No. 06-1249

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE VERMONT SUPREME COURT

BRIEF FOR PETITIONER

BERT W. REIN
KARYN K. ABLIN
BRENDAN J. MORRISSEY
WILEY REIN LLP
1776 K Street, NW
Washington, DC 20006
(202) 719-7000

ALLAN R. KEYES
R. JOSEPH O'ROURKE
RYAN, SMITH, CARBINE, LTD.
98 Merchants Row
P.O. Box 310
Rutland, VT 05702-0310
(802) 786-1000

SETH P. WAXMAN
Counsel of Record
PAUL R.Q. WOLFSON
CATHERINE M.A. CARROLL
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006
(202) 663-6000

WILLIAM J. RUANE
WYETH
Five Giralda Farms
Madison, NJ 07940
(973) 660-6105

Counsel for Petitioner

QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration ("FDA") pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, preempt state-law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

PARTIES TO THE PROCEEDING

Petitioner Wyeth was the defendant and appellant in the courts below. Respondent Diana Levine was the plaintiff and appellee in the courts below.

CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

TABLE OF CONTENTS

TABLE OF CONTENTS—Continued

TABLE OF CONTENTS—Continued

TABLE OF AUTHORITIES

CASES

TABLE OF AUTHORITIES—Continued

Page(s)

TABLE OF AUTHORITIES—Continued

CONSTITUTIONAL AND STATUTORY PROVISIONS

TABLE OF AUTHORITIES—Continued

TABLE OF AUTHORITIES—Continued

REGULATIONS

TABLE OF AUTHORITIES—Continued

LEGISLATIVE MATERIALS

TABLE OF AUTHORITIES—Continued

OTHER AUTHORITIES

IN THE

Supreme Court of the United States

No. 06-1249

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

BRIEF FOR PETITIONER

OPINIONS BELOW

The decision of the Vermont Supreme Court is reported at 944 A.2d 179 (Vt. 2006) (Pet. App. 1a-48a). That court denied Wyeth's motion for reargument in an unreported order (Pet. App. 75a-76a). The trial court's decision denying Wyeth's Motion for Judgment as a Matter of Law (Pet. App. 49a-74a) is unreported.

JURISDICTION

This Court has jurisdiction pursuant to 28 U.S.C. § 1257(a). The Vermont Supreme Court entered its judgment on October 27, 2006 and denied a timely motion for reargument on December 11, 2006. The peti-

tion for writ of certiorari was filed on March 12, 2007 and granted on January 18, 2008.

RELEVANT CONSTITUTIONAL, STATUTORY, AND REGULATORY PROVISIONS

The following constitutional, statutory, and regulatory provisions are set forth in relevant part in the appendix to the petition for writ of certiorari:

- The Supremacy Clause, U.S. Const. art. VI, cl. 2 (Pet. App. 77a);
- Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 352, 355, 393 (Pet. App. 78a-111a);
- Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (Pet. App. 112a);
- 21 C.F.R. § 314.70 (Pet. App. 113a-125a).

PRELIMINARY STATEMENT

The Federal Food, Drug, and Cosmetic Act (FDCA) and its amendments charge the Food and Drug Administration (FDA) to protect and promote the public health by reviewing the safety and efficacy of new prescription drugs before permitting their interstate distribution. FDA review of a New Drug Application requires careful balancing of the benefits offered by the drug against the potential risks that inevitably accompany the use of any prescription medicine. *Cf. Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004-1005 (2008) (analyzing analogous approval requirements for medical devices). The authority to control the content of all the information in a drug's labeling is central to FDA's ability to strike that balance. The agency's comprehensive authority over drug labeling enables FDA to manage the risks associated with each drug in a manner that reduces the potential for harm, while en-

suring that the most efficacious treatments remain available to patients who need them.

Carrying out precisely this balancing of risks and benefits, FDA determined that Wyeth's drug Phenergan is safe and effective for use in the treatment of nausea, and it approved labeling for that drug that permitted intravenous injection as an acceptable method of administering the drug. FDA reached and adhered to this conclusion with full knowledge that exposure of arterial blood to Phenergan can result in severe injury, including gangrene, and that intravenous injection—including "IV push" injection—can lead to inadvertent arterial exposure if performed incorrectly. FDA did not direct Wyeth to contraindicate—i.e., eliminate as a permissible method of administration—IV push or other forms of IV injection, but instead chose to preserve the added effectiveness of intravenous administration and manage this known risk by requiring Wyeth to include carefully tailored warnings and instructions on the drug's labeling. Indeed, since at least 1967, FDA has repeatedly reviewed Phenergan's labeling with respect to arterial blood exposure and mandated that Wyeth distribute the drug only under the verbatim labeling approved by FDA. Absent any newly discovered evidence concerning the nature or degree of these risks, any modification by Wyeth of the contents of these warnings would violate the FDCA and FDA's implementing regulations.

In this case, a Vermont jury was nevertheless permitted to find Wyeth liable for failing to change Phenergan's labeling to eliminate IV push injection from the approved methods of administration. The Vermont Supreme Court affirmed that verdict even though the labeling already contained numerous warnings about the risks associated with IV injection of Phenergan,

and even though respondent never showed or even contended that Wyeth had any material new information about those risks that FDA had not already taken into account when it approved Phenergan's labeling. Compliance with the state-law labeling requirements underlying that verdict would require Wyeth to modify Phenergan's FDA-approved labeling in violation of the FDCA. Moreover, enforcement of this state-law duty would nullify the *ex ante* expert and statutorily mandated balancing of therapeutic benefits and safety risks that FDA performed in approving Wyeth's Phenergan labeling. It would substitute the *ex post* judgment of lay jurors whose members consider drug safety through the lens of a single patient's injury, rather than from the perspective of the overall public health, with the countervailing benefits of the drug to the entire potential patient population in mind. Indeed, counsel for respondent expressly invited the jury to override FDA's decision, telling them "[t]he FDA doesn't make the decision, you do." JA 212.

The judgment below, concluding that Phenergan's labeling should have contraindicated a method of administration that FDA had permitted, thus conflicts with the federal regulatory regime under the FDCA in two ways. First, Wyeth could not change Phenergan's labeling to comply with Vermont law without violating federal law. Second, the state-law requirement frustrates both Congress's objective of having an expert agency balance a drug's risks and benefits and FDA's implementation of that objective in the case of Phenergan. In light of this clear conflict, and under this Court's settled Supremacy Clause precedent, respondent's claims are preempted, and the judgment below should be reversed.

STATEMENT OF THE CASE

I. STATUTORY AND REGULATORY FRAMEWORK

A. Evolution Of FDA's Statutory Authority

The statutory regime under which FDA regulates prescription drugs reflects a pervasive and particularized federal role in regulating the safety and effectiveness of their labeled uses. Drug labeling has been subject to federal control since the 1906 enactment of the Pure Food and Drugs Act. Pub. L. No. 59-384, 34 Stat. 768 (1906). The 1906 Act authorized the federal government to seize drugs that were adulterated or misbranded and to prosecute their manufacturers. *Id.* §§ 1, 2, 5, 10. "Misbranded" drugs included drugs with labeling that was "false or misleading in any particular." *Id.* § 8. The Act did not require premarketing approval, but even during this limited early stage of federal supervision, Congress showed concern about disparate state-law labeling standards and an intent to bring about uniform national labeling. *See* H.R. Rep. No. 59-2118, at 4 (1906) (expressing concern regarding "the varying requirements as to standards and labels in different States" for food products); 40 Cong. Rec. 1217 (1906) (statement of Sen. Nelson) ("[T]he bill will, whenever there is a conflict between the State law and this law, leave this law controlling and be the means of equalizing and doing justice to all parts of the country, instead of having the difficulties we now encounter in many of the States.").

Reacting to mounting evidence of drug safety problems, Congress enacted the FDCA in 1938. Pub. L. No. 75-717, 52 Stat. 1040 (1938). The FDCA precluded interstate shipment of a new drug unless FDA determined that the drug was "safe for use under the conditions prescribed, recommended, or suggested in the

proposed labeling thereof," *id.* § 505(a), (d), 52 Stat. at 1052, and it required that the labeling of all drugs provide "adequate directions for use" and "adequate warnings" against unsafe uses and methods of administration, *id.* § 502(f); *see also id.* §§ 201(p), 301(a), 502, 505(a), (d), 52 Stat. at 1041-1042, 1050-1052 (codified as amended at 21 U.S.C. §§ 321(p), 331(a), 352, 355(a), (d)). The statute prohibited manufacturers from distributing a new drug until a New Drug Application (NDA) for that drug was effective, and it required "specimens of the labeling proposed to be used for such drug" to be submitted as a central component of that NDA. *See id.* § 505(a), (b), 52 Stat. at 1052 (codified as amended at 21 U.S.C. § 355(a), (b)). Thus, if a manufacturer altered a drug's labeling without submitting the proposed changes to FDA, the drug would no longer be one for which an NDA was effective, and interstate distribution of the drug would be unlawful and subject to criminal and civil penalties. *See id.* §§ 201(p), 301(a), (d), 302(a), 303(a), 304, 307, 505(a), (d)(1), 52 Stat. at 1041-1046, 1052 (1938) (codified as amended at 21 U.S.C. §§ 321(p), 331(a), (d), 332(a), 333(a), 334, 337, 355(a), (d)).

