No. 15-449

IN THE

Supreme Court of the United States

JOHNSON & JOHNSON AND MCNEIL-PPC, INC.,

Petitioners,

v.

LISA RECKIS AND RICHARD RECKIS,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE SUPREME JUDICIAL COURT OF MASSACHUSETTS

BRIEF OF THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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BRIEF OF THE CHAMBER OF COMMERCE OF THE UNITED STATES OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

INTEREST OF THE *AMICUS CURIAE*[1]

The Chamber of Commerce of the United States of America ("the Chamber") is the world's largest business federation. The Chamber represents 300,000 direct members and indirectly represents the interests of more than three million companies and professional organizations of every size, in every industry, 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 vital concern to the Nation's business community.

The Chamber is well situated to address the issue of preemption raised in this case. Its members are engaged in commerce in each of the 50 states and are subject to a wide range of federal regulations. Those members often confront potential conflict between the mandatory duties imposed by federal law and state common-law standards

[1] The parties received timely notice of *amicus curiae*'s intent to file this brief and filed consents to the filing of *amicus* briefs with the Clerk. Under Rule 37.6 of the Rules of this Court, *amicus curiae* states that no counsel for a party authored this brief in whole or in part and that no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person or entity, other than *amicus curiae*, its members, or its counsel, has made a monetary contribution intended to fund this brief's preparation or submission.

applied to the same conduct in product liability cases. The Chamber is uniquely suited to offer a broader perspective on preemption than the parties may provide and interested in ensuring that the regulatory environment in which its members operate is uniform and consistent throughout the nation.

SUMMARY OF ARGUMENT

Petitioners' brief explains why the Massachusetts Supreme Judicial Court's ("SJC's") decision misapplies this Court's "clear evidence" standard under *Wyeth v. Levine*, 555 U.S. 555 (2009), for determining when conflict preemption applies, exacerbates a split of authority among the lower courts, and calls for corrective action by this Court. The Chamber submits this brief to demonstrate that the SJC's opinion fundamentally misunderstands the teaching of three recent decisions of this Court regarding the operation and preemptive effect of the federal drug labeling regime in state-law tort cases involving a collision between drug labeling mandated by the federal Food and Drug Administration ("FDA") and state product liability judgments premised on the failure to change that labeling. *See Mut. Pharm. Co. v. Bartlett*, 133 S. Ct. 2466 (2013); *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011); *Wyeth v. Levine*, 555 U.S. 555, 568 (2009). The Chamber also discusses how the SJC's decision improperly second-guesses FDA's judgment in implementing the federal drug regulatory regime and requires immediate review by this Court.

The federal drug labeling regime imposes comprehensive, mandatory duties on drug manufacturers. Congress has charged FDA with making expert

determinations of both the substance of risk information that must appear on a drug's labeling and how best to communicate that information, whether to laypersons for over-the-counter ("OTC") drugs or to physicians for prescription drugs. Drug manufacturers must use only the labeling that FDA approves. In the absence of an FDA-authorized exception permitting changes to this labeling, the Supremacy Clause forbids states from imposing labeling-based liability on manufacturers following this mandate.

This Court in *Wyeth* identified the sole exception that may enable a manufacturer to make a labeling change without prior FDA approval – FDA's "changes-being-effected" ("CBE") regulation – a procedure that makes it possible to comply with state drug labeling obligations without violating federal law. *See Wyeth*, 555 U.S. at 568; 21 C.F.R. § 314.70(c)(6)(iii). The availability of that regulation gave rise to the Court's differing preemption findings in *Mensing* and *Bartlett*, on the one hand, and *Wyeth*, on the other. *Compare Mensing*, 131 S. Ct. at 2578 (preemption), *and Bartlett*, 133 S. Ct. at 2477 (preemption), *with Wyeth*, 555 U.S. at 581 (no preemption).

But the CBE procedure is not open-ended. Rather it applies *only* where a manufacturer has new information not previously presented to FDA that alters the risk profile of a drug. *See* 21 C.F.R. §§ 314.3, 314.70(c)(6)(iii). Even where such new information exists, this Court in *Wyeth* instructed that if a change is one as to which, as here, there is "clear evidence" that FDA would not allow it, conflict preemption applies. *See Wyeth*, 555 U.S. at 571.

