COMMONWEALTH OF MASSACHUSETTS
SUPREME JUDICIAL COURT
Docket No. SJC-11677

LISA RECKIS and RICHARD RECKIS,
Individually and as Parents and Natural Guardians of
their minor child, SAMANTHA T. RECKIS,

Plaintiffs-Appellees,

v.

JOHNSON & JOHNSON and McNEIL-PPC, INC. d/b/a McNEIL
CONSUMER & SPECIALTY PHARMACEUTICALS,

Defendants-Appellants.

On Direct Appeal from Plymouth Superior Court
Civil Action No. PLCV2007-00064

BRIEF FOR *AMICUS CURIAE* THE CONSUMER HEALTHCARE PRODUCTS ASSOCIATION SUPPORTING APPELLANTS

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INTEREST OF *AMICUS CURIAE*

The Consumer Healthcare Products Association (CHPA) is a nonprofit association that represents the makers of over-the-counter (OTC) medicines and nutritional supplements. CHPA is one of the oldest trade associations in the United States. It has more than 75 active members that manufacture or market OTC medicines and nutritional supplements, as well as more than 150 associate members who supply goods and services to the active members. CHPA members provide millions of Americans with safe, effective, and affordable therapies to treat many common ailments. CHPA is committed to promoting the increasingly vital role of OTC medicines and nutritional supplements in America's healthcare system through science, education, and advocacy. CHPA monitors legal issues that affect its members and offers its perspectives in cases that raise such issues.

This case presents an important legal issue: whether manufacturers of OTC medicines approved under the new drug application (NDA) process can be held liable under state law for not providing warnings that the Food and Drug Administration (FDA) specifically considered and rejected. CHPA members have a vital interest in the labeling of OTC medicines, and in not being subject to labeling obligations under state law

that create an impossible conflict with federal law. Therefore this legal issue is of critical importance to CHPA. State-law failure-to-warn lawsuits asserting that manufacturers should label their OTC medicines in a manner that FDA has rejected would place CHPA's members in an untenable position. CHPA supports Defendants-Appellants' position that Plaintiffs-Appellees' failure-to-warn claims are preempted in this case.

ARGUMENT

The labeling changes demanded by Plaintiffs-Appellees are fundamentally inconsistent with FDA's goals for OTC drug labeling, and FDA has specifically rejected these changes in this context.

I. FDA Requires That OTC Drug Labeling Provide Clear, Concise, and Understandable Information to Consumers.

The goal of OTC drug labeling is to provide consumers with "concise and easy to understand" information so that consumers can select and use OTC medicines safely and effectively. 64 Fed. Reg. 13,254, 13,254 (Mar. 17, 1999).[1] FDA has explained that "consumers are becoming more actively involved in

[1] *See also* 78 Fed. Reg. 67,985, 67,986 (Nov. 13, 2013) (OTC drug labeling "conveys information in a clear, standardized format to enable patient self-selection of an appropriate drug and enhance the safe and effective use of the drug").

their own health care," and that therefore "it is increasingly important that OTC drug product labeling provide consumers with uniform and understandable information for the safe and effective use of these products." 62 Fed. Reg. 9,024, 9,027 (Feb. 27, 1997).

To further this goal, FDA has implemented a simplified and standardized "Drug Facts" format for OTC labeling to "improv[e] the ability of consumers to find, read, and understand important safety and use information." 64 Fed. Reg. at 13,276; *see* 21 C.F.R. § 201.66.[2] FDA explained that "[m]odifying and simplifying the manner in which the information is presented can improve the legibility and understandability of OTC drug product labeling." 62 Fed. Reg. at 9,024.

To improve "understandability" for consumers, OTC drug labeling does not use unfamiliar medical or scientific terminology. Instead, information in OTC drug labeling is written in "plain English." 62 Fed.

[2] In contrast to the seventeen categories of detailed information required in prescription drug labeling, FDA's regulations require that OTC drug labeling contain nine categories of concise and understandable information. These categories include, for example, active ingredient(s), use(s), warning(s), and directions. 21 C.F.R. § 201.66(c).

Reg. at 9,031.[3] FDA has stated that information in OTC drug labeling should be written "at a 4th to 5th grade reading level and no higher than an 8th grade reading level." FDA, *Guidance for Industry, Label Comprehension Studies for Nonprescription Drug Products*, at 5 (Aug. 2010). FDA often requires OTC drug manufacturers to conduct label comprehension studies to "assess whether literate and low literate individuals" can understand the key safety and efficacy messages in OTC drug labeling. *Id.* at 2-6.