In 1962, Congress enlarged FDA's authority by requiring the agency to determine that a drug is not only safe, but also effective "under the conditions prescribed, recommended, or suggested in the proposed labeling thereof" before approving it for distribution. Drug Amendments of 1962, Pub. L. No. 87-781, § 102(b), (c), 76 Stat. 780, 781 (codified as amended at 21 U.S.C. § 355(b), (d)). Congress also gave FDA post-approval authority to require manufacturers to submit reports "of data relating to clinical experience," including adverse drug events, to enable FDA to determine whether to withdraw approval under 21 U.S.C. § 355(e)

on the ground that a drug is not safe or effective under labeled conditions of use. *Id.* § 103(a), 76 Stat. at 782-783 (codified as amended at 21 U.S.C. § 355(k)(1)).[1]

Since the 1962 amendments, determination of a drug's safety has thus been "inseparable from consideration of the drug's effectiveness." *See* S. Rep. No. 87-1744, at 15 (1962). With respect to any NDA, FDA must weigh the safety risks associated with a new drug against the therapeutic benefits it offers and strike a balance between those often competing considerations by regulating "the conditions prescribed, recommended, or suggested in the proposed labeling." *See* 21 U.S.C. § 355(d); *see also* 21 C.F.R. § 314.50(d)(5)(viii) (requiring NDAs to include a "summary of the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions stated in the labeling"); FDA, *Guidance for Industry*, *Development and Use of Risk Minimization Action Plans* 4 (Mar. 2005), *available at* http://www.fda.gov/cder/guidance/6358fnl.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"). In this way, FDA fulfills its dual mission to "protect the public health" by barring access to unsafe or ineffective drugs, and to "promote the public health"

---

[1] With the enactment of the Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. IX, 121 Stat. 823, 922-962, FDA has enhanced authority to require post-approval labeling changes where "new safety information" comes to light. *See, e.g.*, *id.* §§ 901(a), 902(a), 121 Stat. at 922-926, 943 (codified at 21 U.S.C. §§ 352(z), 355(o)(1), (4)).

by ensuring prompt access to effective and beneficial medicines. 21 U.S.C. § 393(b).

B. FDA's Regulation Of Drug Labeling

"Drug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985).[2] As such, FDA regulation of labeling serves as "[t]he centerpiece of risk management." 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). FDA-approved 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.*

FDA regulates drug labeling both through rules of general applicability promulgated under its broad regulatory authority, *see* 21 U.S.C. § 371(a), and through particularized review of the labeling for each individual drug. Under general FDA regulations, a drug's labeling must include "a summary of the essential scientific information needed for the safe and effective use of the drug." 21 C.F.R. § 201.56(a)(1). Labeling must describe the drug and its clinical pharmacology, its indications and usage, contraindications, warnings, precautions, and instructions on dosage and methods of administration, and those sections must appear in a specified order. *Id.* § 201.56(d)(1), (e)(1). FDA regulations also specifically describe the required content of each of those sections, *id.* §§ 201.57, 201.80, and mandate that

---

[2] The term "labeling" means "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." 21 U.S.C. § 321(m).

the labeling describe "adverse reactions," "other potential safety hazards," "limitations in use imposed by them," and "steps that should be taken if they occur," *id.* §§ 201.57(c)(6), 201.80(e).

To ensure that these requirements are met, FDA reviews the labeling submitted with each NDA and supplemental NDA as part of the approval process. FDA may approve an NDA only if it finds that the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof"; that there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof"; and that the proposed labeling is not "false or misleading in any particular." 21 U.S.C. § 355(d). And FDA may withhold approval until the manufacturer makes any necessary changes to the labeling. 21 C.F.R. § 314.105(b); *see also id.* § 314.110(a). Once FDA approves an NDA, it requires the manufacturer to distribute the drug only under the precise labeling approved in the NDA. *See id.* § 314.105(b) ("[A]pproval will be conditioned upon the applicant incorporating the specified labeling changes exactly as directed, and upon the applicant submitting to FDA a copy of the final printed labeling prior to marketing.").[3]

[3] Accordingly, upon approving any NDA, FDA instructs the manufacturer that the drug's final printed labeling must match the labeling that was included in the NDA. *See, e.g.*, Letter from Center for Drug Evaluation and Research, FDA, to Idenix Pharms. Inc. approving NDA 22-011 (Tyzeka) (Oct. 25, 2006), *available at* http://www.fda.gov/cder/foi/appletter/2006/022011s000ltr.pdf ("The final printed labeling (FPL) must be identical to the agreed upon enclosed labeling[.]").

The FDCA permits manufacturers to distribute only those drugs that FDA has certified to be safe and effective *under labeled conditions of use*. 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d) (emphasis added). Because the FDCA thus prohibits the distribution of drugs for which no application is effective, and because the FDA-approved labeling is a central component of an effective application, a manufacturer may not change a drug's FDA-approved labeling without obtaining FDA's prior approval of 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), (b)(3). A narrow exception to this rule in the FDA regulations permits a manufacturer who has filed a supplemental NDA 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).[4]

This regulation—known as the "changes being effected," or "CBE," regulation—codifies a longstanding FDA policy under which the agency exercises its enforcement discretion not to take action against a manufacturer that modifies a drug's FDA-approved labeling to add or strengthen warnings without prior approval if the change reflects newly discovered risk information.

---

[4] FDA regulations also permit manufacturers to make minor editorial changes to a drug's labeling and changes to the labeling's description of the drug or how it is supplied without submitting a supplemental NDA, so long as the manufacturer documents the change in its annual report to FDA. *See* 21 C.F.R. § 314.70(d)(1), (2)(ix), (2)(x).

See 30 Fed. Reg. 993, 993-994 (Jan. 30, 1965); 73 Fed. Reg. 2848, 2848-2849 (proposed Jan. 16, 2008); *see also* U.S. Br. 13 (Dec. 21, 2007) (CBE regulation constitutes a "limited exception" to prior approval requirement only for changes addressing "*newly discovered risks* from the use of [a] drug" (quoting 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982)) (emphasis added in U.S. Br.)). FDA retains ultimate authority to approve or disapprove of the labeling change and to take enforcement action against the manufacturer for misbranding if the change "makes the labeling false or misleading." 71 Fed. Reg. at 3934; *see also* 21 C.F.R. § 314.70(c)(7). Thus, "the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act." 71 Fed. Reg. at 3934.

II. FACTUAL BACKGROUND

A. FDA's Regulation Of Phenergan's Labeling

This case involves a prescription drug called Phenergan® Injection, or simply "Phenergan," which treats nausea and other ailments.[5] FDA approved Phenergan in 1955. JA 266-267. Since then, with Wyeth's cooperation, FDA has engaged in extended review and regulation of Phenergan's uses and risks and the information in its labeling. Phenergan has been approved as safe and effective when administered by deep intramuscular ("IM") or intravenous ("IV") injection. *See, e.g.*, JA 390. As Phenergan's labeling indicates, IV administration produces clinical effects four times faster than IM administration and is therefore beneficial for patients in need of rapid treatment. *See* JA 390; *see also* JA 40-41,

[5] Phenergan is Wyeth's brand name for promethazine hydrochloride, a drug sold by several different drug manufacturers.

60-61; *infra* nn. 10, 11. In one method of IV administration, known as "IV push," the drug is injected (or "pushed") by a syringe that is inserted directly into a patient's vein or into the flexible tubing of an infusion set leading to a needle already inserted into a patient's vein. IV administration can also occur through an "IV drip," whereby the drug is introduced into an infusion system consisting of a hanging IV bag of saline solution that drips down a flexible tube from the bag to a needle or catheter inserted into a patient's vein. *See* JA 46-50.

In 1967, Wyeth advised FDA that it had received a report of a patient who developed gangrene requiring amputation when blood in the patient's arteries came into contact with Phenergan. JA 268-269. At that time, the risk associated with arterial blood exposure to Phenergan was already known, and Phenergan's labeling already warned against intra-arterial injection or perivascular extravasation, which could lead to inadvertent arterial exposure. JA 269.[6]

After the 1967 report, FDA worked closely with Wyeth through a series of communications and meetings to refine Phenergan's warnings with respect to IV administration. In 1973, Wyeth filed a supplemental application seeking approval of certain labeling changes. JA 270. By that time, Phenergan's labeling already advised in two places that intramuscular injection was the "preferred parenteral route of administration." *Id.* The "Dosage and Administration" section stated that "proper intravenous administration . . . is

[6] Perivascular extravasation occurs when a drug intended for intravenous administration escapes from the vein into the surrounding tissue, where it may come into contact with arterial blood. Intra-arterial injection is injection directly into an artery.

well tolerated," but warned that use of this route was "not without some hazard" because, as the labeling noted, "gangrene requiring amputation" could result from exposure of arterial blood to Phenergan through inadvertent intra-arterial injection or perivascular extravasation. JA 276, 277. The "Warnings" section further warned that "[d]ue to the close proximity of arteries and veins in the area most commonly used for intravenous injection, extreme care should be exercised," and specified the maximum concentration and rate of injection for IV administration. JA 276. At FDA's request, Wyeth agreed to add a second statement in the "Warnings" section that IV use of Phenergan was "not without hazard." JA 271, 276.

In 1975, FDA undertook further review of the drug and its labeling. *See* JA 280. As part of that review, Wyeth met with FDA officials to discuss inadvertent intra-arterial injection and other risks of Phenergan and thereafter filed a supplemental NDA to revise Phenergan's labeling. *Id.* FDA responded in May 1976 and instructed Wyeth to make several labeling changes, including adding an upper-case warning that "INT[RA-]ARTERIAL INJECTION MAY RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 279-280, 283. FDA also required Wyeth to add an upper-case instruction designed to enhance the safe IV administration of Phenergan: "ASPIRATION OF DARK BLOOD DOES NOT PRECLUDE INTRA-ARTERIAL NEEDLE PLACEMENT AS BLOOD IS DISCOLORED UPON CONTACT WITH PROMETHAZINE." JA 282.[7]

[7] Ordinarily, aspiration of a small amount of blood back into the needle before injection helps determine whether a needle is in

FDA convened an Advisory Committee meeting in October 1976 at which IV administration of Phenergan and the risks arising from arterial blood exposure were again evaluated. *See* JA 287-296. The Committee—composed primarily of medical doctors and researchers—approved the continued contraindication of intra-arterial injection on Phenergan's labeling, JA 289, and proposed a further warning that "[i]f a Tubex system is used for intravenous injection, the drug should be injected into a satisfactorily functioning intravenous set." JA 294.[8] Notably, however, the Committee did not recommend that FDA require Wyeth to eliminate IV administration, including IV push, from the drug's labeling.

