QUESTION PRESENTED

Does federal conflict preemption, as held and applied in *PLIVA, Inc. v. Mensing*, 131 S. CT. 2567 (2011), to preempt state law tort claims against a manufacturer of generic prescription drugs, apply also to preempt state law tort claims, based on inadequate or defective labels, against a manufacturer of "over-the-counter" (OTC) non-prescription drugs, whose labels are likewise governed by mandatory FDA regulations, with no available mechanism to change the drug label unilaterally, without first obtaining FDA approval?

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INTEREST OF THE *AMICUS CURIAE*

Product Liability Advisory Council, Inc. ("PLAC") is a non-profit association with 100 corporate members that represent a broad cross-section of American and international product manufacturers, including manufacturers of prescription and over-the-counter drug medication, such as Bayer Corporation, Eli Lilly and Company, Johnson & Johnson, Merck & Co., Inc., Pfizer, Inc., Teva Pharmaceuticals USA, Inc., and Merck & Co., Inc. (now known as Merck Sharp & Dohme Corp.)[1]

All PLAC members are engaged in commerce in each of the 50 states, as well as commerce among several nations in both hemispheres. All corporate members seek to contribute to the improvement and reform of the law of the United States and elsewhere, with an emphasis on the law governing the liability of manufacturers of products sold in the United States and throughout the world. PLAC's

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[1]A list of PLAC's corporate members is attached as Appendix A. The parties have consented to PLAC's filing this brief, and their letters of consent are on file with the Clerk. In accordance with Rule 37.6, *amicus* states that no counsel for a party involved in this case authored 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 memorandum and motion for leave to file. No person other than *amicus*, its members or its counsel made a monetary contribution to the preparation or submission of this memorandum or motion.

perspective is derived from the experience of a corporate membership that spans a diverse group of industries in various facets of the manufacturing sector.

Since 1983, PLAC has filed over 950 briefs as *amicus curiae* in both state and federal courts, including in this Court, presenting the broad perspective of product manufacturers seeking fairness and balance in the application and development of the law as it affects product liability. Because of its unique ability to provide a broader perspective on federal preemption than perhaps that of the individual parties, and because of its keen interest in ensuring that the federal regulatory environment in which its members operate is rational and consistent, PLAC was permitted to file *amicus* briefs in three preemption cases recently decided by this Court.[2]

The most recent preemption case in which PLAC filed an *amicus* brief is *Wyeth v. Levine*.[3] *Wyeth*, which held preemption did not apply, is pertinent to the federal preemption at issue here, because the principles of federal conflict preemption

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[2] *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000); *United States v. Locke*, 529 U.S. 89, (2000); and *Wyeth v. Levine*, 555 U.S. 555, 129 S. Ct. 1187 (2009).

[3]555 U.S. 555, 129 S. Ct. 1187 (2009).

articulated there were clarified and distinguished in this Court's subsequent decision in *PLIVA, Inc. v. Mensing*,[4] which held preemption applied. The rationale behind the different result reached in PLIVA supports preemption here.

The issue of federal conflict preemption, as articulated and applied in PLIVA, directly implicates the broad national concern of PLAC and its members, many of whom are makers of OTC drugs subject to FDA regulations governing their labels. PLAC's interest in achieving uniformity of rulings in national litigation involving product liability claims based on inadequate drug labels in each of the fifty states encompasses a similar interest in obtaining a uniformity of federal law governing preemption of state law claims, where appropriate. This brief is limited to emphasizing the difference between *Wyeth* and *PLIVA* and why PLIVA should control the issue of federal preemption as applied to makers of OTC non-prescription drugs, like Infant's Tylenol that is at issue here.

SUMMARY OF THE ARGUMENT

This case presents the third leg in this Court's preemption analysis that began with *Wyeth* and continued with *PLIVA*.

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[4] 131 S. CT. 2567, 180 L. Ed. 2d 580 (2011).