Under FDA's approach, OTC drug labeling does not contain lengthy, detailed warnings about the product. To the contrary, OTC drug labeling is space-constrained,[4] and therefore contains concise warnings. The main purpose of warnings in OTC drug labeling is to alert consumers to signs and symptoms that indicate they should stop use and see a doctor. *See* 64 Fed. Reg. at 13,258-259 (OTC drug labeling must clearly educate consumers about "when to stop use and contact a doctor after taking the product"). The goal is ***not***

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[3] *See* FDA, OTC Drug Facts Label, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143551.htm (stating that the "Drug Facts label uses simple language" and "plain-speaking terms to describe the facts about each OTC drug").

[4] *See* 40 Fed. Reg. 11,717, 11,717 (Mar. 13, 1975) ("[T]here is a space limitation on the number of statements that can appear on the labeling.").

to provide consumers with a list of every possible adverse reaction or condition associated with use of the product. FDA has explained that warnings in OTC drug labeling must alert consumers to any "signs of toxicity" or other symptoms that "would necessitate immediately discontinuing use of the product" and contacting a doctor. *Id.* at 13,262; *see* 21 C.F.R. § 201.66(c)(5)(vii).[5]

FDA has made clear that more detailed labeling information, like that sought here by Plaintiffs-Appellees, is better directed to medically trained health care practitioners. Thus, prescription drug labeling directed to health care practitioners contains more detailed scientific and medical information. *See* 21 C.F.R. §§ 201.56, 201.57.[6] The labeling for prescription drugs is lengthy and complex, and includes extensive data and information about the risks and benefits of the product. *See* 65

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[5] *See also* FDA, *Guidance for Industry, Labeling OTC Human Drug Products - Questions and Answers*, at 4 (Dec. 2008) ("You must include . . . any signs of toxicity or other reactions that would require a consumer to immediately stop using the drug product.").

[6] *See also* 65 Fed. Reg. 81,082, 81,082 (Dec. 22, 2000) (noting that prescription drug labeling "communicate[s] essential, science-based prescribing information to health care professionals").

Fed. Reg. 81,082, 81,083 (Dec. 22, 2000).[7] FDA has explained that the "use of medical and scientific terminology is necessary to effectively communicate to practitioners information about a product's risks and benefits." 71 Fed. Reg. 3,922, 3,961 (Jan. 24, 2006). Given this use of "technical language," the information in prescription drug labeling "is relatively inaccessible to consumers." 60 Fed. Reg. 42,581, 42,583 (Aug. 16, 1995).[8] Thus, inherent in FDA's decision to allow a medicine like ibuprofen to be available over-the-counter is a decision that simple patient-directed warnings are appropriate for that medicine, in place of the more medically-oriented warnings Plaintiffs-Appellees demand, which would be appropriate (if at all) in the context of prescription drug labeling.

FDA has clearly articulated why warnings like those sought by Plaintiffs-Appellees are inappropriate

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[7] FDA's regulations provide that prescription drug labeling must contain seventeen categories of scientific and medical information about the product. *See* 21 C.F.R. §§ 201.56(d), 201.57(c). These categories include, for example, warnings and precautions, adverse reactions, mechanism of action, pharmacodynamics, pharmacokinetics, and clinical studies.

[8] *See also* 44 Fed. Reg. 37,434, 37,449 (June 26, 1979) ("The Commissioner believes that much prescription drug labeling directed to physicians would not be helpful to patients.").

for OTC medicines. Excessive warnings would defeat the purpose of enabling consumers to engage in informed self-medication. As FDA has explained, consumers may respond in different ways to overwarning, but these different responses all have negative consequences. Overwarning may dissuade some consumers from using safe and effective OTC medicines. FDA has explained that warnings in OTC drug labeling are "not intended to worry consumers" or "encourage them to choose other medications."[9] FDA has explained that excessive warnings in labeling "could discourage appropriate use of a beneficial drug." 73 Fed. Reg. at 2,851.[10] In *Dowhal v. SmithKline Beecham Consumer Healthcare*, 88 P. 3d 1 (Cal. 2004), the California Supreme Court highlighted this negative consequence of overwarning in OTC labeling. The court stated that the "risk of harm may be so remote that it is outweighed by the greater risk that a warning will

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[9] FDA, Consumer Health Information, *FDA Warns of Rare Acetaminophen Risk* (Aug. 2013), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM363067.pdf.