In 1979, FDA issued a final rule requiring wholesale updates to the content and formatting of prescription drug labeling for all drugs subject to an approved NDA. *See* 44 Fed. Reg. 37,434 (June 26, 1979). FDA subsequently made clear that labeling changes made to comply with the new regulations "would be subject to prior approval by FDA following the submission of supplemental applications." 45 Fed. Reg. 32,550, 32,550 (May 16, 1980). When Wyeth submitted proposed labeling changes to comply with FDA's general mandate, it stated in its application that the draft labeling was being "submitted for FDA review and approval before

---

an artery or a vein because arterial blood is brighter red than venous blood. *See* JA 47. Contact with Phenergan causes discoloration of the blood, however, which makes aspiration an unreliable method of protecting against intra-arterial injection. JA 282, 390.

[8] The Tubex® system described in Phenergan's labeling is a type of injection set that consists of a single-use cartridge preloaded with a dose of Phenergan and a reusable plastic injector. *See* JA 43, 391.

being put into use; no labeling changes, therefore, are to be made at this time." JA 299.

During its review of Wyeth's supplemental application, FDA informed Wyeth that further revisions to Phenergan's labeling "relative to the recognition and management of unintended intra-arterial injection" were under consideration. JA 307-308. By that time, Phenergan's labeling already advised that "[w]hen administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily." JA 324. The labeling also instructed that if a patient complains of pain during IV injection of Phenergan, "the injection should immediately be stopped to provide for evaluation of possible arterial placement or perivascular extravasation." JA 324.

FDA requested several further labeling changes to supplement these statements. JA 309-319. Specifically, FDA instructed Wyeth to revise the existing warning concerning the risk of gangrene from arterial exposure to state that "[t]here are reports of necrosis leading to gangrene, requiring amputation, following injection of [Phenergan]," and to list several instructions for preventing inadvertent intra-arterial injection, including a statement that "[i]njection through a properly running intravenous infusion [set] may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 311-312. FDA did not withdraw its approval of IV administration of Phenergan or instruct Wyeth to remove IV push administration from the approved methods of administration identified in the labeling.

In 1988, Wyeth submitted a further supplemental application with new proposed labeling that implemented FDA's instructions. *See* JA 334-335. Wyeth's proposal included the following statement: "Injection into an intravenous infusion set that is known to be running properly should decrease the possibility of inadvertently injecting [Phenergan] intra-arterially. In addition, this results in delivery of a lower concentration of any arteriolar irritant." JA 341; *see also* JA 339-340.

In 1997—explaining that it had taken extra time to review Phenergan's proposed labeling changes to ensure that it had "dotted every 'i' and crossed every 't,'" JA 354—FDA ordered Wyeth to make various labeling changes regarding the dosage and administration of Phenergan, JA 355-365, but to "[r]etain verbiage in current label" concerning inadvertent intra-arterial injection, thus rejecting the previously proposed changes, JA 359.[9] Consistent with the FDCA and its implementing regulations, FDA stated that its approval of the supplemental application was contingent on Wyeth implementing these revisions as FDA directed. JA 356, 365. Wyeth accordingly submitted the revised labeling in compliance with FDA's decision, *see* JA 366-380, and FDA approved the revised labeling, JA 381-383. The approval letter advised Wyeth that the final printed labeling "must be identical to the draft package insert" approved in the letter. JA 382.

---

[9] FDA identified the "current" labeling as the version Wyeth submitted at FDA's request in August 1996. *See* JA 356 ("current labeling" refers to labeling submitted in August 1996); *see also* JA 346-352 (Wyeth letter to FDA dated August 6, 1996, enclosing then-current labeling).

B. The Labeling In Place When Respondent Was Treated In 2000

As of 2000, following some 45 years of FDA oversight, Phenergan's labeling included repeated, prominent notice—in four separate sections—of the risk of gangrene arising from inadvertent arterial exposure and gave detailed instructions on how to minimize that risk. The "Warnings" section explained:

> Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or inadvertent intra-arterial injection. Reports compatible with inadvertent intra-arterial injection of Phenergan Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances.

JA 390. The "Adverse Reactions" and "Dosage and Administration" sections each stated in bold, uppercase type: "INTRA-ARTERIAL INJECTION [CAN] RESULT IN GANGRENE OF THE AFFECTED EXTREMITY." JA 391. The "Contraindications" section likewise stated: "Under no circumstances should Phenergan Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene[.]" JA 390.

To minimize the risk of arterial blood exposure to Phenergan, both the "Contraindications" and "Dosage and Administration" sections advised that "[t]he preferred parenteral route of administration" is "by deep intramuscular injection." JA 390, 391. The labeling

also noted, however, that IV administration was an option, although "not without some hazard." JA 391. To preserve the option of IV administration for those patients who needed it while minimizing the attendant risk, the "Warnings" section instructed:

> When used intravenously, Phenergan Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.

JA 390. The "Dosage and Administration" section repeated these instructions. JA 391. The "Warnings" section further advised:

> Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with Phenergan Injection. Use of syringes with rigid plungers or of small bore needles might obscure typical arterial backflow if this is relied upon alone.

JA 390. This section also instructed that "[i]n the event that a patient complains of pain during intended intravenous injection of Phenergan Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation." *Id.*

C. Respondent's Treatment With Phenergan

On April 7, 2000, respondent Diana Levine sought treatment at Northeast Washington County Community Health, Inc. (the "Health Center") for a severe migraine headache and associated nausea. JA 18-19, 103;

Pet. App. 2a. Respondent was initially treated with Demerol for the migraine headache and Phenergan for the nausea. JA 19, 38. Both were administered via deep intramuscular injection, the preferred method of administration identified in Phenergan's labeling. *Id.*; Pet. App. 2a.

Respondent returned to the Health Center later that day because she had not obtained effective relief. JA 19, 38-39; Pet. App. 2a. A physician assistant, Jessica Fisch, then administered a second dose of Demerol and Phenergan intravenously by IV push, injecting the medication from a syringe into the tubing of an IV infusion set that led to a needle she had inserted into what she thought was respondent's vein. JA 19, 39, 106.

Fisch testified at trial that she chose to administer the drugs intravenously because the earlier intramuscular injection "hadn't worked at all," and she "felt that in order to give her some relief, that [she] would give it intravenously and try to get it in a more effective and swifter manner." JA 104. Respondent's supervising physician, Dr. John Matthew, testified at trial that IV injection "provides quicker relief" than IM injection and that it would not have been appropriate to administer Phenergan via IM injection once the Demerol was being administered intravenously "[b]ecause the Demerol would be circulating quickly through her brain and potentially causing her to have vomiting while the Phenergan absorbing IM would be slower and delayed so we might have aggravated her nausea and vomiting." JA 41; *see also* JA 40, 60-61.[10]

---

[10] Dr. David Greenblatt, a physician and clinical pharmacologist called by the defense, testified that "there are circumstances in which an intramuscular injection is unreliable," including injec-

Although Phenergan's labeling specified a dosage range for nausea of 12.5 to 25 mg, JA 391, Fisch gave respondent a 50 mg dose, *see* JA 105—double the labeled amount. Moreover, Fisch administered the entire 50 mg double dose without pausing, despite respondent's complaints of pain—pain she later described as "one of the most intense pains that [she] had ever felt" to that point, JA 179-181—even though the labeling instructed that IV injection should stop immediately if the patient complains of pain. JA 111, 183, 390. Respondent thereafter developed the symptoms of arterial exposure and gangrene, requiring amputation of her forearm. Pet. App. 2a.

---

tions into overweight patients, which may "be injected into fat and be poorly absorbed," and injections into patients who are dehydrated, seriously ill, or suffering from cardiac disease, who may have "poor blood flow to a muscle," which inhibits absorption. JA 200-201. Dr. Thomas Garvey III testified that IV push injection in particular would be appropriate for "[s]omebody who has been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into" because "[i]f they're vomiting, you want to get in right away, get in, give the drug." JA 195. Dr. Greenblatt further testified:

> [I]t's a judgment that is made by a treating physician who's treating a given patient and, if there is serious distress due to nausea and vomiting, if it won't stop, if the patient is miserable, if the patient is losing fluid and becoming dehydrated and very ill, then the physician in that urgent situation looks at what's available and, with knowing the risks of IV [Phenergan], would nonetheless make a judgment that the benefit to the patient is worthy of accepting that risk.

JA 201.

III. PROCEEDINGS BELOW

A. Trial Court Proceedings

After settling a malpractice suit against Fisch, the Health Center, and the supervising physician, respondent sued Wyeth in a Vermont trial court, alleging state-law claims for inadequate warnings and instructions. Those claims directly challenged FDA's decision to approve labeling that preserved IV administration of Phenergan as an available option for health care providers. The Amended Complaint alleged that Phenergan is

> not reasonably safe for intravenous administration because the foreseeable risks of harm posed by the intravenous administration of the drug are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health care providers, knowing of such foreseeable risks and benefits, would not prescribe the drug intravenously for any class of patients.

JA 15 (¶ 6).

Respondent tried the case under this theory. During opening statements, respondent's attorney claimed that Wyeth "had the obligation to publish instructions that would prevent this from happening. And there was a simple instruction that they could have written[:] 'Do not use this drug intravenously.' That's what the case is about." JA 32; *see also* JA 31. At trial, respondent's expert, Dr. Matthew, asserted, "I think the drug should be labeled 'Not for IV use.' If it were going to be used IV, I think that it should say that it has to be in a running—established IV running at a certain rate." JA 59; *see also* JA 63. Dr. Matthew also testified that "the instructions and warnings and so forth as they're

printed I think are inadequate, insufficient. I don't think the drug should be used IV." JA 65.