The SJC, however, did not even acknowledge the bounds on the availability of the CBE regulation to effectuate a unilateral labeling change (subject to later FDA approval), much less analyze whether threshold prerequisites were met. Rather, it implicitly assumed that the regulation was open-ended. Moreover, while observing that the "clear evidence" standard in *Wyeth* was undefined, the SJC interpreted that standard so narrowly as to render it virtually impossible for a manufacturer to satisfy it.

The SJC's overly broad reading of the CBE regulation and overly narrow reading of the Court's "clear evidence" test effectively creates a *per se* rule against labeling preemption for branded drugs sold under an FDA-approved New Drug Application ("NDA"). This would undermine FDA's role as the expert agency charged with determining the content, form, and words used to communicate drug safety information. It also would pressure manufacturers repeatedly to propose labeling changes that FDA already had fully considered, thereby burdening the agency with the task of addressing superfluous proposals, so that manufacturers are able to comply with federal law without risk of sanction under state law.

The SJC's decision reflects a fundamental misapprehension of the preemptive effect of the federal drug labeling regime and only adds to the rampant confusion among the courts regarding the scope of the "clear evidence" standard set forth in *Wyeth*, which this Court has not yet defined. *See infra* Part II. Review of the SJC's decision would provide an excellent vehicle for this Court to give much-needed guidance regarding this important issue.

ARGUMENT

I. THE DECISION BELOW MISAPPREHENDS MANUFACTURERS' NARROW ABILITY TO SEEK LABELING CHANGES UNDER THE FEDERAL DRUG REGULATORY REGIME AND IMPROPERLY SECOND-GUESSES FDA'S JUDGMENT IN IMPLEMENTING THAT REGIME.

A. The Federal Drug Regime Is Comprehensive And Establishes A Mandatory Federal Duty To Adhere To FDA-Approved Labeling.

Congress gave FDA pervasive responsibility for regulating the safety and effectiveness of a drug's labeled uses in the Food, Drug, and Cosmetic Act ("Act") and related amendments. Under the Act's premarket approval regime, a manufacturer may only ship a drug in interstate commerce after filing a New Drug Application ("NDA") – including "full reports of investigations" concerning safety and effectiveness and the proposed labeling – and obtaining FDA's approval that the drug is safe and effective "for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" and includes "adequate direction for use." 21 U.S.C. §§ 321(p), 331(a), 352(f), 355(a), (b), (d)(1); 21 C.F.R. § 314.50. Making an approved drug available OTC requires a further FDA determination that laypeople can use it safely and effectively when it is sold with FDA-approved labeling. *See* 21 U.S.C. § 353(b).

FDA has long recognized that the use of any drug entails some degree of risk and that marketing approval

should rest on FDA's scientific determination that a drug's overall health care benefit outweighs its risks. *See* FDA, *Draft Guidance for Industry: Development and Use of Risk Management Action Plans* at 4 (Mar. 2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf (describing FDA's risk-benefit assessment as measuring whether, under labeled conditions of use, "the clinical significance and probability of [a drug's] beneficial effects outweigh the likelihood and medical importance of its harmful or undesirable effects"); *see also* 21 C.F.R. § 314.50(d)(5)(viii) (requiring NDAs to discuss "why the benefits exceed the risks under the conditions stated in the labeling"). This Court likewise has recognized FDA's need to balance risks and benefits, observing that "[i]n order for the FDA to consider a drug safe, the drug's 'probable therapeutic benefits must outweigh its risk of harm.'" *Bartlett*, 133 S. Ct. at 2471 (quoting *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000)).[2]

In striking this critical balance, FDA's regulation of labeling serves as "[t]he centerpiece of risk management." *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). FDA-approved