[10] *See also* 73 Fed. Reg. 49,603, 49,605-606 (Aug. 22, 2008) (stating that "overwarning" in labeling "may deter appropriate use of medical products").

scare consumers into foregoing use of a product that in most cases will be to their benefit." *Id.* at 14.[11]

Overwarning may also cause some consumers to ignore or overlook important warnings in the labeling. FDA has explained that excessive warnings could "decrease the usefulness and accessibility of important information by diluting or obscuring it." 73 Fed. Reg. 2,848, 2,851 (Jan. 16, 2008).[12] Indeed, "[o]verwarning has the effect of not warning at all. The reader stops paying attention to excess warnings." *Id.* (citation and internal quotation marks omitted).[13]

In *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861 (7th Cir. 2010), the court reiterated FDA's

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[11] *See also Dowhal*, 88 P. 3d at 14 ("[A] truthful warning of an uncertain or remote danger may mislead the consumer into misjudging the dangers stemming from use of the product, and consequently making a medically unwise decision.").

[12] *See also* 73 Fed. Reg. 49,603, 49,605-606 (Aug. 22, 2008) (noting that "overwarning" may "overshadow more important warnings"); 53 Fed. Reg. 30,522, 30,530 (Aug. 12, 1988) ("The agency agrees that too many warning statements reduce the impact of important statements."); *cf.* FDA, *Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers*, at 42 (2001) ("Including too many warnings and precautions, over-warning, dilutes the strength of all of the hazard alerts.").

[13] *See also* Transcript, Nonprescription Drugs Advisory Committee Meeting, at 16 (Sept. 25, 2006) (Andrea Leonard-Segal, M.D., FDA, Director, Division of Nonprescription Clinical Evaluation) ("[A]t what point do we pack so much information into the label that people stop reading it . . . .").

concern that overwarning in OTC drug labeling may cause some consumers to overlook important risk information. *Id.* at 869. The court stated:

> The plaintiff argues that the label on the bottle of Children's Motrin should have added "rash" to the other allergic reactions warned against and should have mentioned SJS/TEN as one of the possible allergic reactions and (since virtually no consumer who was not a physician would have heard of the disease) recited its horrific consequences. But then the label would have had to describe as well every other serious disease that might, however infrequently, be caused, or even just arguably caused (for it is unclear whether ibuprofen can cause SJS/TEN), by ibuprofen. And it would have to recite the symptoms of the disease if it was rare. ***The resulting information overload would make label warnings worthless to consumers***.

Id. (emphasis added).

In sum, FDA requires that OTC drug labeling contain concise and simple information to enable consumers' safe and effective use of OTC products. OTC drug labeling should not contain unfamiliar medical terminology or excessive warnings that could discourage appropriate use of beneficial drugs.

II. Plaintiffs-Appellees' State-law Failure-to-Warn Claims Are Preempted By Federal Law.

A. Under the Supreme Court's decision in *Wyeth v. Levine*, Failure-to-Warn Claims Regarding the Labeling of an NDA-Approved OTC Drug Are Preempted Where FDA Specifically Rejected Plaintiffs' Proposed Warning.

The Supremacy Clause provides that federal law "shall be the supreme Law of the Land . . . any Thing in the Constitution or Laws of any State to the Contrary notwithstanding." U.S. Const., Art. VI, cl. 2. Where state law "directly conflict[s]" with federal law, "state law must give way." *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567, 2577 (2011) (citation and internal quotation marks omitted). Under established conflict preemption principles, state-law claims are preempted where "it is impossible for a private party to comply with both state and federal requirements." *Id.* (citation and internal quotation marks omitted).

In *Wyeth v. Levine*, 555 U.S. 555 (2009), the Supreme Court articulated a "clear evidence" standard for impossibility preemption in the context of FDA labeling regulation. *Id.* at 571-73. The innovator prescription drug manufacturer in *Wyeth* was allowed to use FDA's "changes being effected" (CBE) regulation to strengthen the warning in its labeling without prior FDA approval. *Id.* at 568-71; *see* 21 C.F.R. § 314.70(c)(6)(iii). FDA has the "authority to reject labeling changes made pursuant to the CBE regulation."