Wyeth held there was no federal conflict preemption between state and federal law because under FDA regulations, makers of brand name prescription drugs, under a "changes being effected" (CBE) regulation, have a regulatory mechanism to make unilateral changes to drug labels without first obtaining FDA approval.

PLIVA, on the other hand, held that because makers of generic prescription drugs do not have an equivalent CBE regulation that allowed them to make unilateral changes to their labels, compliance with state tort law governing warnings was not possible, without first obtaining FDA approval. Compliance with state law is "impossible," under PLIVA's analysis, when federal law prohibits a party from doing independently what state law requires, and conflict preemption is not dependent on possible actions the FDA might take. PLIVA, Inc., 131 S. CT. at 2572. Preemption therefore applied to preempt state law tort claims based on allegedly inadequate warnings that the FDA had approved.

Here, because makers of OTC non-prescription drugs are likewise subject to mandatory FDA regulations governing their drug labels, with no corresponding CBE or equivalent regulation permitting unilateral changes without FDA approval, state law claims against OTC manufacturers should likewise be preempted under federal law.

ARGUMENT

As McNeil correctly argues, under the Food, Drug, and Cosmetic Act (FDCA),[5] Congress requires FDA approval of all medications, prescription and non-prescription alike, as "safe and effective" before they may be sold in this country. 21 U.S.C. §§ 355(d), 393(b)(2)(B); McNeil Petition, p.2.

Approval of brand-name prescription drugs, and the regulation of their labels, is governed by the new drug application (NDA) procedure contained in 21 U.S.C. §355, and corresponding regulations. McNeil Petition, p. 3.

Approval of generic prescription drugs is governed under the abbreviated new drug application (ANDA) procedure found in 21 U.S.C. 355(j).

OTC drugs, which are not subject to laws governing prescription drugs, are subject to FDA regulation under an alternate monograph procedure, under which an FDA-appointed advisory review panel evaluates the drug's safety and effectiveness and regulates its labeling. McNeil Petition, p. 5. The question is whether federal conflict preemption applies to preempt state law claims, based on

[5] 21 U.S.C. §301 *et seq*.

inadequate labels, against OTC manufacturers subject to FDA's OTC monograph regulations.

a. Principles of Conflict Preemption

The concept behind conflict, or impossibility, preemption originates from the recognition that a party subject to two legal regimes cannot comply with both when compliance with one renders compliance with the other impossible. When the conflict is between federal and state law, the federal law prevails under the Supremacy Clause of the United States Constitution: "Where state and federal law 'directly conflict,' state law must give way."[6] State and federal law conflict where it is " 'impossible for a private party to comply with both state and federal requirements.' "[7]

The issue in *Wyeth* was whether the FDA's approval of a warning label on Phenergan, a prescription medication, made it impossible for Wyeth, the drug maker, to comply with Vermont state law that required a warning of the higher risk of intra-arterial infection and gangrene when administered under one of two approved methods

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[6] *PLIVA, Inc. v. Mensing*, 131 S. Ct. at 2577, citing *Wyeth v. Levine*, 555 U.S. at 583, 129 S. CT. At 1187 (Thomas, J., concurring).

7 Id., quoting *Freightliner Corp. v. Myrick*, 514 U.S. 280, 287, 115 S. Ct. 1483, 131 L. Ed. 2d 385 (1995).

that was more specific than the one provided in the FDA approved label.

This Court rejected Wyeth's argument that compliance with state law was impossible, for two reasons. The first reason was the existence of a specific FDA "changes being effected" (CBE) regulation that "permits a manufacturer to make certain changes to its label before receiving the agency's approval," to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product."[8] Because the CBE regulation permitted Wyeth unilaterally to strengthen its warning, subject to later FDA approval or rejection, the Court held Wyeth had not proven that compliance with Vermont law was "impossible." Second, the Court reasoned that, given the FDA's authority to reject (or rescind) changes made pursuant to the CBE regulation, Wyeth had failed to present "clear evidence that the FDA would not have approved a change to Phenergan's label,"[9] or would have rejected any different warning pursuant to the CBE regulation, had one been proposed.

