarding a use of the device not identified in the proposed labeling if . . . there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling . . . [and] such use could cause harm.

21 U.S.C. §360c(i)(1)(E)(i)(I-II).

Thus, "FDA can require a [device] manufacturer to provide additional labeling that addresses potential off-label uses." *Reeves v. AcroMed Corp.*, 44 F.3d 300, 305-06 (5th Cir. 1995) (citing §895.25). "Any additional state duties on top of those imposed by federal law, even if nominally limited to off-label uses, might check innovation, postpone access to life-saving devices, and impose barriers to entry without sufficient offsetting safety gains." *Caplinger v. Medtronic, Inc.*, 784 F.3d 1335, 1346 (10th Cir. 2015) (Gorsuch, J.). As to an off-label use, a "manufacturer may not change the label, even to add warnings, until it submits the proposed

change . . . and obtains FDA approval." *Cornett v. Johnson & Johnson*, 998 A.2d 543, 556 (N.J. App. Div. 2010) (citations omitted), *aff'd*, 48 A.3d 1041 (N.J. 2012).[10]

Given the high percentage of off-label prescriptions for both drugs and medical devices, the ruling here is an ominous portent for all FDA-compliant manufacturers. Such manufacturers are bound to follow FDA labeling requirements, so the kind of massive liability imposed here for obeying federal labeling mandates is not a form of negligence. It is not a form of strict liability. Rather, liability for failure to change labels to include what FDA prohibits is a form of absolute liability that would prove disastrous for these industries, and ultimately for the public health.

II. To Avoid Absolute Liability, This Court Should Address, as a Matter of First Impression, Preemption of State-Law Duties Requiring Off-Label Warnings That FDA Has Not Permitted.

The barrier here to absolute liability is federal preemption under the Constitution's Supremacy Clause. U.S. Const., Art. VI, cl. 2. Preemption exists, *inter alia*, when it is "impossible for a private party to comply

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[10] *See McGuan v. Endovascular Technologies, Inc.*, 106 Cal. Rptr.3d 277, 281-82 (Cal. App. 2010) (FDA's power to "condition its approval on adherence to various requirements" extends to "off-label promotion"); *In re Orthopedic Bone Screw Products Liability Litigation*, 1996 WL 221784, at *6 (E.D. Pa. April 8, 1996) ("[t]hrough [§895.25(a)] the FDA regulates off-label uses of medical devices").

with both state and federal requirements." *Mutual Pharmaceutical Co. v. Bartlett*, 570 U.S. 472, 480 (2013) (citation and quotation marks omitted) ("*Bartlett*"). "FDA regulations set out requirements for the content, the format, and the order of the safety information on the drug label. *Albrecht*, 139 S. Ct. at 1673 (citing 21 C.F.R. §201.57(c)).

While "it has long been settled that state laws that conflict with federal law are without effect," a mere "possibility of impossibility is not enough." *Albrecht*, 139 S. Ct. at 1679 (citations and quotation marks omitted). Thus, there must be a direct conflict, where FDA says "yes" (or "no") while at the same time state law says "no" (or "yes") – along the lines of those present in *Bartlett* and *Mensing*.

Bartlett involved design defect claims against generic prescription drugs. Drug designs cannot be changed unilaterally. "Once a drug – whether generic or brand-name – is approved, the manufacturer is prohibited from making any major changes to the 'qualitative or quantitative formulation of the drug product, including active ingredients, or in the specifications provided in the approved application.' " 570 U.S. at 477 (citation omitted). Further, "because of [its] simple composition, the drug is chemically incapable of being redesigned." *Id.* at 484.[11] Hence, impossibility preemption. For both reasons, a manufacturer "cannot legally

[11] Not all drugs are chemically "simple" as described in *Bartlett*, since some are combinations of more than one active ingredient. Risperdal, however, like the drug in *Bartlett*, is a "one-molecule drug." *Id.*

make [the drug] in another composition," and if it did "the altered chemical would be a new drug that would require its own [new drug application] to be marketed in interstate commerce." *Id.* (citation and quotation marks omitted).

Likewise, in *Mensing*, the statutory scheme for generic drugs – requiring "sameness" in labeling with the predicate branded (or "innovator") drug – supported preemption by reason of impossibility despite the plaintiff's reliance on FDA's CBE regulation. 564 U.S. at 614. FDA "interpret[ed] the CBE regulation to allow changes to generic drug labels only when a generic drug manufacturer changes its label to match an updated brand-name label or to follow the FDA's instructions." *Id.* (citing FDA *amicus* brief). Plaintiff's reliance on the CBE regulation in *Mensing* thus "violate[d] the statutes and regulations requiring a generic drug's label to match its brand-name counterpart's." *Id.* (citations omitted). Deferring to FDA's interpretation, *Mensing* found the CBE regulation inapplicable and held that it was impossible simultaneously to comply with a federal requirement of "sameness" and a state-law duty demanding more extensive generic drug warnings. *Id.* at 614-15.