555 U.S. at 571. The Supreme Court stated that "absent clear evidence that the FDA would not have approved a change to [the] label," the failure-to-warn claims were not preempted. *Id.* Because the manufacturer "offered no such evidence," the Court found no conflict preemption. *Id.* at 572.[14]

Like innovator prescription drug manufacturers, manufacturers of NDA-approved OTC drugs may use the CBE regulation to alter their labeling without prior FDA approval. *See* 21 C.F.R. § 314.70(c)(6)(iii). Thus, *Wyeth*'s "clear evidence" standard applies in failure-to-warn cases involving the labeling of NDA-approved OTC drugs.

Under *Wyeth*, state regulation of pharmaceuticals can coexist with federal regulation provided that state law does not conflict with the approach of FDA — the federal agency charged with ensuring the safety

[14] In *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), the generic prescription drug manufacturer did not have the option to use the CBE process to alter its labeling without prior FDA approval. *Id.* at 2575. The Supreme Court determined that the failure-to-warn claims were preempted because the manufacturer could not "independently do under federal law what state law requires of it." *Id.* at 2579, 2581. The Court reaffirmed the "clear evidence" standard in *Wyeth*, stating that, where the CBE regulation is applicable, the drug manufacturer can "show, by 'clear evidence,' that the FDA would have rescinded any change in the label and thereby demonstrate that it would in fact have been impossible to do under federal law what state law required." *Id.* at 2581 n.8.

and efficacy of medicines. 555 U.S. at 571. The "clear evidence" standard is satisfied when state law is trying to force a result that is at odds with the clear intent of FDA. Such a direct conflict renders compliance with both state law and FDA regulation impossible.

B. Implied Conflict Preemption Principles Apply To State Product Liability Lawsuits Concerning OTC Products.

In 1997, Congress expressly preempted certain state law requirements relating to OTC drugs, and provided in a "saving clause" that state product liability law is not expressly preempted. Neither of these provisions alters the applicability of ordinary conflict preemption principles to this case.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) added a new statutory section to the FDCA entitled "National Uniformity for Nonprescription Drugs." 21 U.S.C. § 379r; FDCA § 751. Section 379r contains an express preemption provision relating to OTC drugs, which provides that no state "may establish or continue in effect any requirement . . . that is different from or in addition to" any requirement under the FDCA. 21 U.S.C. § 379r(a)(2). This section also includes a saving clause for state product liability actions. 21 U.S.C. § 379r(e) ("Nothing in this section shall be

construed to modify or otherwise affect any action or the liability of any person under the product liability law of any State.").

The saving clause in section 379r(e) does not alter the ordinary conflict preemption analysis. Instead, the saving clause simply exempts product liability lawsuits from the *express* preemption provision in section 379r(a).

The U.S. Supreme Court has held that a saving clause to an express preemption provision "does *not* bar the ordinary working of conflict pre-emption principles." *Geier v. Am. Honda Motor Co., Inc.*, 529 U.S. 861, 869 (2000); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 352 (2001) ("neither an express pre-emption provision nor a saving clause" precludes conflict preemption analysis); *Int'l Paper Co. v. Ouellette*, 479 U.S. 481, 493 (1987) (the saving clause in section 505(e) of the Clean Water Act "merely says that '[n]othing *in this section*,' *i.e.*, the citizen-suit provisions, shall affect an injured party's right to seek relief under state law; it does not purport to preclude pre-emption of state law by other provisions of the Act"); *City of Milwaukee v. Illinois*, 451 U.S. 304, 328-29 (1981) (interpreting the saving clause in section 505(e) of

the Clean Water Act to mean "what it says: that nothing *in* § 505, the citizen-suit provision, should be read as limiting any other remedies which might exist").

In a state-law case concerning an OTC product, the California Supreme Court determined that the saving clause in section 379r(d)(2) for Proposition 65 did not preclude the application of conflict preemption principles. *Dowhal*, 88 P. 3d at 6-10. The court explained that *Geier* "established a strong presumption that Congress does not ordinarily intend to bar conflict preemption" and that the saving clause does not suggest an intent to preclude conflict preemption. *Id.* at 7-9.

Thus, despite the existence of the saving clause, conflict preemption analysis applies in state product liability lawsuits concerning OTC medicines.