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[8]*Wyeth*, 555 U.S. at 568, 129 S. Ct. at 1196, citing and quoting 21 CFR §314.105(b) and 21 CFR §314.70(c)(6)(iii)(A).

[9]*Id.*, 555 U.S. at 571, 129 S. Ct. at 1198.

This Court reached the opposite conclusion in *PLIVA*, decided in June, 2011. The issue there concerned the preemptive effect of FDA regulations governing the labeling of generic prescription drugs containing metoclopramide, which has a risk of causing tardive dyskenesia, a severe neurological disorder, among 29% percent of those who take it over several years. Lawsuits in Minnesota and Louisiana sought damages for developing tardive dyskenesia, based on inadequate warnings under each state's product liability laws. The Eighth and Fifth Circuit Courts of Appeals both held that the state law claims were not preempted.[10]

This Court reversed and held that the state law claims were preempted because compliance with either state's law was not possible. Makers of generic prescription drugs are bound by federal law and regulation to use only those warning labels already approved for the brand-name drug;[11] but

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[10]*Mensing v. Wyeth, Inc.*, 588 F. 3d 603 (8th Cir. 2009); *Demahy v. Actavis, Inc.*, 593 F. 3d 428 (5th Cir. 2010).

[11]The Court's conclusion was based on its analysis of the Drug Price Competition and Patent Term Restoration act, 98 Stat. 1585, commonly called the Hatch-Waxman Amendments, 21 U.S.C. §355(j)(2)(A). "Under this law, 'generic drugs' can gain FDA approval simply by showing equivalence to a reference listed drug that has already been approved by the FDA. This allows manufacturers to develop generic drugs inexpensively, without duplicating the clinical trial already performed on the equivalent brand-name drug." *PLIVA, Inc.*, 131 S. Ct. at 2574.

they do not, the Court concluded, have available to them, as do makers of brand-name prescription drugs, the option under the CBE regulation to change unilaterally their generic warning labels after FDA had approved them. The Court reached this conclusion by deferring to the FDA's interpretation of CBE and generic labeling regulations that "the Manufacturers could [not] have used the CBE process to unilaterally strengthen their warning labels. The agency interprets 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."[12]

The Court specifically rejected the argument that compliance with state law was not "impossible" while generic manufacturers still had the opportunity to attempt label changes by soliciting FDA assistance in implementing changes to the brand-name label.[13] The Court held that compliance with state law is "impossible" when federal law prohibits a party from doing *independently* what

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[12]*PLIVA, Inc.*, 131 S. Ct. at 2575.

[13]The Court also rejected the argument that federal law permitted the generic manufacturers to issue "Dear Doctor" letters directly to treating physicians because such letters "would inaccurately imply a therapeutic difference between the brand and the generic drug and thus could be impermissibly misleading." *PLIVA, Inc.*, 131 S. Ct. at 2576.

state law requires, and conflict preemption is not dependent on possible actions the FDA might take:

> We can often imagine that a third party or the Federal Government *might* do something that makes it lawful for a private party to accomplish under federal law what state law requires of it. In these cases, it is certainly possible that, had the Manufacturers asked the FDA for help, they might have eventually been able to strengthen their warning label. Of course, it is also *possible* that the Manufacturers could have convinced the FDA to reinterpret its regulations in a manner that would have opened the CBE process to them. . . .
>
> If these conjectures suffice to prevent federal and state law from conflicting for Supremacy Clause purposes, it is unclear when, outside of express pre-emption, the Supremacy Clause would have any force. We do not read the Supremacy Clause to permit an approach to pre-emption that renders conflict pre-emption all but meaningless.[14]

In holding that conflict preemption applied – because it was impossible for the manufacturers there to comply with both federal and state law – the

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[14]*PLIVA, Inc.*, 131 S. Ct. at 2579 (emphasis in original).