Dr. Harold Green, another of respondent's witnesses, also criticized FDA's approval of Phenergan's labeling, testifying that, in his opinion, "somebody at the FDA made an administrative error and approved it." JA 82. In his view, the drug should not have been approved for intravenous administration. JA 79-80. Respondent's FDA expert similarly "disagree[d] with FDA's conclusions" to approve Phenergan's labeling. JA 98. While acknowledging that "FDA knew about the risks associated with this product," JA 97, he claimed that "the benefits do not outweigh the risks" of Phenergan and that "the labeling was inadequate," JA 99, 100.[11] None of respondent's witnesses, nor her counsel, ever contended that Wyeth had any new information about the risks of Phenergan that FDA had

[11] Defense expert witnesses, in contrast, testified that FDA's approval decision was correct and medically sound. One expert disagreed that FDA's 1997 letter directing Wyeth to retain the verbiage in the current label "reflect[ed] an administrative error." JA 189-190. Another expert likewise testified that Phenergan's labeling was adequate and "provide[s] enough instruction to physicians or physician's assistants for the safe use of the product." JA 198-199. He disagreed that "the intravenous use of Phenergan should be banned," JA 200, explaining:

> There are clinical situations in which to produce the needed relief . . . IV may be the preferable or the only way it may be administered. There are obvious risks to IV administration and they are extensively and adequately warned against and, if the treating physician decides that the need to produce relief on that patient is urgent, then it's reasonable to give them the drug IV to produce that relief if it's done properly.

Id.

not already considered in approving Phenergan's labeling.

During closing arguments, respondent's counsel again took issue with Phenergan's FDA-approved labeling, arguing that Wyeth "should have pulled their drug . . . from intravenous use. At a minimum, they should have required that you use a free-flowing IV." JA 211. He also invited the jury to override FDA's labeling approval decision: "Thank God we don't rely on the FDA to . . . make the safe[ty] decision. You will make the decision." *Id.* "The FDA doesn't make the decision, you do." JA 212.

The court's jury instructions likewise invited the jury to disregard FDA's regulatory judgment: "You must decide the extent to which Wyeth should have warned and advised of the risks and injuries which could result from an injection of Phenergan of the type conducted in this case." JA 217. The court reiterated that "[i]t's for you to decide the nature and scope of the warning required," and that "[t]he warning must reasonably advise of the risks and provide adequate instructions to the physician or other medical professional for its safe use." JA 217-218; *see also* JA 220. The jury returned a verdict in favor of respondent and awarded $7.4 million in damages.[12] JA 225-226, 233-235; Pet. App. 3a.

In motions for summary judgment and judgment as a matter of law, Wyeth argued that respondent's claims were preempted. The trial court rejected that argu-

[12] The judgment was adjusted to $6,774,000 to account for prejudgment interest and the settlement in respondent's prior malpractice suit. JA 236; Pet. App. 3a.

ment, ruling that FDA's regulation of labeling sets only minimum standards and thus cannot conflict with additional state-law labeling requirements, and that the FDA's CBE regulation would have permitted Wyeth to strengthen the warnings on Phenergan's labeling without prior FDA approval. JA 21-23, 247-252.

B. Vermont Supreme Court Appeal

On appeal to the Vermont Supreme Court, Wyeth again contended that respondent's claims were preempted because Wyeth could not comply with both its federal duty to distribute Phenergan only under the precise labeling approved by FDA, which permitted IV push administration, and its Vermont common-law duty to alter that labeling to foreclose IV push. Wyeth further argued that enforcing a state-law requirement that foreclosed a method of administration approved by FDA would obstruct Congress's objective of protecting the public health by having an expert agency balance drug risks and benefits and FDA's specific fulfillment of that objective with respect to Phenergan. Pet. App. 6a, 16a, 18a. The Vermont Supreme Court rejected both arguments and affirmed. Pet. App. 19a, 28a, 34a.

The Vermont Supreme Court first held that it would not be impossible for Wyeth to comply with both federal and state-law labeling duties because FDA approval of a drug's labeling is merely a "first step" that sets minimum safety standards, and the CBE regulation "appears to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a, 15a, 17a. The court gave no weight to the comprehensive and mandatory nature of the FDA labeling regime or to FDA's specific directive to Wyeth to "[r]etain verbiage in current label." It held instead that preemption would operate only if

Wyeth could show that FDA would have rejected the precise labeling change sought by respondent. Pet. App. 17a-19a; *see also* Pet. App. 36a-37a.

The court rejected Wyeth's claim that the state-law duty underlying respondent's suit would obstruct the objectives of FDA's regulatory regime. In the court's view, all such "obstacle" preemption claims were foreclosed by language in the 1962 amendments to the FDCA that limited preemption claims arising from those amendments to cases of "'direct and positive conflict between such amendments and [a] provision of State law.'" Pet. App. 21a (quoting Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. at 793). The court reasoned that "direct and positive conflict[s]" denoted only those conflicts giving rise to "impossibility" preemption and thus "remove[d] from [its] consideration the question of whether common-law tort claims present an obstacle to the purposes and objectives of Congress." Pet. App. 21a; *see also* Pet. App. 21a-24a.

Chief Justice Reiber dissented, concluding that "compliance with state law in this case would require Wyeth to eliminate uses of Phenergan approved by the FDA and required to be included in the Phenergan labeling." Pet. App. 35a. He explained that "FDA clearly addressed the risks attending IV administration of the drug[,] . . . approved IV administration generally, and specifically warned of the dangers of direct IV administration, including inadvertent arterial injection possibly resulting in amputation." Pet. App. 38a. "These assessments are, in fact, the very essence of the FDA's approval and are in furtherance of the federal objective of advancing public health by balancing the risks and benefits of new drugs and facilitating their optimal use." *Id.* A jury's consideration of drug safety "through the lens of a single patient who has already

been catastrophically injured," in contrast, "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a. He further concluded that respondent sought a labeling change "that would directly contradict language approved and mandated by the FDA," and that the CBE regulation would not have permitted Wyeth to change Phenergan's labeling in the manner respondent sought. Pet. App. 39a-40a.

SUMMARY OF ARGUMENT

It is well established that "state law that conflicts with federal law is without effect." *Cipollone* v. *Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted). Respondent's state-law tort claims conflict with the regime Congress established in the FDCA in two ways.

First, it would have been impossible for Wyeth to comply with the purported state-law duty to modify Phenergan's labeling to contraindicate intravenous administration of Phenergan without violating the FDCA. State law conflicts with federal law and is preempted "when compliance with both federal and state regulations is a physical impossibility." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Under the FDCA, FDA's approval of a drug's labeling is inextricably intertwined with its approval of the drug itself. The approval process requires FDA to determine whether a new drug is safe and effective under the conditions set forth in the labeling. FDA must also determine whether the labeling satisfies the comprehensive and detailed requirements of federal law, and its ultimate approval of a new drug is conditioned on the manufac-

turer's adopting any changes to the labeling exactly as FDA directs. Once approved, therefore, the labeling ordinarily may not be modified without FDA authorization, and Wyeth would have violated the FDCA had it changed Phenergan's labeling in the manner required by respondent's claims.

The Vermont Supreme Court's contrary conclusion rested on an erroneous interpretation of an FDA regulation that governs when labeling changes may be put into temporary effect without prior FDA approval. As properly construed by FDA, that regulation establishes a limited safe harbor from enforcement for manufacturers that implement labeling changes prior to FDA approval when the change reflects newly acquired information about a drug's risks. That reading is supported by the history of the regulation and its relationship to the purposes of the FDCA as a whole; it is also the interpretation that FDA has reasonably advanced. In this case, respondent has never suggested that Wyeth had any new information about the risks of IV administration of Phenergan that would have warranted a change without FDA approval. Rather, when FDA approved the Phenergan labeling that was in place when respondent was injured, it did so with full information about the risks and benefits of the drug, and it instructed Wyeth to use labeling that FDA had concluded best accommodated those risks and benefits. Wyeth was not permitted to depart from FDA's conclusion—as state law would have required—without violating the FDCA and FDA's regulations.

Respondent's claims are also preempted for the independent reason that they "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). In the FDCA, Congress established

a regime in which an expert agency approves a new drug for distribution under specifically reviewed labeling, based on particularized judgments about the relative risks and benefits of that new drug. Those judgments advance the overall public health by recognizing that the benefits of a particular treatment for certain patients can justify the approval of a drug for uses consistent with its labeling even where its use may also present risk of harm. To minimize risk while preserving the availability of beneficial treatments, FDA reviews the warnings and other information on a drug's labeling and seeks to manage the relevant risks by specifying the information it concludes is necessary to advise users how to use the drug safely and effectively. Thus, contrary to the Vermont Supreme Court's conclusion, the regime Congress created does not establish mere minimum safety standards that a State may freely supplement without limit, but strikes a balance between often competing objectives. FDA carried out Congress's intent by approving labeling for Phenergan that recognized IV injection as a permissible option for health care providers in light of its superior efficacy and speed of relief while providing detailed information on the risks of IV injection and how to avoid them.

Vermont law, in contrast, would displace FDA's expert judgment and substitute the verdicts of lay jurors in fifty States who consider drug safety after the fact on a case-by-case basis, focusing on a single patient's catastrophic injury, rather than the potential benefits of the drug to the public as a whole—an approach that inherently will produce risk-averse determinations. Moreover, respondent's state-law claims interfere with FDA's fulfillment of Congress's intent in the case of Phenergan by second-guessing FDA's determination that, with appropriate warnings and in-

structions on the labeling, the benefits of IV administration of Phenergan outweigh the well-known risk of harm. Because recognition of the state tort action in this case would frustrate the purposes of federal law both by substituting the verdicts of lay juries for the expert balancing Congress directed FDA to conduct and by upsetting the particular balance FDA struck with respect to Phenergan, respondent's claims are preempted.

ARGUMENT

Article VI of the Constitution makes "the Laws of the United States . . . the supreme Law of the Land." U.S. Const. art. VI, cl. 2. "[T]he Supremacy Clause invalidates all state laws that conflict or interfere with an Act of Congress." *Rose* v. *Arkansas State Police*, 479 U.S. 1, 3 (1986) (per curiam). Such a conflict arises "when compliance with both federal and state regulations is a physical impossibility," or when "state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982) (internal quotation marks omitted). Respondent's state-law claims present both types of conflict and are therefore preempted.