This case, like *Mensing* and *Bartlett*, comes before this Court "in the context of a particular set of circumstances." *Albrecht*, 139 S. Ct. at 1678. Those circumstances likewise demonstrate the applicability of implied conflict preemption. For the weighty public health reasons detailed above, FDA has said "no" to manufacturers unilaterally adding warnings and other information

about off-label uses to their approved labeling. *See* 21 C.F.R. §§201.57(c)(2)(ii); 201.57(c)(6)(i) (verbatim identical to 21 C.F.R. §201.57(e) (2003)); 201.57(c)(9)(15)(i); 201.80(c)(3)(iv); 201.80(e); 201.80(m)(1)(i) (all concerning drug labeling); *cf.* 21 U.S.C. §360c(i)(1)(E)(i)(I-II); 21 C.F.R. §§895.25(b) (imposing similar restrictions on off-label statements in device labeling). Since this case affects both drugs and medical devices it is as important to the FDA regulatory scheme as the generic-specific decisions in *Mensing* and *Bartlett*.

State law, however, as interpreted below said "yes" – imposing a duty to include an off-label warning FDA had not allowed. Plaintiffs here relied only on the CBE regulation, like the plaintiff in *Mensing*. They successfully argued below that the general CBE regulation controlled over FDA's more specific regulations governing when off-label information should appear in approved drug (and medical device) labeling.

As in *Mensing*, the result below cannot be correct. Generally, drug manufacturers are "charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Albrecht*, 139 S. Ct. at 1677 (quoting *Levine*, 555 U.S. at 571), but as *Mensing* and *Bartlett* demonstrate, specific exceptions to this general rule exist. Thus the maxim "the specific controls the general" counsels against construing the CBE regulation broadly, so as to nullify FDA's off-label-specific regulations requiring Agency pre-approval of any inclusion of this type of information in drug (and device) labeling. *E.g.*, *Bloate v. United States*, 559 U.S. 196, 207 (2010)

("[a] specific provision . . . controls ones of more general application") (quoting *Gozlon-Peretz v. United States*, 498 U.S. 395, 407 (1991)). As in *Bloate*, "[t]here is no question that" FDA's regulations prohibiting unilateral addition of off-label information are "more specific" than the CBE regulation, which as *Levine* held, applies to drug warnings generally. 555 U.S. at 570 ("the very idea that the FDA would bring an enforcement action against a manufacturer for strengthening a warning pursuant to the CBE regulation is difficult to accept").

"Context" is as important here as FDA's regulatory structure. *Bloate*, 559 U.S. at 210. In *Levine*, the Court pointed out that neither the defendant nor the government (which appeared as *amicus* on behalf of FDA) "ha[d] identified a case in which the FDA has done so" – that is, had prosecuted a use of the CBE regulation. 555 U.S. at 570. Here, the same evidentiary shoe appears to be on the other foot. PLAC has searched both judicial precedent and the information on CBE supplements appearing on the FDA's website, and as far as PLAC can determine FDA has never[12] allowed a CBE supplement that sought to add information about an "off-label," "unindicated," or "unapproved" use. Thus,

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[12] FDA announced the public availability of CBE supplements in September, 2006. FDA, "Draft Guidance for Industry on Public Availability of Labeling Changes in 'Changes Being Effected' Supplements; Availability (CDER Sept. 20, 2006), available at <https://www.regulations.gov/contentStreamer?documentId=FDA-2006-D-0038-0001&contentType=pdf>.

the CBE alternative that the court below hypothesized, 224 A.3d at 15, is non-existent in practice.

Case law is sparse, but supportive. *Byrd v. Janssen Pharmaceuticals, Inc.*, 333 F.Supp.3d 111 (N.D.N.Y. 2018), involved identical facts – the same drug and the same off-label information-based claim. *Byrd* recognized that "the plain language" of applicable FDA regulations "prohibited Defendants from unilaterally updating [the drug's] label regarding pediatric use," and further that "Defendants could not unilaterally add safety information relative to unapproved populations" generally. *Id.* at 117 (N.D.N.Y. 2018).