[2] An alternative path to FDA approval is available for "generic" drugs that are bioequivalent to a drug that is the subject of an FDA-approved NDA. *See* 21 U.S.C. § 355(j). A generic drug may gain FDA approval if its manufacturer submits an Abbreviated New Drug Application that establishes that the drug is, *inter alia*, bioequivalent to an NDA-approved drug and includes the same labeling as that drug. *See id.* § 355(j)(2)(A)(iv), (v), (4)(F), (G). "[G]eneric drug manufacturers have an ongoing federal duty of 'sameness.'" *Mensing*, 131 S. Ct. at 2575 (citation omitted).

prescription drug labeling "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." *Id.*; *see also* FDA, *Guidance: Drug Safety Information – FDA's Communication to the Public* 7 (Mar. 2007), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf ("FDA-approved drug product labeling is the primary source of information about a drug's safety and effectiveness, and it summarizes the essential scientific information needed for the safe and effective use of the drug."). OTC-approved labeling serves the same purpose in communicating to lay patients.

FDA comprehensively dictates the form and substance of all drug labeling. The OTC drug labeling at issue here is subject to detailed requirements concerning both its content and its formatting and must include information regarding warnings, contraindications, allergic reactions, and directions for use. *See* 21 C.F.R. § 201.66. Once FDA approves a drug's labeling, a manufacturer is required to distribute the drug *only* under that precise labeling. *See* 21 C.F.R. § 314.105(b). A manufacturer, having received approval of its NDA, may not discretionarily change a drug's FDA-approved labeling without obtaining FDA's prior approval through a supplemental NDA. *See* 21 U.S.C. §§ 355(a), (b)(1)(F), (c)(1)(A), (d); *see also* 21 C.F.R. § 314.70(b)(2)(v)(A). Marketing a drug with a label that is not FDA-approved is unlawful. *See* 21 U.S.C. §§ 321(p), 331(a), (d), 332(a), 333(a), 334, 337, 355(a), (d).

Manufacturers holding an NDA have been accorded a narrow regulatory exception to this mandatory duty – the so-called "changes-being-effected" ("CBE") regulation – which permits a manufacturer to file a supplemental NDA and to implement a labeling change before FDA has acted on the application if the change is intended "[t]o add or strengthen a contraindication, warning, precaution, or adverse reaction" or "[t]o add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). The CBE process, however, may only be invoked if the change is based on "newly acquired information" that "reveal[s] risks of a different type or greater severity or frequency than previously included in submissions to FDA." *Id.* §§ 314.3, 314.70(c)(6)(iii); *see also Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 49,603, 49,608 (Aug. 22, 2008) (observing that "a CBE supplement is appropriate to amend the labeling for an approved product only to reflect newly acquired information"); *Supplemental New-Drug Applications*, 30 Fed. Reg. 993, 993-94 (Jan. 30, 1965); *Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices*, 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008); *New Drug and Antibiotic Regulations*, 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (CBE regulation is available "to correct concerns about newly discovered risks from the use of the drug" and to "make available important new information about the safe use of a drug product"). Further, the regulation applies "only if there is sufficient evidence of a causal association" between the drug and the risk at issue. 73 Fed. Reg. at 49,603, 49,604. "It is technically a violation of federal law to

propose a CBE that is not based on reasonable evidence." *Mason v. SmithKline Beecham Corp.*, 596 F.3d 387, 392 (7th Cir. 2010); *accord In re Depakote*, 87 F. Supp. 3d 916, 922 (S.D. Ill. 2015). The wording of the CBE regulation itself makes clear that the CBE process cannot be used to challenge fully informed FDA labeling decisions.

The current CBE regulation, in place since 2008, did not "substantively change the standards for submission of CBE or prior review supplements" or "alter the agency's current practices" but merely "codif[ies] the agency's longstanding view concerning when a change to the labeling of an approved drug … may be made in advance of the agency's review and approval of such change." 73 Fed. Reg. at 49,603, 49,606; *see also id.* at 49,604 ("This rule is intended to describe FDA's existing labeling standards and policies, but does not amend the standards under which sponsors must provide warnings regarding risks …."). CBE changes are interim; "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934.