I. Respondent's Claims Are Preempted Because It Is Impossible For Wyeth To Comply With Both The State-Law Duties Those Claims Impose And Its Federal Labeling Duties

The FDCA required Wyeth to distribute Phenergan only with the labeling that FDA had approved. FDA's CBE regulation did not permit any modification to the labeling in the absence of newly acquired risk information, which did not exist in this case. Vermont

law, by contrast, imposed a tort-law requirement that Wyeth alter that labeling to foreclose IV administration, or at least IV push injection. Because these two commands are irreconcilable, Vermont law must yield.

A. The FDCA And Vermont Law Imposed Irreconcilable Requirements On Wyeth

FDA's approval of a new drug reflects the agency's definitive judgment that a drug is safe and effective under the conditions of use identified in the drug's labeling, and that the drug as so labeled may lawfully be distributed in interstate commerce. Under this regime, Wyeth was required to distribute Phenergan only with the labeling that FDA had approved. Had Wyeth unilaterally altered the labeling to change the warnings with respect to arterial blood exposure or to eliminate IV push as an approved method of administration, it would have been in violation of federal law and subject to enforcement action by FDA for unauthorized distribution or misbranding. *See* 21 U.S.C. §§ 331(a), (d), 333(a), 334(a), 352, 355(a), (d); 21 C.F.R. § 314.105(b).

As discussed, *supra* pp. 8-10, FDA review of a New Drug Application is a rigorous process that focuses on whether the drug is safe and effective under the labeled conditions of use and whether its labeling complies with extensive and detailed regulations. FDA approval of a drug's labeling is thus part and parcel of its approval of the drug itself. Indeed, should FDA find any deficiencies in the proposed labeling during its review of an NDA, FDA will specify exactly how those deficiencies should be corrected; final approval of the NDA is "conditioned upon the applicant incorporating the specified labeling changes exactly as directed." 21 C.F.R. § 314.105(b).

With limited exceptions discussed below, a manufacturer may not make any changes to a drug after it has been approved, including changes in labeling, without submitting a supplemental application and obtaining FDA's prior approval. 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3). Federal law thus required Wyeth to submit any proposed change in Phenergan's labeling for FDA review and prohibited Wyeth from implementing that change without FDA's approval.

Similar features of FDA's premarket approval of Class III medical devices recently led this Court to find preemption of state-law tort claims in that analogous context. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008). In *Riegel*, the Court held that once a Class III medical device receives premarket approval, the FDCA (as amended by the Medical Device Amendments of 1976 (MDA)) forbids the manufacturer to make any change without FDA permission, including a change to the approved labeling, that would "affect safety or effectiveness." *Id.* at 1005. Any change must be submitted by supplemental application for FDA approval before implementation. *Id.* The Court thus held that FDA's detailed, individualized review of the safety and effectiveness of each Class III medical device imposed a federal-law "requirement" that approved devices be made "with almost no deviations from the specifications in its approval application," and preempted conflicting state-law requirements applicable to the device. *Id.* at 1006-1007.

The same holds true for prescription drugs, which are subject to an approval process that is closely similar

to the MDA's premarket approval process.[13] For both drugs and Class III devices, manufacturers must submit full reports of investigations showing whether the product is safe and effective as well as specimens of the proposed labeling. *Compare* 21 U.S.C. § 355(b)(1) (drugs) *with id.* § 360e(c)(1) (devices). In both instances, FDA conducts a detailed, individualized review of the product and is required to deny approval if that product has not been shown to be safe and effective for "use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof." *Compare id.* § 355(d) (drugs) *with id.* § 360e(d)(2) (devices). And in both instances, the manufacturer may not make "changes in labeling" without first submitting a supplemental application and obtaining FDA approval, except under narrow circumstances not implicated here. *Compare* 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3), (c)(6)(iii) (drugs) *with id.* § 814.39(a)(2), (d)(1), (d)(2)(i)-(iii) (devices).[14]

---

[13] Indeed, the premarket approval process for medical devices was modeled on the NDA process for approval of new drugs. *See* H.R. Rep. No. 94-853, at 16 (1976) (FDA authority to regulate safety and effectiveness of devices "is derived from drug law"); *id.* at 17 (standard for determining effectiveness of devices is "derived from existing provisions of the [FDCA] relating to drugs"); H.R. Conf. Rep. No. 94-1090, at 62 (1976) (placing devices previously regulated as drugs into "comparable regulatory status" under device law); 21 U.S.C. § 360j(*l*)(3)(A)(ii) ("[R]equirements applicable to [Class III] device[s] before the enactment date under [the NDA provision] shall continue to apply to such device[s]."); *see also* U.S. Br. 9 ("FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices[.]").

[14] Like premarket approval of Class III medical devices, FDA's review of New Drug Applications thus stands in sharp contrast to the "substantial equivalence" review at issue in *Medtronic*,

Federal law thus required Wyeth to distribute Phenergan only with the FDA-approved labeling, which preserved IV injection, including by IV push, as an approved method of administration. Consistent with that requirement, FDA's 1997 letter to Wyeth approving the Phenergan labeling in place at the time of respondent's injury instructed that "[t]he final printed labeling . . . must be identical to" the FDA-approved draft version. JA 382.

The Vermont verdict in this case, to the contrary, rested on a state-law duty to change that labeling to eliminate the option of IV administration, or, at a minimum, IV push. No less than a state statute or regulation, this common-law claim is preempted if it imposed a duty that conflicts with federal law. *See Riegel*, 129 S. Ct. at 1007-1008 ("[C]ommon-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." (internal quotation marks omitted)); *see also Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 350-353 (2001); *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 881-886 (2000). Here, Wyeth could not have complied with both its federal and Vermont duties. In these circumstances, the federal duty under the FDCA must prevail. *See, e.g.*, *Crosby* v. *National Foreign Trade Council*, 530 U.S. 363, 372 (2000) ("We will find preemption

---

Inc. v. *Lohr*, 518 U.S. 470 (1996), under which FDA enforces only generally applicable labeling requirements that "reflect[] 'entirely generic concerns about device regulation generally'" and involve no device-specific review for safety and efficacy. *See Riegel*, 128 S. Ct. at 1006-1007 (quoting *Lohr*, 518 U.S. at 501).

where it is impossible for a private party to comply with both state and federal law[.]").

B. The Vermont Court Misinterpreted The CBE Regulation

The Vermont Supreme Court conceded that this case might be "very different" if federal law required Wyeth to use only FDA-approved labeling. Pet. App. 10a. It held, however, that FDA's CBE regulation, 21 C.F.R. § 314.70(c)(6)(iii), eliminated the conflict between federal and Vermont law by allowing a manufacturer to make "unilateral changes to drug labels," without obtaining prior approval, "whenever the manufacturer believes it will make the product safer." Pet. App. 13a. This construction of FDA's regulations is wrong. The CBE regulation permits labeling changes only when the change reflects newly discovered information about a drug's safety that was not previously considered by FDA. Because respondent has not shown or even alleged that Wyeth had any such information concerning the risks of IV administration of Phenergan, the CBE regulation would not have permitted Wyeth to make the labeling changes that respondent's tort suit required.

As discussed, Congress required FDA to review individual drug labeling as part of the NDA process and to hold manufacturers to that approved labeling. Congress did this by expressly tying FDA review and approval of a drug to the labeling under which that drug would be distributed and by making the labeling itself a required and central part of the NDA. *See* 21 U.S.C. § 355(a), (b)(1)(F), (c)(1)(A), (d). Allowing a manufacturer to alter that labeling unilaterally in a manner that affects safety or effectiveness—when it has no material new information that was not available to FDA, but

simply disagrees with how FDA exercised its expert judgment with respect to a risk of which it was fully aware—would undermine the core premise upon which FDA approval of the drug is conditioned: the determination that the drug is safe and effective *as labeled*, *id.* § 355(d). Moreover, alteration of labeling departs from the NDA, making the drug an unauthorized "new drug" for which no NDA is effective; its shipment in interstate commerce would therefore be expressly forbidden by the FDCA. *Id.* § 355(a); *see also id.* §§ 321(p), 331(d). As interpreted by the Vermont Supreme Court, the CBE regulation would thus be so inconsistent with the drug approval scheme established by the FDCA that its promulgation would likely lie outside FDA's statutory authority. *Cf. FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125 (2000) (FDA "may not exercise its authority in a manner that is inconsistent with the administrative structure that Congress enacted into law" (internal quotation marks omitted)); *Board of Governors of Fed. Reserve Sys.* v. *Dimension Fin. Corp.*, 474 U.S. 361, 374 (1986) (agency's "rulemaking power is limited to adopting regulations to carry into effect the will of Congress as expressed in the statute").

The history of the CBE regulation demonstrates that it was never intended to carry the broad meaning the Vermont Supreme Court attributed to it. The 1938 FDCA made no provision for changes to approved labeling. In 1944, FDA by regulation provided for labeling changes, but made clear that they could be effected only if a manufacturer filed a supplemental application and obtained FDA's approval prior to implementing the change. 9 Fed. Reg. 12,255, 12,256 (Oct. 10, 1944). In 1956, FDA amended the regulation to make the preapproval requirement even more explicit, providing

that "[a] supplemental application should be submitted for any change . . . that may alter . . . the labeling," and that "[i]f a material change is made from the representations in an effective application for a new drug before a supplement is effective for such change, the application may be suspended." 21 Fed. Reg. 5576, 5579 (July 25, 1956). Suspension would prohibit further distribution of the drug in interstate commerce. *See* 21 U.S.C. § 355(a).