Court concluded that "it is enough to hold that when a party cannot satisfy its state duties without the Federal Government's special permission and assistance, which is dependent on the exercise of judgment by a federal agency, that party cannot independently satisfy those state duties for pre-emption purposes."[15]

b. Errors in the State Court's Analysis and Application of the Principles of Conflict Pre-emption

With due respect, there are two critical legal errors in the Louisiana Third Circuit's analysis and application of the principles of conflict pre-emption articulated in *Wyeth* and *PLIVA, Inc*.

The first error is the appellate court's assumption that the CBE regulation was an available mechanism that would have allowed McNeil, or any other brand-name drug manufacturer, to independently change the label of Infants' Tylenol, which is an OTC drug, not a prescription medication. The appellate court cited McNeil's status as a maker of brand-name drugs, as opposed to generic drugs, as the basis for distinguishing *PLIVA,Inc*.'s analysis and holding. It is true that *PLIVA, Inc*. distinguished W*yeth* because "the federal regulations [i.e., the CBE regulation]

[15]*PLIVA, Inc*., 131 S. Ct. at 2580-2581.

applicable to Wyeth allowed the company, of its own volition, to strengthen its label in compliance with its state tort duty."[16] The difference in the holdings of the two cases however turned, not on Wyeth's status as a maker of brand-name drugs, but on Wyeth's ability through the CBE regulation to take independent action to effect changes in its label.

The regulatory ability to make unilateral or independent changes to labels is not available to makers of either brand-name or generic OTC drugs. The CBE regulation,[17] on which *Wyeth* relied to find that compliance with state law was possible, applies only to *prescription* drugs; it does not apply to nor govern the labeling of OTC drugs, such as Infants' Tylenol.[18] Federal regulations in 21 CFR 201.57 state specifically that "The requirements in this section apply only to prescription drug products described in 201.56(b)(1) and must be implemented according to the schedule specified in 201.56(c) . . . ." The CBE regulation at issue in *Wyeth* refers specifically to changes in label requirements in 21

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[16]PLIVA, Inc., 131 S. Ct. at 2581.

[17] 21 CFR 314.70(c)(6)(iii).

[18]Federal regulations governing the labeling of prescription drugs is found at 21 CFR 201.57 *et seq*.

CFR 201.57, the regulation that governs the labeling of *prescription* drugs.[119]

Labeling of OTC drugs is governed by federal regulations found at 21 CFR 330 *et seq*.[20] Under those regulations, the FDA employs a monograph procedure for OTC drugs, by which the FDA Commissioner appoints an advisory review panel of qualified experts "to evaluate the safety and effectiveness of OTC drugs, to review OTC drug labeling, and to advise him on the promulgation of monographs establishing conditions under which OTC drugs are generally recognized as safe and effective and not misbranded."[21]

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[19] 21 CFR 314.70(c)(6)(iii) states, in relevant part: "Changes in the labeling to reflect newly acquired information, except for changes to the information required in 201.57(a) of this chapter . . . to accomplish any of the following: (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under 201.57(c). . . ."

[20]21 CFR 330.1 states, in pertinent part: "An over-the-counter (OTC) drug listed in this subchapter is generally recognized as safe and effective and is not misbranded if it meets each of the conditions contained in this part and each of the conditions contained in any applicable monograph. Any product which fails to conform to each of the conditions contained in this part and in an applicable monograph is liable to regulatory action."

[21]21 CFR 330.10(a).