B. *Wyeth*, *Mensing*, And *Bartlett* Establish That The Federal Drug Labeling Regime Preempts All State Tort Claims Premised On Alleged Labeling Inadequacies Unless The Proposed Labeling Change Could Have Been Validly Submitted Under FDA's CBE Regulation.

Where a manufacturer has no unilateral ability to alter its labeling before obtaining FDA's approval to do so, this Court has made clear that state law may not impose product liability premised on the alleged inadequacy of

FDA-approved labeling. In *Mensing*, this Court held that an injured consumer's state-law inadequate labeling claim against a generic drug manufacturer was preempted in light of the manufacturer's conflicting federal law labeling duties. 131 S. Ct. at 2581. The Court reasoned that "generic drug manufacturers have an ongoing federal duty" to maintain the same labeling that appears on the reference listed drug and cannot change that labeling unilaterally through the CBE regulation or otherwise. *Id.* at 2575. Therefore, "it was impossible for the Manufacturers to comply with both their state-law duty to change the label and their federal law duty to keep the label the same." *Id.* at 2578. Because "state law imposed a duty on the Manufacturers to take a certain action, and federal law barred them from taking that action," the action was barred by the Supremacy Clause. *Id.* at 2581. The Court also explicitly rejected the argument that the availability of avenues to propose changes for FDA approval sufficed to avoid a conflict of federal and state commands. *See id.* at 2577-81.

In *Bartlett*, this Court again sustained preemption of a state product liability verdict on the prescriptive nature of the federal drug labeling regime. Consistent with *Mensing*, the Court found that "federal law prevents generic drug manufacturers from changing their labels" but that "New Hampshire's design-defect cause of action imposed a duty on Mutual to strengthen sulindac's warnings." 133 S. Ct. at 2475-76; *see also id.* at 2471 ("Generic manufacturers are prohibited from making any unilateral changes to a drug's label."). It concluded that "it was impossible for Mutual to comply with both its state-law duty to strengthen the warnings on sulindac's label and its federal-law duty not to alter sulindac's label.

Accordingly, the state law is preempted." *Id.* at 2473; *see also id.* at 2479 ("Federal law requires a very specific label for sulindac, and state law forbids the use of that label.").

In *Wyeth*, the Court also acknowledged that "FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label" and that "[g]enerally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application." 555 U.S. at 568. It held, however, that Wyeth, as an NDA holder, had an opportunity in that case to modify its labeling without prior FDA consent under FDA regulations and thus was not faced with an irreconcilable conflict. *Id.* at 581.

The *Wyeth* Court premised its rejection of preemption on the CBE regulation. *Id.* at 568. It observed that that "regulation permitted Wyeth to unilaterally strengthen its warning" and that therefore, "[o]n the record before us, Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements." *Id.* at 573.

Taken together, these cases teach that labeling-based product liability claims can survive a preemption challenge if, and only if, a defendant would have been able to modify its FDA-approved labeling on its own initiative in the manner sought by the plaintiff. A finding that such a change was possible, however, must rest both on the availability of an avenue for unilateral change and a showing that a defendant could properly have used that avenue. *See* 21 C.F.R. §§ 314.3, 314.70(c)(6)(iii); *Wyeth*, 555 U.S. at 571.

As Petitioners explain, no such avenue was available in this case. Respondents asserted that their daughter's injury would have been averted if the label "warned that a rash could be the start of 'Toxic Epidermal Necrolysis' or, if not identified by name, a 'life-threatening disease.'" Pet. 19; App. 3a. Yet FDA already had been presented these proposed labeling changes and, after comprehensively considering the available risk information, rejected that language, thus foreclosing those labeling revisions. *See* Pet. 18.

C. The SJC Misunderstood This Court's Preemptive Framework And The Narrow Circumstances In Which A Manufacturer May Submit And Obtain A Labeling Change.

In rejecting Petitioners' preemption defense, the SJC misapplied in two respects this Court's test that if a proposed labeling change is one as to which, as here, there is "clear evidence" that FDA would not allow it, conflict preemption applies. *See Wyeth*, 555 U.S. at 571.