To allow labeling changes reflecting new drug safety information to be "placed into effect at the earliest possible time," FDA issued the predecessor to the current CBE regulation in 1965. 30 Fed. Reg. 993 (Jan. 30, 1965). The regulation provided that a manufacturer could submit a supplemental application proposing certain kinds of labeling changes, and then implement those changes without waiting for FDA approval, if the manufacturer notified FDA that the change was being effected and gave a full explanation of the basis for the proposed change. *Id.* at 993-994. Permissible changes included the addition of "additional warning, contraindication, side-effect, and precaution information." *Id.* Although, as FDA made clear, distribution of the drug without prior FDA approval of the labeling change would be unlawful, FDA stated that it would not pursue sanctions against manufacturers who changed labeling only to include new or strengthened cautionary material based on new safety information:

> It will be the policy of the Food and Drug Administration to take no action against a drug or applicant solely because changes of the kinds described in . . . this section are placed in effect by the applicant prior to his receipt of a written notice of approval of the supplemental new-drug application[.]

Id. at 994. The regulation was thus an exercise of FDA's enforcement discretion under the FDCA, intended to enable prompt adoption of changes needed "in the interest of drug safety." *Id.* at 993. FDA warned, however, that nothing in the regulation limited FDA's ultimate authority to suspend or withdraw approval of an NDA or take action against a drug or manufacturer that otherwise violated the FDCA. *Id.* at 994.

In 1982, FDA proposed to revise the CBE regulation into what is effectively its present form. The proposal explained that the regulation applied to changes made "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." 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982) (emphases added). All other labeling changes, except minor, editorial revisions, remained subject to the prior approval requirement. *Id.* at 46,635.[15] FDA adopted the revised regulation in 1985. 50 Fed. Reg. 7452, 7498-7499 (Feb. 22, 1985). In promulgating the final CBE rule, FDA explained that the category of labeling changes that could be made without prior FDA approval had to be narrow because "[s]ubstantive changes in labeling . . . are more likely than other

[15] These statements were consistent with FDA's earlier statements about the CBE regulation. Though FDA had said in 1979 that its regulations did not prohibit labeling changes made to add or strengthen warnings without prior FDA approval, 44 Fed. Reg. 37,434, 37,447 (June 26, 1979), it maintained the view at that time that such changes were permissible "whenever possibly harmful adverse effects associated with the use of the drug are discovered," *id.*, suggesting that only changes reflecting newly acquired risk information would be permitted.

changes to affect the agency's previous conclusions about the safety and effectiveness of the drug." *Id.* at 7470.

Consistent with this history, FDA has recently made clear that the CBE regulation provides only a "limited exception" to the general rule requiring prior approval of labeling changes. U.S. Br. 13. As the Solicitor General and FDA have explained, the CBE regulation is properly read to permit labeling changes without prior approval only when the change is "based on material new information—not information that was previously available to FDA, nor even cumulative new information that does not add materially to the information that was previously available to the agency." *Id.* 14. Even then, FDA retains authority to approve or reject the change, and to take enforcement action against any change that results in misbranding. *Id.* at 15. For this reason, "in practice manufacturers typically consult with FDA before making labeling changes" under the CBE regulation. *Id.*

Earlier this year, FDA reaffirmed this interpretation in a proposed rulemaking. 73 Fed. Reg. 2848, 2850 (Jan. 16, 2008) (defining information appropriate for CBE supplement as "data, analyses, or other information not previously submitted to the agency, or submitted within a reasonable time period prior to the CBE supplement, that provides novel information about the product, such as a risk that is different in type or severity than previously known risks about the product"). Reviewing the history of the CBE regulation, FDA stated that its proposal would "codify the agency's longstanding view" on when labeling changes may be effected without prior approval—namely, when necessary "only to reflect newly acquired information." *Id.* at 2848-2850.

FDA's interpretation of its CBE regulation as a limited exception applicable only where newly acquired, scientifically significant information requires an immediate response is "controlling unless plainly erroneous or inconsistent with the regulation." *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997) (internal quotation marks omitted); *see also Federal Express Corp.* v. *Holowecki*, 128 S. Ct. 1147, 1155 (2008) (deferring to agency's "permissible reading" of its own regulation, where regulation's scope was "less than clear"; agency is entitled to deference "when it adopts a reasonable interpretation of regulations it has put in force"). Deference is particularly appropriate here, where the regulation reflects the agency's exercise of specifically delegated discretion to enforce a complex regulatory scheme. *See Heckler* v. *Chaney*, 470 U.S. 821, 835 (1985) (FDCA's enforcement provisions "commit complete discretion to [FDA] to decide how and when they should be exercised"); *see also id.* at 831-832; *Chevron U.S.A. Inc.* v. *Natural Res. Def. Council, Inc.*, 467 U.S. 837, 865 (1984).

In this case, the CBE regulation—properly construed—did not permit Wyeth to deviate from Phenergan's FDA-approved labeling without prior FDA approval. While a different issue might have been presented had Wyeth learned of significant new risk information not presented to FDA, respondent has never suggested that Wyeth acquired any such new information, or that FDA was not already completely aware of all the risks. Indeed, respondent's counsel argued the opposite, stating to the jury that reports of adverse events associated with arterial blood exposure to Phenergan have existed "since at least 1969," and that "these reports are in the FDA database." JA 31. Respondent's expert similarly conceded that "FDA knew

about the risks associated with this product." JA 97. In these circumstances, Wyeth had no good-faith basis to invoke the CBE regulation, and it would have been impossible for Wyeth to comply with the state-law duty underlying respondent's claims by changing Phenergan's labeling to contraindicate use of IV push injection without violating these federal requirements. The claims are therefore preempted.

II. Requiring Wyeth To Comply With A State-Law Duty To Foreclose IV Push Administration Would Obstruct The Purposes And Objectives Of The Act And Its Implementation By FDA

State law is preempted when it "stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Hines*, 312 U.S. at 67. In the FDCA, Congress established a drug-approval regime in which an expert scientific agency makes uniform, national judgments about the safety and effectiveness of prescription drugs by balancing therapeutic benefits against safety risks *ex ante*, taking into account the interests of all potential patients. FDA struck precisely that type of balance in approving IV administration of Phenergan and in determining what warnings and instructions were appropriate to manage its associated risks. Vermont, by contrast, seeks to alter that balance by substituting the judgment of lay juries that focus on individual patients' injuries on a case-by-case basis, effectively disregarding the countervailing benefits of the drug to the public as a whole. *See Riegel*, 128 S. Ct. at 1008. The Vermont judgment thus frustrates both Congress's objective of having an expert agency serve as the ultimate regulator of the labeled conditions of use for which a drug is approved and FDA's specific fulfillment of that objective in establishing an elaborate and balanced network

of cautions and instructions on Phenergan's labeling with respect to the risks of IV administration. Respondent's claims are therefore preempted.[16]

A. Congress Mandated FDA To Make Particularized, Labeling-Specific Decisions That Balance Competing Considerations To Advance The Public Health

In determining whether a state law interferes with the full purposes and objectives of Congress, courts consider "the entire scheme of the statute"—its text, its context, and the policies underlying it. *Hines*, 312 U.S. at 67 n.20. Here, the regulatory scheme Congress established provides that FDA's drug-approval and labeling decisions must strike a balance between protecting the public from dangerous misuses of drugs and advancing public health by ensuring that beneficial treatments are available to those who need them.

Congress placed responsibility for resolving the tension between these competing objectives in an expert federal agency. In general, FDA regulation serves the dual objectives of protecting the public from dangerous products and promoting public health by facilitating access to beneficial treatments. *See* 21 U.S.C. § 393(b) (requiring FDA to "protect the public health by ensuring that . . . drugs are safe and effective" and to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a

[16] This case does not present the question whether the FDCA preempts claims that do not implicate labeling, such as manufacturing defect claims. Accordingly, Wyeth confines its argument to the preemptive effect of the Act's labeling requirements and FDA's implementation of those requirements.

timely manner"). These objectives are particularly relevant in the context of drug labeling, which serves as the "centerpiece of risk management" and "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. at 3934.

Labeling decisions require an understanding of what information a physician or other health care provider needs in order to make informed judgments about what course of treatment is appropriate for a particular patient. FDA must take account of the known risks and benefits of each condition of use for which a drug is labeled and carefully regulate that labeling to ensure that it includes the right balance of warnings and instructions that promotes 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.

Congress thus required a scientific review process presided over by an expert agency that assesses the risk-benefit profile of a drug under labeled conditions of use and actively manages that labeling to ensure that it advances the drug's safe and beneficial use.[17] FDA's

[17] FDA's oversight of prescription drug labeling is thus very different from the role played by the Environmental Protection Agency with respect to pesticide labeling. As this Court explained in *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431 (2005), although EPA reviews pesticide labels to ensure against misbranding, EPA does not conduct individualized review of the efficacy of individual pesticides or confirm efficacy claims on a pesticide's labeling. *See id.* at 440 ("EPA's approval of a pesticide label does not reflect any

scientific judgment on these issues warrants deference. *See, e.g.*, *Weinberger* v. *Bentex Pharms., Inc.*, 412 U.S. 645, 653-654 (1973) ("[t]he determination whether a drug is generally recognized as safe and effective . . . necessarily implicates complex chemical and pharmacological considerations" and is "peculiarly suited to initial determination by the FDA."); *Nutraceutical Corp.* v. *Von Eschenbach*, 459 F.3d 1033, 1043 (10th Cir. 2006) ("The review of scientific literature is properly in the province of the FDA, to which this Court grants deference based on its expertise."), *cert. denied*, 127 S. Ct. 2295 (2007); *Schering Corp.* v. *FDA*, 51 F.3d 390, 399 (3d Cir. 1995) ("[FDA's] judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference from us.").