C. Plaintiffs' Failure-to-Warn Claims Are Preempted By Federal Law.

Under *Wyeth*'s "clear evidence" standard, Plaintiffs-Appellees' state-law failure-to-warn claims are preempted by federal law. Plaintiffs-Appellees asserted that the labeling of Defendants-Appellants' OTC ibuprofen product should have explicitly warned that skin reddening, rash, or blisters could be the start of a "life-threatening disease" or more

specifically of Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN). At trial, Richard Reckis testified that he would not have given his daughter a third dose of ibuprofen had the label stated that redness, rash, or blisters could "be the pathway to a life-threatening disease" or "could be the warning sign of toxic epidermal necrolysis or Stevens-Johnson Syndrome." *See* Defs.' Brief, at 25. The "clear evidence" standard is satisfied in this case because FDA carefully considered and rejected the warning that Plaintiffs-Appellees propose. The regulatory record strongly supports impossibility preemption.

In 2000, FDA adopted a class labeling template for all OTC ibuprofen products. The "**WARNINGS**" section of the template stated in relevant part: "**Allergy Alert**: Ibuprofen may cause a severe allergic reaction," including "hives," "facial swelling," "asthma (wheezing)," and "shock."

In 2005, FDA conducted a thorough assessment of the risks and benefits of all approved non-steroidal anti-inflammatory drugs (NSAIDs), which include ibuprofen products. During this review, FDA analyzed the risks of SJS and TEN associated with NSAIDs. FDA determined that the labeling of OTC ibuprofen products

"should be revised to warn of the potential for skin reactions."[15] FDA updated the OTC ibuprofen class labeling template to include, under the **Allergy Alert** subheading, three early symptoms of SJS and TEN — "skin reddening," "rash," and "blisters" — and the statement "If an allergic reaction occurs, stop use and seek medical help right away."[16]

In February 2005, a group led by plaintiff-side litigation experts — including Plaintiffs-Appellees' expert Dr. Randall Tackett — submitted a citizen petition to FDA concerning the risks of SJS and TEN associated with the use of ibuprofen products. *See* Citizen Petition, Dr. Roger E. Salisbury, No. 2005P-0072/CP1 (Feb. 15, 2005). The petition asked that FDA conduct a "full risk assessment" relating to ibuprofen and the occurrence of SJS and TEN. *Id.* at 1. The petition also requested that FDA require manufacturers of prescription ibuprofen to amplify the current

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[15] FDA, Decision Memorandum, Analysis and Recommendations for Agency Action Regarding Non-Steroidal Anti-Inflammatory Drugs and Cardiovascular Risk, at 16 (Apr. 6, 2005), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106201.pdf.

[16] FDA, Supplemental Request Letter and Labeling Template, at 4 (June 15, 2005), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106252.pdf.

warning about SJS and TEN in the labeling. *Id.*[17] Further, the petition requested that FDA withdraw approval of OTC pediatric ibuprofen products or, at a minimum, require manufacturers of OTC ibuprofen to include explicit warnings about the life-threatening reactions of SJS and TEN in the labeling. *Id.* at 1, 24. In particular, the petition requested that the OTC ibuprofen labeling state that "rashes and blisters" are "early symptoms [that] may progress to more serious and potentially life-threatening diseases," including SJS and TEN. The petition proposed the following warnings:

> **Serious Skin Reactions**: Ibuprofen may cause serious skin reactions that begin as rashes and blisters on the skin, and in the areas of the eyes, mouth and genitalia. These early symptoms may progress to more serious and potentially life-threatening diseases, including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. Seek immediate medical attention if any of these symptoms develop while taking ibuprofen.
>
> **Stop use and ask a doctor if**
> ▪ a skin rash or blisters on the eyes, mouth or genitalia occur because these symptoms may be an early sign of rare and life-

[17] The petition explained that the prescription drug labeling for ibuprofen discussed the risks of SJS and TEN in the Adverse Reactions section. The petition sought inclusion of risk information on SJS and TEN in the Warnings section. Citizen Petition, at 3-4.

> threatening reactions including Erythema Multiforme, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Id. at 24-25.

In August 2005, FDA issued an interim response to the citizen petition. The agency stated that it "has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials." Letter from Jane A. Axelrad, Associate Director for Policy, FDA Center for Drug Evaluation and Research, to Roger E. Salisbury, M.D., No. 2005P-0072/CP1, at 1 (Aug. 5, 2005).