First, the SJC treated the CBE regulation as an open-ended license enabling Petitioners to depart from FDA-approved labeling at their discretion instead of the narrow exception – activated only by newly acquired information that alters the safety profile of a drug – that it is. *See* App. 19a-20a, 25a-28a; *supra* Part I.A. The SJC failed to consider that FDA, having considered the approved labeling treatment of the risk of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis ("SJS/TEN") in detail, had made it clear that any departure from FDA's prescribed language would be disapproved in the absence of new information. And the SJC did not even acknowledge

that new information was a prerequisite to the availability of the CBE regulation, much less identify any such information not already presented to FDA that it believed made the CBE procedure available to the Petitioners. *See* Pet. 23 ("The court did not even speculate (much less give a reason to believe) that Petitioners (or any other manufacturer) had relevant information or analysis not available to FDA when it answered the Citizen Petition.").

Second, the SJC defined the type of "clear evidence" that FDA would reject so narrowly that the SJC's construction would all but eviscerate conflict preemption with respect to state tort law actions involving drugs that are the subject of an approved NDA. Respondents had "argued solely that the warning should have mentioned the possibility that redness, rash, or blisters could lead to a life-threatening disease." App. 27a-28a. But a 2005 Citizen Petition predating this action already had sought language that encompassed the plaintiffs' proposed warning, requesting that ibuprofen's labeling state that the drug "may cause serious skin reactions that begin as rashes and blisters on the skin" and that "[t]hese early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis." App. 142a. FDA, however, while agreeing to add "the symptoms associated specifically with SJS and TEN" – namely, "skin reddening," "rash," and "blisters" – to the "Allergy Alert" section, rejected the "life threatening disease" language as unnecessary to alert lay users to seek professional care – as Mr. Reckis did here – and detrimental to the effective pediatric use of ibuprofen. App. 161a-162a.

The SJC refused to consider this "clear evidence" of a likely agency rejection of the warning proposed by the plaintiffs. It reasoned that because FDA did not explain *why* it was rejecting the "life-threatening disease" language in addition to rejecting the disease names themselves, "[w]hether the FDA also would consider including a mention of life-threatening diseases, by itself, to be inappropriate and off limits on the OTC label is anybody's guess." App. 23a. The SJC's application of the "clear evidence" test has rendered that test impotent and unworkable.

To begin with, the SJC ignored the careful and comprehensive consideration that FDA devoted to ibuprofen's labeling, which was far more detailed than the labeling consideration documented in *Wyeth*. Here, FDA explicitly stated that it had "engaged in a comprehensive review of the risks and benefits, including the risks of SJS and TEN, of all approved NSAID products, including ibuprofen." App. 148a. This included a review of all "U.S. postmarketing adverse event reports of SJS and TEN in association with the use of ibuprofen products" "during its marketing history from 1975 through March 2005." App. 152a.

Based on this examination, FDA engaged in an "extensive, comprehensive revision of both OTC and prescription labeling for all NSAID products," including ibuprofen. App. 163a. It considered the best way to advise laypeople of the risks associated with SJS TEN and how to deal with those risks. It decided to advise consumers of the symptoms of SJS/TEN and to direct them "to stop use and seek medical attention immediately" if they experience those symptoms, but not to identify the

diseases themselves in the OTC labeling. App. 162a. It determined that its OTC labeling "most appropriately communicate[s] the risks and benefits associated with" ibuprofen. App. 163a. This careful consideration stands in sharp contrast to FDA's consideration of the labeling change sought in *Wyeth*, where there was no indication that FDA had given more than "passing attention to the issue." *Wyeth*, 555 U.S. at 572.

Moreover, the SJC's decision hinges on the implausible speculation that FDA failed to consider its well-established ability to adopt language that was a subset of the language that had been proposed – an ability that is explicit in FDA's own regulations. *See* 21 C.F.R. § 10.30(e)(3) (providing that FDA may grant or deny Citizen Petition "in whole or in part, and may grant such other relief or take other action as the petition warrants"). Moreover, such a hostile approach to finding clear evidence that FDA would reject a change would produce an unworkable system. As a plurality of this Court in *Mensing* has instructed, under this type of scenario:

> The Manufacturers would be required continually to prove the counterfactual conduct of the FDA and brand-name manufacturer in order to establish the supremacy of federal law. We do not think the Supremacy Clause contemplates that sort of contingent supremacy. The *non obstante* provision suggests that pre-emption analysis should not involve speculation about ways in which federal agency and third-party actions could potentially reconcile federal duties with conflicting state duties. When the "ordinary meaning" of federal law

> blocks a private party from independently accomplishing what state law requires, that party has established pre-emption.