FDA carried out this obligation to balance competing objectives in the specific case of Phenergan. In approving Wyeth's supplemental application in 1997, as it had in its prior Phenergan labeling actions, FDA sought to maximize Phenergan's therapeutic benefit by balancing the well-known and clearly labeled risk of inadvertent arterial exposure against the benefit of more potent and expeditious anti-nausea relief. On the one hand, intravenous injection of Phenergan offers unique benefits relative to other forms of administration and is

---

determination on the part of EPA that the pesticide will be efficacious or will not damage crops or cause other property damage." (internal quotation marks omitted)). For example, in the dispute before the Court in *Bates*, "EPA never passed on the accuracy of the statement" in the labeling challenged in that case. *Id.* Under the FDCA, in contrast, a drug's labeling is central to FDA's review of the safety and efficacy of the drug, and FDA carefully monitors the content and format of each drug's labeling.

the most effective medicine for some patients. *See supra* nn. 10, 11; JA 40-41, 104, 194-195, 200-201. On the other hand, there is a risk that human error during IV injection of Phenergan will cause arterial exposure resulting in serious injury to the patient. Rather than require the contraindication of IV administration altogether (or even just IV push), FDA approved labeling that maintained IV injection as an approved method of administration and managed the attendant risk through a carefully tailored set of warnings and instructions. FDA thus concluded that the network of limitations and warnings in Phenergan's labeling appropriately warned users of the serious risks of IV injection—risks of which FDA was fully informed—and provided information on how IV administration could be done safely.

The Vermont Supreme Court thought that the overriding objective of the FDCA was solely to protect consumers from dangerous products, Pet. App. 20a, and that FDA's approval of a drug and its labeling was therefore nothing more than "a first step in the process of warning consumers," Pet. App. 15a. On that view, federal law sets only minimum safety standards that manufacturers may freely supplement with unlimited additional warnings. Pet. App. 20a. The court thus concluded that a state law requiring manufacturers to add further warnings beyond what FDA required, or to contraindicate methods of administration that FDA had approved as safe and effective, poses no problem under the FDCA because such a requirement would serve the same purpose as federal law—namely, to "encourag[e] pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers." Pet. App. 15a.

As an initial matter, that reasoning is wrong in this case because FDA concluded that Phenergan's labeling

was *not* "inadequate to protect consumers." Pet. App. 15a. Rather, FDA's approval of the 1997 supplemental application indicated its determination that Phenergan was safe and effective under the labeled conditions of use, including use by IV injection. 21 U.S.C. § 355(d). More fundamentally, however, the Vermont Supreme Court erred in concluding that Congress's sole objective in the FDCA was to protect consumers from dangerous products, and that federal requirements therefore constitute only minimum safety standards.[18] The regulatory scheme that Congress established in the FDCA and that FDA implemented in the specific case of Phenergan serves competing goals: to protect the public from unreasonable risk of harm, while ensuring the availability of beneficial treatments, all of which carry a certain degree of risk. *See supra* pp. 7-8, 41-42; *see also Riegel*, 128 S. Ct. at 1009. And an approved drug's labeling must provide sufficient instructions for safe and effective use, while avoiding limitations that foreclose beneficial use of a drug in an effort to avoid all risk of human error. For these reasons, as the United States has explained, "'FDA interprets the [FDCA] to establish both a "floor" and a "ceiling"' with respect to drug labeling," U.S. Br. 11 (quoting 71 Fed. Reg. at 3935) (alteration in U.S. Br.), and "FDA's approval of labeling for a new drug reflects FDA's expert judgment that the labeling strikes the appropriate balance,"

[18] In any event, even if state and federal law share the same ultimate goal, state law is still preempted if it "interferes with the methods by which the federal statute was designed to reach this goal." *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987). "The fact of a common end hardly neutralizes conflicting means[.]" *Crosby*, 530 U.S. at 379.

id. The Vermont Supreme Court erred in concluding otherwise.

B. The Vermont Judgment Conflicts With Congress's Public-Health Objectives

Respondent's state-law claims frustrate the public-health objectives underlying the FDCA—and FDA's implementation of the FDCA in the case of Phenergan—by interfering with Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives. Pursuant to Congress's mandate, FDA made an expert judgment that the benefits of a speedier and more potent method of administration outweighed the risks associated with IV administration of Phenergan, and that the labeling properly explained the risks and how to avoid them and thus should be retained. FDA based that judgment on its assessment of the overall public health. Under Vermont law as applied below, in contrast, a single lay jury reweighs those risks and benefits, focusing not on the public health as a whole, but on the harm suffered by a single patient. As this Court observed in *Riegel*, a jury "sees only the cost of a more dangerous design, and is not concerned with its benefits; the patients who reaped those benefits are not represented in court." 128 S. Ct. at 1008. As such, juries will be systematically more risk-averse, which can undermine the public health by leading manufacturers to include excessive warnings on labeling or to remove effective methods of administration from the labeling.[19]

---

[19] Chief Justice Reiber made a similar point in dissent below, noting that "the jury does not assess reasonableness in the context of public health and the associated risk-benefit analysis," but rather "views the safety of the drug through the lens of a single

This Court has made clear that where federal law strikes a balance between competing objectives, "that is not a judgment the States may second-guess." *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989). Rather, state regulation "must yield to the extent that it clashes with the balance struck by Congress." *Id.* Thus, in *Geier* v. *American Honda Motor Co.*, 529 U.S. 861 (2000), this Court held that state tort law was preempted to the extent that it reached a different balance among several competing objectives than the balance the federal policy had struck. *Id.* at 874-881.

This case presents a conflict between state and federal law analogous to the one the Court addressed in *Geier*. The federal safety regulation at issue in *Geier* "deliberately provided the manufacturer with a range of choices among different passive restraint devices," which "would bring about a mix of different devices introduced gradually over time." 529 U.S. at 864-865, 875. The goal of the federal scheme was not to set minimum airbag standards—seeking "the more airbags, and the sooner, the better," *id.* at 874—but to accommodate multiple competing concerns, *id.* at 875. This Court held that the federal objective preempted the alleged tort duty because the duty "would have presented an obstacle to the variety and mix of devices that the federal regulation sought" and "stood as an obstacle to the general passive restraint phase-in that the federal regulation deliberately imposed." *Id.* at 881.

---

patient who has already been catastrophically injured," an approach that "is virtually guaranteed to provide different conclusions in different courts about what is 'reasonably safe' than the balancing approach taken by the FDA." Pet. App. 48a.

Here, as in *Geier*, FDA balanced competing concerns of safety and therapeutic benefit by considering the risks of IV administration of Phenergan and preserving the option for physicians to administer Phenergan by IV push in appropriate cases, subject to carefully crafted warnings and instructions in the labeling. Vermont sought to foreclose that option here by basing a damage award on its availability, an award imposed by a lay jury that reconsidered the precise risk information FDA had already weighed. Thus, just as in *Geier*, respondent's claims stand as an obstacle to the accomplishment and execution of federal objectives and are preempted.[20]

In contrast, this Court has rejected preemption claims in cases where federal law did not impose particularized requirements that reflected an accommodation of competing concerns. In *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470 (1996), for example, the Court held that

---

[20] *See also Buckman*, 531 U.S. at 348-350 (holding state tort claims challenging manufacturer's fraudulent misrepresentations to FDA to be preempted because they threatened to "skew[]" the "balance sought by [FDA]" in exercising its options to punish and deter fraud and thus would "inevitably conflict" with FDA's statutory responsibilities); *Barnett Bank of Marion County, N.A.* v. *Nelson*, 517 U.S. 25, 31, 37 (1996) (finding preemption where state law prohibited activities that federal law authorized); *Ouellette*, 479 U.S. at 494-497 (state law that "upset[] the balance of public and private interests so carefully addressed" by federal statute and that potentially undermined "Congress's considered judgment as to the best method of serving the public interest and reconciling . . . often competing concerns" was preempted); *de la Cuesta*, 458 U.S. at 156 (by "limiting the availability of an option" the federal agency considered essential to its objectives, state created an "obstacle to the accomplishment and execution of the full purposes and objectives" of federal law (internal quotation marks omitted)).

the "substantial equivalency" regime for FDA approval of certain medical devices did not preempt common-law claims because the approval process reflected only general concerns about device regulation, not particularized determinations about the safety and effectiveness of specific devices. *Id.* at 501. The case was thus "quite unlike a case in which the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on manufacturers or producers." *Id.*[21] FDA's approval of Phenergan's labeling, in contrast, constitutes precisely the kind of case distinguished in *Lohr*: FDA considered and resolved the competing considerations relevant to IV administration of Phenergan and implemented that decision by requiring Wyeth to distribute the drug only with specified labeling.

---

[21] *See also Riegel*, 128 S. Ct. at 1006-1007; *supra* n.14. This Court's decision in *Sprietsma* v. *Mercury Marine*, 537 U.S. 51 (2002), is similarly distinguishable. There, the Court found no preemption because the Coast Guard had decided to take no regulatory action at all on the question whether boats should be equipped with propeller guards. Contrary to the federal government's position in *Geier*, the Coast Guard in *Sprietsma* made clear that it perceived no conflict between state-law boat safety requirements and the federal regulatory scheme under the Federal Boat Safety Act, which expressly described the Coast Guard's regulations as setting "minimum safety standards." *Id.* at 58 n.6, 67-68. And unlike FDA's particularized review of each prescription drug it approves, the Coast Guard in *Sprietsma* did not undertake to "certify the acceptability of every recreational boat subject to its jurisdiction." *Id.* at 69.

Consistent with this conclusion, FDA has explained that, in its view, a state-law requirement that a manufacturer include additional warnings, instructions, or other information on a drug's labeling beyond what FDA has required would upset the balance struck under federal law between drug risks and benefits. 71 Fed. Reg. at 3934-3936. By requiring labeling to rule out methods of administration or other uses that FDA has approved, or to include excessive warnings and cautionary material sufficient to appease a risk-averse jury, a state-law duty to warn "can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use" and "discourage appropriate use of a beneficial drug," thereby "undermining the objectives of the act." *Id.* at 3935.[22] Thus, because respondent's claims frustrate the purpose of the FDCA's labeling requirements and stand as an obstacle to the

[22] As this Court observed in *Geier*, where Congress has delegated authority to an expert agency to implement a comprehensive regulatory scheme in a technical area, it is appropriate to give weight to the agency's conclusion that state regulation would pose an obstacle to the achievement of federal objectives: "The agency is likely to have a thorough understanding of its own regulation and its objectives and is uniquely qualified to comprehend the likely impact of state requirements." 529 U.S. at 883 (internal quotation marks omitted); *see also Lohr*, 518 U.S. at 496 ("Because the FDA is the federal agency to which Congress has delegated its authority to implement the provisions of the Act, the agency is uniquely qualified to determine whether a particular form of state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." (footnote and internal quotation marks omitted)); *Colacicco* v. *Apotex, Inc.*, 521 F.3d 253, 274-276 (3d Cir. 2008) (FDA's view that imposition of liability under state law for failure to warn would interfere with federal regulatory objectives is entitled to deference).

achievement of Congress's objectives, the claims are preempted.[23]

C. The 1962 Amendments To The FDCA Do Not Limit The Application Of This Court's Settled Conflict Preemption Principles

The Vermont Supreme Court rejected Wyeth's argument that respondent's state-law claims present an obstacle to Congress's purposes and objectives on the ground that section 202 of the 1962 Amendments to the FDCA limited the statute's preemptive effect to cases where compliance with both state and federal law was impossible. Pet. App. 21a. Section 202 states:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law . . . unless there is a direct and positive conflict between such amendments and such provision of State law.