In June 2006, FDA issued a written response to the citizen petition. FDA noted that it had conducted a "comprehensive analysis" of the risks of SJS and TEN associated with the use of ibuprofen and concluded that the risks "are significantly less than cited in the [citizen] petition." Letter from Steven K. Galson, M.D., M.P.H., Director, FDA Center for Drug Evaluation and Research, to Roger E. Salisbury, M.D., No. 2005P-0072/PAV1, at 2-5 (June 22, 2006). FDA explained that it was granting the petition in part, insofar as it had already directed manufacturers of OTC ibuprofen products to include the terms skin reddening, rash, and blisters in the **Allergy Alert**. FDA rejected the petition's request to include

additional language in the OTC labeling about SJS and TEN, including references to "life-threatening reactions" or to the names of the diseases. FDA stated that it would not be useful to include the terms "SJS," "TEN," "Stevens-Johnson syndrome," and "toxic epidermal necrolysis" in the OTC drug labeling "because most consumers are unfamiliar with these terms." *Id.* at 8. FDA explained that "effective OTC labeling communicates warning information in a manner that consumers can quickly and easily identify and understand." *Id.* at 8-9.

FDA determined that "a description of symptoms is more appropriate" for the OTC labeling. *Id.* at 9. FDA noted that, in connection with its 2005 comprehensive review of NSAIDs, it had already requested all manufacturers of OTC ibuprofen products to include, under the **Allergy Alert** subheading, three early symptoms of SJS and TEN and a statement to stop use and seek medical attention if an allergic reaction occurs. *Id.* The agency explained that the "description of symptoms" of SJS and TEN, combined with "advice to stop use and seek medical attention immediately," will appropriately "alert and educate consumers to the nature of the allergic reactions associated with SJS and TEN." *Id.* Importantly, the

agency ***rejected*** the petition's request to include a warning that these three symptoms may be the start of "life-threatening diseases," including SJS and TEN.

Finally, FDA rejected the petition's request to withdraw the OTC status of pediatric ibuprofen. The agency stated that "the overall benefit versus risk profile for ibuprofen products remains very favorable" and that it is important for the public health to have a "range of therapeutic options for the short-term relief of pain." *Id.* FDA explained that "other available OTC drugs for short-term relief of pain and fever can also be associated with serious, potentially life-threatening adverse events." *Id.*

This regulatory history establishes that *Wyeth*'s "clear evidence" standard is met and that preemption is appropriate in this case. FDA thoroughly considered the issue of the labeling of OTC ibuprofen products regarding the risk of life-threatening skin reactions, including SJS and TEN.[18] FDA conducted a comprehensive review of the risks of NSAIDs and decided to add three early symptoms of SJS and TEN to the OTC ibuprofen class labeling template. The 2005

[18] FDA's careful attention to the labeling issue in this case contrasts with FDA's mere "passing attention" to the labeling issue in *Wyeth*. *Wyeth*, 555 U.S. at 572.

citizen petition specifically requested that FDA require OTC ibuprofen labeling to warn that rash and blisters could be the prelude to "life-threatening" skin reactions, such as SJS and TEN. In its 2006 response to the citizen petition, FDA rejected this labeling change. FDA explained that unfamiliar medical terms are not useful in OTC labeling, and that the agency's inclusion of the early symptoms of SJS and TEN in the class labeling will alert consumers to stop use of the product and contact a doctor. In view of the rarity of SJS and TEN, and the "very favorable" risk-benefit profile of OTC ibuprofen and its importance to public health, FDA chose ***not*** to include language in the OTC ibuprofen class labeling template specifically referencing SJS and TEN or warning that the diseases could be "life-threatening."

FDA has explained in its regulations that its decision on a citizen petition is a "final decision" that "constitutes final agency action" and is reviewable in the courts. 21 C.F.R. § 10.45(d). The agency's 2006 response to the 2005 citizen petition therefore constitutes official agency action. FDA's rejection of the citizen petition's proposed warning constitutes "clear evidence" that FDA "would not have approved" the Plaintiffs-Appellees' proposed change in

OTC ibuprofen's labeling. *Wyeth*, 555 U.S. at 571. Therefore, it was impossible for Defendants-Appellants to comply with both state-law requirements and FDA's labeling regulations. State law "must give way," and Plaintiffs-Appellees' claims are preempted. *PLIVA*, 131 S. Ct. at 2577.