Mensing, 131 S. Ct. at 2580; *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 354 (2001) (Stevens, J., concurring in the judgment) (suggesting that claims should not be preempted if "respondent's state-law fraud claim [did] not depend upon speculation as to the FDA's behavior in a counterfactual situation but [were] grounded in the agency's explicit actions").

D. The SJC's Decision Improperly Second-Guesses FDA's Judgment In Determining The Form And Content Of Drug Labeling.

In addition to effectively ignoring this Court's preemption jurisprudence, the SJC's decision disregarded that FDA exercises comprehensive authority to mandate the form, substance, and mode of communicating risk information on drug labeling in a manner that most effectively protects and promotes the public health.

Congress has charged FDA with determining that OTC drugs are capable of being used safely and effectively by consumers without prescriber assistance. 21 U.S.C. § 353(b). "A major element of FDA's authority to ensure the safe and effective use of drug products is through FDA's review, approval, and monitoring of drug product labeling." *Over-The-Counter Human Drugs; Proposed Labeling Requirements*, 62 Fed. Reg. 9024, 9043 (Feb. 27, 1997). FDA must take account of the known risks and benefits of each labeled condition of use and carefully regulate the labeling to ensure that it optimizes beneficial use of

the drug while minimizing associated risks. "[A]dditional requirements for the disclosure of risk information are not necessarily more protective of patients," because "[e]xaggeration of risk could discourage appropriate use of a beneficial drug." 71 Fed. Reg. at 3935.

FDA has substantial expertise in determining not only the frequency and severity of the risk to be communicated but also the most effective means of communicating that information. In the OTC context, the agency comprehensively overhauled the OTC labeling content and format requirement to "establish[] a standardized format and standardized content requirements for the labeling of over-the-counter (OTC) drug products" in order "to assist consumers in reading and understanding OTC drug product labeling so that consumers may use these products safely and effectively." *Over-The-Counter Human Drugs; Labeling Requirements*, 64 Fed. Reg. 13,254, 13,254 (Mar. 17, 1999). During that overhaul, "the agency received more than 1,800 comments from health professionals and students, professional organizations, trade associations, manufacturers, consumers, and consumer organizations." *Id.*

FDA also conducted two studies – "a survey of more than 900 respondents to evaluate consumer preference for design variations in drug labeling formats" and "a survey of more than 1,200 consumers on the influence of variations in labeling formats on the communication of directions for use and required warnings." *Id.* The agency considered these two studies, the over 1,800 comments it received, "information gathered from the leading literature on label design, graphics, and readability, and information drawn from the agency's own expertise in

drug labeling" in finalizing its OTC labeling regulations. *Id.* at 13,273. Through that proceeding and others, the agency has developed deep expertise in determining how risk information is best communicated directly to patients.

FDA exercised its expertise in both risk assessment and effective communication of those risks to lay patients in its response to the 2005 Citizen Petition concerning ibuprofen. FDA reaffirmed its judgment that that drug could be safely used by laypeople, refusing to "reconsider the OTC status of the pediatric formulation of ibuprofen." App. 162a-163a. Instead, it found that "the overall benefit versus risk profile for ibuprofen products remains very favorable when they are used according to the labeled instructions" and that "[i]t is in the interest of the public health to maintain in the pediatric OTC market a range of therapeutic options for the short-term relief of pain." App. 163a.