> [T]his common-sense interpretation of 21 C.F.R. §201.57(e) (2004) (as conferring on the FDA the sole authority to add safety information regarding an off-label use of a medication) is supported by the structure of the FDA's regulations, which treat labels as containing adequate directions for intended use.

Id.

Additional FDA context reinforces this reading of the relevant regulations. *Byrd* pointed out that FDA's regulation concerning boxed warnings, 21 C.F.R. §201.57(c)(1),[13] is phrased identically – such warnings "may be required by the FDA" – and that this regulation has overwhelmingly been recognized as

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[13] FDA regulations provide for "prominent 'boxed' warnings about risks that may lead to death or serious injury." *Albrecht*, 139 S. Ct. at 1673 (citing §201.57(c)). *See also* 21 C.F.R. §201.80(e). Boxed warnings are also known as "black box" warnings.

preemptive, notwithstanding the more general CBE regulation. 333 F.Supp.3d at 117-18. Implied conflict preemption exists in boxed warning cases for the same reason as here: because only FDA may require boxed labels, tort claims demanding such labeling are impliedly preempted by FDA's mandatory pre-approval requirement under *Mensing* and *Bartlett*.

Thus, *Fulgenzi v. PLIVA, Inc.*, 711 F.3d 578 (6th Cir. 2013), recognized that the plaintiff "cannot claim that [defendant] should have included an aggressive black-box warning; any such allegations are preempted under *Mensing*." *Id.* at 587. The Third Circuit agreed in *In re Avandia Marketing, Sales Practices & Products Liability Litigation*, 639 Fed. Appx. 874 (3d Cir. 2016), that "[o]nly the FDA may issue a black box warning, however, so [defendant] could not have included such a warning absent a directive from the FDA." *Id.* at 879 n.9 (also citing *Mensing*). Numerous federal district court decisions are in accord.[14]

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[14] *Amos v. Biogen Idec, Inc.*, 249 F.Supp.3d 690, 699 (W.D.N.Y. 2017) ("a drug manufacturer cannot add or change a black box warning without permission from the FDA"); *In re Depakote*, 87 F.Supp.3d 916, 924 (S.D. Ill. 2015) (defendant "could not have *unilaterally* changed the Black Box Warning") (emphasis original); *Koho v. Forest Laboratories, Inc.*, 17 F.Supp.3d 1109, 1117 (W.D. Wash. 2014) ("Defendants are correct that they had no authority to add a 'black box warning' "); *Ray v. Allergan, Inc.*, 863 F.Supp.2d 552, 561 (E.D. Va. 2012) ("[defendant] is correct in contending that the CBE process could not be used to add a black box warning"); *Ehlis v. Shire Richwood, Inc.*, 233 F.Supp.2d 1189, 1197-98 (D.N.D. 2002) (FDA has "exclusive authority" to mandate boxed warnings), *aff'd*, 367 F.3d 1013 (8th Cir. 2004). *Accord Muzichuck v. Forest Laboratories, Inc.*, 2015

Preemption is a purely legal issue under *Albrecht*, and the Court need "simply ask [itself] whether the relevant federal and state laws irreconcilably conflict." *Albrecht*, 139 S. Ct. at 1679 (citation and quotation marks omitted). Asking that question here leads to only one plausible result – the decision below, upholding a $70 million verdict, is seriously in error. Moreover, that error threatens to upset FDA's delicate balance affecting the widespread medical practice of off-label use of prescription drugs and medical devices. Thus, this case is of critical importance, not only to FDA's regulatory scheme, but to the public health as a whole. To preserve both, in this time of pandemic-driven crisis, the petition for *certiorari* should be granted.

CONCLUSION

For the foregoing reasons, as well as the reasons stated in the Petition, PLAC respectfully requests that the Court grant the Petition for a Writ of Certiorari filed by Petitioners Janssen Pharmaceuticals, Inc., Johnson & Johnson Co., and Janssen Research & Development, LLC, and enforce the allocation of authority enacted by Congress, administered by FDA, and

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WL 235226, at *6, 10 (N.D. W.Va. Jan. 16, 2015); *Guenther v. Novartis Pharmaceutical Corp.*, 2013 WL 4648449, at *5 (M.D. Fla. Aug. 29, 2013); *Ray v. Allergan, Inc.*, 2012 WL 2120018, at *7 (E.D. Va. June 1, 2012); *In re Bextra & Celebrex Marketing Sales Practices & Product Liability Litigation*, 2006 WL 2374742, at *8 (N.D. Cal. Aug. 16, 2006).

reinforced in *Buckman* and *Mensing*, by reversing the decision of the Pennsylvania Superior Court.

Respectfully submitted,

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