The Seventh Circuit's decision in *Robinson v. McNeil Consumer Healthcare*, 615 F.3d 861 (7th Cir. 2010), supports the conclusion that Plaintiffs-Appellees' failure-to-warn claims are preempted. *Robinson* similarly involved a product liability action alleging that the labeling of OTC ibuprofen failed to warn of SJS and TEN. *Id.* at 863-64. In recounting the regulatory history, the court explained that FDA required the addition of "skin reddening, rash, and blisters" to the OTC labeling for ibuprofen but "though later requested to do so, the agency decided not to require mention of SJS/TEN." *Id.* at 870. The court stated that FDA correctly reasoned that the inclusion of SJS and TEN "would confuse rather than enlighten." *Id.* The court determined that *Wyeth*'s "clear evidence" standard was satisfied due to FDA's rejection of the citizen petition's request to include explicit mention of SJS and TEN in the OTC labeling for ibuprofen. *Id.* at 873.

In other cases concerning the labeling of OTC ibuprofen and the risks of SJS and TEN, several federal district courts have determined that FDA's 2006 response to the citizen petition did not satisfy *Wyeth*'s "clear evidence" standard.[19] Setting aside whether these cases were correctly decided, they are distinguishable from this case.

The plaintiffs' claims in those cases were not limited to a failure to warn about "life-threatening reactions," or the specific diseases SJS and TEN, but included allegations that the labeling failed to warn about the early symptoms of SJS and TEN (e.g., rash)[20] or the particular consequences of SJS and TEN (e.g., massive skin loss).[21] In the cases regarding early symptoms, the courts determined that the "clear evidence" standard was not met because FDA ultimately decided to include the early symptoms of SJS and TEN

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[19] *See Hunt v. McNeil Consumer Healthcare*, No. 11-457, 2014 WL 1116358, at **4-5 (E.D. La. Mar. 11, 2014); *Newman v. McNeil Consumer Healthcare*, No. 10-CV-01541, 2012 WL 39793, at **7-9 (N.D. Ill. Jan. 9, 2012); *Wolfe v. McNeil-PPC, Inc.*, 773 F. Supp. 2d 561, 568-69 (E.D. Pa. 2011); *Lofton v. McNeil Consumer & Specialty Pharms.*, 682 F. Supp. 2d 662, 677-78 (N.D. Tex. 2010).

[20] *See Wolfe*, 773 F. Supp. 2d at 568 (alleging a failure to warn about the early symptoms of SJS and TEN); *Lofton*, 682 F. Supp. 2d at 677-78 (same).

[21] *See Hunt*, 2014 WL 1116358, at *4 (alleging a failure to warn about the severe consequences of SJS); *Newman*, 2012 WL 39793, at *7 (same).

in the OTC labeling for ibuprofen.[22] In the cases regarding the severe consequences of SJS and TEN, the courts concluded that FDA's rejection of the citizen petition did not constitute "clear evidence" because FDA did not reject the specific warnings proposed by the plaintiffs (e.g., blindness).[23] In this case, however, it is clear that FDA rejected Plaintiffs-Appellees' proposed warning — a warning about the risk of "life-threatening" skin reactions, or the specific diseases SJS and TEN. The 2005 citizen petition proposed that the labeling of OTC ibuprofen products include a warning about "potentially life-threatening diseases," including SJS and TEN, and FDA rejected the inclusion of this information in the OTC ibuprofen labeling template. Therefore, in this case, FDA's 2006 rejection of the citizen petition satisfies the "clear evidence" standard.

FDA's recent decision regarding the labeling of OTC acetaminophen products with respect to the risks of SJS and TEN reinforces the agency's 2006 determination regarding the labeling of OTC ibuprofen products. In August 2013, FDA explained that there is

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[22] *See Wolfe*, 773 F. Supp. 2d at 568-69; *Lofton*, 682 F. Supp. 2d at 678.

[23] *See Hunt*, 2014 WL 1116358, at *4; *Newman*, 2012 WL 39793, at *6.

a link between acetaminophen and serious skin reactions, including SJS and TEN, and concluded that the labeling of OTC acetaminophen products should warn of the early symptoms of SJS and TEN.[24] FDA requested manufacturers of OTC acetaminophen products to include in the labeling a similar warning to the warning FDA added to the OTC ibuprofen class labeling template in 2005 – the three early symptoms of SJS and TEN ("skin reddening," "blisters," and "rash") and the statement to stop use and seek medical help immediately if a skin reaction occurs. FDA explained that the new warning "is not intended to worry consumers," but is intended to help consumers "recognize and react quickly to the initial symptoms of these rare but serious, side effects."[25] Notably, FDA did not require that the OTC labeling mention "life-threatening" skin reactions, or the medical terms SJS and TEN, because such language would be inconsistent with the agency's policies on OTC drug labeling.