FDA also carefully focused on the best means of communicating to laypeople the risks associated with use of ibuprofen, observing that "effective OTC labeling communicates warning information in a manner that consumers can quickly and easily identify and understand." App. 162a. The agency decided to add the symptoms of SJS/TEN to the OTC labeling coupled with an instruction to stop use and seek medical attention immediately if those symptoms appeared, but it rejected the remainder of the Citizen Petition's proposed warning language, including the "life-threatening diseases" language. App. 162a. It concluded that "the revised labeling templates for both OTC and prescription ibuprofen products *most appropriately communicate the risks and benefits associated with their use.*" App. 163a (emphasis added).

The SJC permitted a lay jury to second-guess FDA's expert judgment concerning the best means of communicating SJS/TEN risk information to consumers. Rather than crediting FDA's determination, the SJC upheld the jury's decision that the labeling was defective. The SJC simply ignored the absence of any new risk information and refused to credit FDA's expert judgment on risk communication and FDA's inevitable rejection of any attempt by the plaintiffs to modify that communication.

In so doing, the SJC eviscerated the "clear evidence" standard of *Wyeth* by ignoring substance and requiring a defendant manufacturer to show that FDA had considered and rejected every hypothetical formulation of risk communication a plaintiff's attorney could contrive. *See* App. 28a; *see also* Pet. 27 ("Under the SJC's ruling, FDA's explicit rejection of proposed labeling language is not preemptive unless the Agency also specifies that it would reject every variation or subset of the proposed language."). The SJC thus has converted FDA's role of determining how best to communicate risks and benefits to laypersons into a meaningless word game. A creative plaintiff will always be able to concoct a set of new words that avoids specific language that FDA has considered and rejected concerning a particular risk. If a plaintiff is able to prevail in a product liability suit by inventing a set of words concerning an already-considered risk that will articulate that risk in a way that a jury prefers to FDA's determination of how best to communicate that risk in the labeling, FDA's role as an expert agency would be gravely undermined. That repudiation of FDA's authority cannot be allowed to stand unreviewed by this Court.

II. REVIEW OF THE SJC'S DECISION IS URGENTLY NEEDED BECAUSE INTERPRETATION OF THIS COURT'S UNDEFINED "CLEAR EVIDENCE" STANDARD IS A RECURRING ISSUE AS TO WHICH LOWER COURTS HAVE EXHIBITED SIGNIFICANT UNCERTAINTY.

As the SJC and numerous other courts have observed, this Court's decision in *Wyeth* "does not define 'clear evidence,' nor does it suggest the level of proof required to constitute such evidence." *Dobbs v. Wyeth Pharms.*, 797 F. Supp. 2d 1264, 1270 (W.D. Okla. 2011); *see also Mason*, 596 F.3d at 391 ("The Supreme Court … did not clarify what constitutes 'clear evidence.'"); *In re Depakote*, 87 F. Supp. 3d at 922 ("In *Wyeth*, the Supreme Court does not define 'clear evidence' …."); App. 20a ("*Wyeth* did not 'define "clear evidence" ….'" (quoting *In re Fosamax (Alendronate Sodium) Prods. Liability Litig.*, 951 F. Supp. 2d 695, 703 (D.N.J. 2013))); *Cross v. Forest Labs.*, __ F. Supp. 3d __, No. 1:05-cv-00170-MPM-SAA, 2015 WL 1534458, at *3 (N.D. Miss. Apr. 6, 2015) ("What constitutes clear evidence is not defined …."), *appeal docketed*, No. 15-60317 (5th Cir. May 1, 2015).

Moreover, "[d]ecisions addressing FDA conflict preemption after [*Wyeth*] do not contain precise definitions of clear evidence." *Dobbs*, 797 F. Supp. 2d at 1270. Thus, "'lower courts are left to determine what satisfies this … standard in each case.'" *Cross*, __ F. Supp. 3d __, 2015 WL 1534458, at *3 (*quoting Dobbs*, 797 F. Supp. 2d at 1270).