The federal regulations specify precise procedures and standards for publishing a proposed monograph in the federal register that establishes the "conditions under which a category of OTC drugs or a specific or specific OTC drugs are generally recognized as safe and effective and not misbranded."[22] After the process for establishing a proposed monograph has been completed, the FDA requires the Commissioner to "publish in the Federal Register a tentative order containing a monograph establishing conditions under which a category of OTC drugs or specific OTC drugs are generally recognized as safe and effective and not misbranded."[23] The regulations permit a 90-day period for review and comment of a published tentative order, but after that period, any "[n]ew data and information submitted after the time specified in this paragraph but prior to the establishment of a final monograph will be considered as a petition to amend the monograph

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[22]21 CFR 330.10(a)(6)(I)-(iv). The FDA established the monograph procedure for OTC drugs in 1972. See 37 Fed. Reg. 14,633. The Advisory Review Panel issued its recommendations for a proposed monograph of OTC internal analgesics, which include acetaminophen, the active ingredient in Infants' Tylenol at issue here, in 1977. See 42 Fed. Reg. 35,346, and the codified federal regulation in 21 CFR 343 *et seq*.

[23]21 CFR 330.10(a)(7).

and will be considered by the Commissioner only after a final monograph has been published in the Federal Register unless the Commissioner finds that good cause has been shown that warrants earlier consideration."[24]

Under these OTC regulations, there is no procedure equivalent to the CBE regulation applicable to *prescription* drugs that allows the maker of OTC drugs to make any unilateral or independent changes to the label requirements once a tentative order for a monograph has been published in the Federal Register. The record and McNeil's petition show that Infants' Tylenol had been operating under a tentative monograph order for years, through and including 2003, when the tragic overdose occurred.[25]

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[24]21 CFR 330.10(a)(7)(v).

[25]FDA published its Tentative Final Monograph for internal analgesics and antipyretics, which include acetaminophen, the active ingredient in Infants' Tylenol at issue here, in 1988. It can be found in the Federal Register at 53 Fed. Reg. 46,204. That 1988 monograph order contains the restriction on label dosing information for children under two years of age. The language can be found at 53 FR 46,257, but for the Court's easy reference, is quoted here in relevant part:

> For products containing acetaminophen, aspirin, or sodium salicylate identified in § 343.10(a), (b), and (f). Adults: Oral dosage is 325 to 650 milligrams every 4 hours or 325 to

McNeil, and all other makers of OTC drugs, whether sold under brand names or generic labels, thus find themselves in the same regulatory position of generic makers of prescription drugs: They are subject to federal regulations that do not allow for unilateral or independent action that would enable them to comply with state tort law duties, without FDA approval or assistance. It is the absence of equivalent CBE regulations to OTC drugs that makes compliance with state tort law "impossible" for OTC monograph orders.

It is understandable that this Court in *Wyeth* was reluctant to find "impossibility" of compliance when regulatory avenues for effecting label changes unilaterally and independently of FDA action or approval were available but never used or attempted. But when those avenues are absent, as they were in PLIVA, and as they are here, possibility of complying with state law becomes impossible, and calls for the application of preemption.

A private party subject to federal law can only do so much. Conflict, or impossibility pre-emption,

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> 500 milligrams every 3 hours or 650 to 1,000 milligrams every 6 hours, while symptoms persist, not to exceed 4,000 milligrams in 24 hours, or as directed by a doctor. . . . *Children under 2 years: Consult a doctor. The dosage schedules above are followed by "or as directed by a doctor*." (Emphasis added).

under federal law, is indeed a demanding defense,[26] but as *PLIVA, Inc.*, makes clear, it is not an "impossible" one, and the Supremacy Clause of the U.S. Constitution does not permit "an approach to pre-emption that renders conflict pre-emption all but meaningless."[27]

CONCLUSION

For the foregoing reasons, PLAC respectfully requests that the petition of McNeil-PPC, Inc., be granted, that a writ of certiorari or review be issued to the Third Circuit Court of Appeal, and the judgment be summarily reversed, or be vacated and the case remanded, or, alternatively, the case be docketed for full briefing and argument.

Respectfully submitted,

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[26] *Wyeth*, 555 U.S. at 573, 129 S. Ct. 1187.

[27] *PLIVA, Inc.*, 131 S. Ct. at 2579.