Additionally, two recent federal district court decisions reinforce the conclusion that *Wyeth*'s "clear

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[24] FDA, Consumer Health Information, *FDA Warns of Rare Acetaminophen Risk* (Aug. 2013), *available at* http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM363067.pdf.

[25] *Id.*

evidence" standard is satisfied in this case. In *In re Fosamax Products Liability Litigation*, 951 F. Supp. 2d 695 (D.N.J. 2013), the plaintiffs asserted that the manufacturer of Fosamax, a prescription osteoporosis drug, failed to warn about the risk of atypical femur fractures. *Id.* at 696. In 2008, the manufacturer submitted a prior approval labeling supplement to FDA, proposing to add information relating to femoral fractures in the Precautions section of the Fosamax labeling. *Id.* at 697-98. In May 2009, one month after the plaintiff's femur fracture, FDA rejected this labeling change. *Id.* at 698. The court determined that FDA's rejection of the labeling change "constitutes clear evidence that the FDA would not have approved a stronger warning prior to [the plaintiff's] fracture." *Id.* at 705.[26] The plaintiffs' claims were therefore preempted. *Id.*

In *Dobbs v. Wyeth Pharmaceuticals*, 797 F. Supp. 2d 1264 (W.D. Okl. 2011), *appeal dismissed per stipulation*, No. 12-6077 (10th Cir. Mar. 14, 2013), the plaintiff brought a products liability action alleging that Effexor, a prescription antidepressant, caused her husband to commit suicide in 2002, and that

[26] The court cited *Robinson* as an analogous case. 951 F. Supp. 2d at 703.

the manufacturer failed to warn of this risk of suicidality. *Id.* at 1266. The court determined that the plaintiff's failure-to-warn claims were preempted because there was "clear evidence that the FDA would have rejected an expanded Effexor [suicidality] warning for patients in [the adult] age group" prior to the 2002 suicide. *Id.* at 1277. The court explained that FDA regulated the labeling of antidepressants on a class-wide basis, and that FDA had carefully evaluated the risk of suicidality associated with antidepressants for over a decade. *Id.* at 1271-72, 1275. The court emphasized "FDA's repeated refusal to extend suicidality warnings to adult patients over the age of 25," both before and after the 2002 suicide. *Id.* at 1276.[27]

In *Fosamax* and *Dobbs*, the courts concluded that the "clear evidence" standard was met where FDA carefully considered and rejected the addition of the plaintiffs' proposed warning to the product's labeling.[28] Similarly, here, FDA thoroughly considered

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[27] The *Dobbs* court noted that, in other cases involving the suicidality warnings of prescription antidepressants, the courts have determined that the "clear evidence" standard was not satisfied. The *Dobbs* court closely analyzed and distinguished these cases. *See* 797 F. Supp. 2d at 1277-80.

[28] For preemption purposes, it does not matter if the FDA-rejected warning was proposed by the drug (continued…)

and rejected the request to include in the OTC ibuprofen labeling template a warning that rash, blisters, or skin reddening could lead to a "life-threatening disease," such as SJS and TEN. This rejection constitutes clear evidence that FDA would not have approved Plaintiffs-Appellees' proposed change to the labeling of OTC ibuprofen. Thus, under *Wyeth*'s standard for impossibility preemption, Plaintiffs-Appellees' failure-to-warn claims are preempted by federal law.

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manufacturer or by a third party in a citizen petition. Several courts have determined that FDA's rejection of a warning proposed in a citizen petition can be the basis for conflict preemption. *See, e.g.*, *Robinson*, 615 F.3d at 873; *Dowhal*, 88 P.3d at 9-11.

CONCLUSION

Plaintiffs-Appellees' state-law failure-to-warn claims are preempted by federal law.

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Certificate of Compliance

I, Paul W. Schmidt, hereby certify pursuant to Mass. R. App. P. 16(k) that the foregoing brief complies with the rules of the court that pertain to the filing of briefs.

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Certificate of Service

I, Paul W. Schmidt, hereby certify that on November 11, 2014, two copies of the foregoing brief of amicus curiae the Consumer Healthcare Products Association were served via first-class U.S. mail on counsel of record for Plaintiffs-Appellees and Defendants-Appellants:

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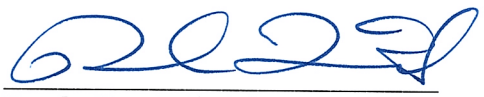

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