Numerous courts have grappled with the operation of conflict preemption following *Wyeth*, *Mensing*, and *Bartlett*, with varying results. Some courts properly have

found that the "clear evidence" test was met, precluding manufacturer liability. For example, the Seventh Circuit, in a case involving the same OTC drug (Children's Motrin) at issue here, reached a result that directly conflicts with the SJC's decision. *See Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861 (7th Cir. 2010). That court affirmed judgment in favor of the manufacturer, observing that:

> The "clear evidence" in this case is the agency's refusal to require a reference to SJS/TEN on the label of over-the-counter drugs containing ibuprofen, when it had been asked to do so in the submission to which the agency was responding. And it would be odd to think that McNeil had a legal duty to guarantee against a risk that the FDA thought not worth warning against.

Id. at 873.

Similarly, also in tension with the SJC, a district court held in a failure-to-warn case involving Fosamax that:

> clear evidence exists that the FDA would not have approved a label change to the Precautions section of the Fosamax label prior to Mrs. Glynn's fracture because Defendant submitted a label change and the FDA rejected it, and the FDA never required Defendant to submit new language or change the label, which demonstrates that the FDA did not think that the label should have been changed at that time.

In re Fosamax (Alendronate Sodium) Prods. Liab. Litig., 951 F. Supp. 2d 695, 703-04 (D.N.J. 2013).

Moreover, in a case involving the antidepressant Effexor, the district court found that "there is clear evidence that the FDA would have rejected an expanded Effexor warning for patients in Mr. Dobbs's age group prior to his 2002 suicide. In fact, it continued to conclude that there was no evidence to support a warning for his age group as late as 2007, after additional studies were completed." *Dobbs*, 797 F. Supp. 2d at 1277. The court observed that "even when it later determined that sufficient evidence existed to support the precaution, it did not approve Wyeth's Effexor-specific label alteration, but dictated a warning that was required of all SSRI manufacturers." *Id.* Again in tension with the SJC, the court stated that it "does not interpret [*Wyeth*] as imposing upon the drug manufacturer a duty to continually 'press' an enhanced warning which has been rejected by the FDA." *Id.* at 1279; *see also In re Depakote*, 87 F. Supp. 3d at 922 (finding "that there is clear evidence that the FDA would not have approved a change to the 1999 label to include a warning of developmental delay" where agency had rejected the same change as not supported by the scientific evidence seven years later).

Many other lower courts, however, have refused to find that FDA would have rejected a labeling change proposed by the plaintiff, sometimes based on the slimmest of distinctions. *See*, *e.g.*, *Forst v. SmithKline Beecham Corp.*, 639 F. Supp. 2d 948, 954 (E.D. Wis. 2009) (finding no clear evidence even though FDA had rejected similar proposed warnings in same year of plaintiff's suicide attempt because "the fact that the agency considered the association between all SSRI's and suicidality on a number of occasions between 1992 and 2004, the time of Mr. Forst's suicide attempt, does not establish that the FDA would

not have approved a proposed change in Paxil's labeling"); *Koho v. Forest Labs., Inc.*, 17 F. Supp. 3d 1109, 1117 (W.D. Wash. 2014) (finding no clear evidence where FDA's rejection of similar warning on antidepressant predated suicide by five years); *Aaron v. Wyeth*, No. 2:07cv927, 2010 WL 653984, at *6 (W.D. Pa. Feb. 19, 2010) (finding no clear evidence because even "[t]hough the FDA disagreed with certain changes to the … labeling proposed by Wyeth, Wyeth did not press its position").

As described above, such an approach places manufacturers in an impossible position. They must comply with the federal drug labeling regime, but cannot avoid liability for using mandatory labeling unless they have unsuccessfully asked FDA to alter that labeling to match the precise wording, adopted *post hoc*, by a particular plaintiff's attorney. Under such a system, manufacturers can only hope to avoid liability by flooding FDA with language variations to attempt to establish "clear evidence" of rejection, thereby forcing FDA to engage in an endless game of labeling "whack-a-mole" as the agency attempts to address these iterative changes. The decision below provides an excellent vehicle for this Court to clarify the operation of the Supremacy Clause under *Wyeth*, *Mensing*, and *Bartlett*, the proper bounds of the CBE regulation, and the determinants of "clear evidence."

CONCLUSION

For the foregoing reasons, this Court should grant the Petition for a writ of *certiorari*.

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Respectfully submitted,

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