---

[23] No "presumption against preemption" applies to alter this analysis. Regulation of drug labeling has now been the domain of the federal government for more than a century, and there is no presumption against federal preemption when States regulate in an area where there has been a history of significant federal presence. *United States* v. *Locke*, 529 U.S. 89, 108 (2000); *see also Buckman*, 531 U.S. at 347-348. Even where the presumption does apply, the existence of an actual conflict between federal and state law, even if implied, requires the state law to yield notwithstanding the presumption. *See Felder* v. *Casey*, 487 U.S. 131, 138 (1988) ("'[A]ny state law, however clearly within a State's acknowledged power, which interferes with or is contrary to federal law, must yield.'" (quoting *Free* v. *Bland*, 369 U.S. 663, 666 (1962)); *de la Cuesta*, 458 U.S. at 153 ("The relative importance to the State of its own law is not material when there is a conflict with a valid federal law, for the Framers of our Constitution provided that the federal law must prevail." (internal quotation marks omitted)).

Pub. L. No. 87-781, § 202, 76 Stat. 780, 793 (1962). In the Vermont Supreme Court's view, a "direct and positive conflict" exists only where compliance with both federal and state law is a physical impossibility. Pet. App. 21a-22a. Its rejection of Wyeth's "impossibility" argument was therefore "a complete answer to the question of preemption." Pet. App. 23a. That conclusion was incorrect.

It is far from clear whether section 202 addresses the preemptive scope of any part of the FDCA regime other than "the amendments made by" the 1962 Act. *See* U.S. Br. 16. But even if section 202 is relevant here, it would not preclude preemption in this case, because that section does nothing more than make clear that the FDCA does not occupy the entire field of all matters relating to prescription drugs, a claim that is not implicated here. By using the phrase "direct and positive conflict," Congress endorsed application of conflict preemption principles, using language from this Court's decisions with a well-settled meaning that includes both "impossibility" and "obstacle" conflict preemption. *See, e.g.*, *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 242-243 (1859) (finding "direct and positive" conflict between federal and state licensing provisions despite possibility of dual compliance); *Missouri, Kan. & Tex. Ry. Co.* v. *Haber*, 169 U.S. 613, 623 (1898) (test for "direct and positive conflict" is whether state provisions may "stand without obstructing or embarrassing the execution of the act of Congress"); *see also Phillips* v. *General Fin. Corp. of Fla.*, 297 So. 2d 6, 8 (Fla. 1974) (test for "direct and positive conflict" is "whether the state law frustrates the operation of the federal law and prevents the accomplishment of its purpose"); *Oefinger* v. *Zimmerman*, 601 F. Supp. 405, 412-413 (W.D. Pa. 1984) (analyzing whether "direct and positive conflict"

existed between state law and federal law under principle of "obstacle" conflict preemption), *aff'd*, 779 F.2d 43 (3d Cir. 1985); *Conkle* v. *Wolfe*, 722 N.E.2d 586, 593-594 (Ohio Ct. App. 1998) (same). Indeed, as this Court has explained:

> The Court has not previously driven a legal wedge—only a terminological one—between "conflicts" that prevent or frustrate the accomplishment of a federal objective and "conflicts" that make it "impossible" for private parties to comply with both state and federal law. Rather, it has said that both forms of conflicting state law are "nullified" by the Supremacy Clause, and it has assumed that Congress would not want either kind of conflict.

Geier, 529 U.S. at 873 (citations omitted). The Third Circuit recently confirmed this view, holding that the "direct and positive conflict" provision in section 202 "merely states that conflict preemption applies." *Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 262 n.8 (3d Cir. 2008).

Consistent with this case law, Congress used the term "direct and positive conflict" in the 1962 Amendments not to narrow conflict preemption, but to foreclose claims of "field preemption"—which is not at issue here—and avoid the ouster of non-conflicting state-law requirements based on the comprehensiveness of FDA's authority under the 1962 Amendments. As a sponsor of the Amendments explained:

> [T]here are some confusing decisions of the Court which hold that whenever the Congress enacts a law it preempts jurisdiction over all matter contained in the act to the exclusion of all State laws. . . . This would merely say that

> this Food and Drug Act shall not be construed as the intent of Congress to abolish all State laws on the same subject where they are not in conflict with the Federal law.

108 Cong. Rec. 21,083 (1962) (statement of Rep. Smith). That was consistent with a then-recent Supreme Court decision that used the phrase "direct and positive" to distinguish conflict preemption from field preemption. *See United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 & n.5 (1954).[24]

In sum, section 202 does not support the implausible conclusion that Congress would tolerate an actual conflict between state and federal law that defeats the purposes of its own legislation and upsets the carefully crafted balance Congress and FDA have reached between the competing objectives of maximizing safety and maximizing therapeutic benefit. Such a conflict exists here. Respondent's claims are therefore preempted.

---

[24] The Vermont Supreme Court relied solely on the Fourth Circuit's decision in *Southern Blasting Services, Inc.* v. *Wilkes County, North Carolina*, 288 F.3d 584 (4th Cir. 2002). But that decision merely held that a preemption clause requiring "direct and positive conflict" signified only that "Congress did not intend to occupy the field" and "simply restates the principle that state law is superseded in cases of an actual conflict with federal law." *Id.* at 590-591. Although the court recited only the "impossibility" prong of the conflict preemption standard, *id.* at 591, it in fact went on to consider whether the local ordinances at issue could be reconciled with congressional purposes and objectives—the essence of an "obstacle" conflict preemption analysis. *Id.* at 592.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

BERT W. REIN
KARYN K. ABLIN
BRENDAN J. MORRISSEY
WILEY REIN LLP
1776 K Street, NW
Washington, DC 20006
(202) 719-7000

ALLAN R. KEYES
R. JOSEPH O'ROURKE
RYAN, SMITH, CARBINE, LTD.
98 Merchants Row
P.O. Box 310
Rutland, VT 05702-0310
(802) 786-1000

SETH P. WAXMAN
Counsel of Record
PAUL R.Q. WOLFSON
CATHERINE M.A. CARROLL
WILMER CUTLER PICKERING
HALE AND DORR LLP
1875 Pennsylvania Ave., NW
Washington, DC 20006
(202) 663-6000

WILLIAM J. RUANE
WYETH
Five Giralda Farms
Madison, NJ 07940
(973) 660-6105

MAY 2008

No. 06-1249

IN THE
Supreme Court of the United States

WYETH,
Petitioner,

v.

DIANA LEVINE,
Respondent.

On Writ of Certiorari to the Supreme Court of Vermont

BRIEF FOR RESPONDENT

RICHARD I. RUBIN
RUBIN, KIDNEY, MYER & DEWOLFE
237 North Main Street
Barre, Vermont 05641
(802) 479-2514

DAVID C. FREDERICK
Counsel of Record
SCOTT H. ANGSTREICH
SCOTT K. ATTAWAY
BRENDAN J. CRIMMINS
KELLOGG, HUBER, HANSEN, TODD, EVANS & FIGEL, P.L.L.C.
1615 M Street, N.W.
Suite 400
Washington, D.C. 20036
(202) 326-7900

August 7, 2008

QUESTION PRESENTED

Whether Food and Drug Administration ("FDA") approval of a prescription drug's labeling preempts state-law failure-to-warn claims in the absence of any express preemption provision in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, or any evidence that FDA considered the risks and benefits of the specific method of administering the drug that caused the injuries upon which the state-law claim is premised.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Page

CASES

STATUTES AND REGULATIONS

LEGISLATIVE MATERIALS

ADMINISTRATIVE MATERIALS

OTHER MATERIALS

INTRODUCTION

For more than a century, patients injured by dangerous drugs have successfully brought state-law failure-to-warn claims against drug manufacturers. Aware of those state-law remedies, Congress did not include an express preemption provision in the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 301 *et seq*. Nor has it ever added a preemption clause for prescription drugs in numerous statutory amendments to the FDCA, even as it enacted an express preemption provision for medical devices. *See Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 1009 (2008).

Until 2002, the Food and Drug Administration ("FDA") viewed such state-law failure-to-warn claims as complementing federal regulatory efforts by bringing to light drug risks unknown or underappreciated by FDA. Until the 1990s, drug companies rarely invoked preemption, because a widely recognized state-law regulatory-compliance defense enabled defendants to avoid liability when the agency's action disproved negligence.

In this case, Diana Levine's arm was amputated after she developed gangrene from an injection of Wyeth's anti-nausea drug Phenergan. The record established that the intravenous push method used to inject the drug directly into Ms. Levine's arm ("IV push") significantly increased the risks of arterial exposure to Phenergan, which causes gangrene, without providing any countervailing benefit. The evidence further showed Ms. Levine could have received the drug's benefit with virtually no risk of arterial exposure had the drug been administered in other, safer ways. Consistent with the FDCA's misbranding provision, which requires drug labeling to

contain "adequate warnings" against "unsafe dosage or methods or duration of administration or application," 21 U.S.C. § 352(f), the Vermont courts found that Wyeth's failure to warn of the greater risks of IV-push administration of Phenergan, or to instruct clinicians not to use that method of administration, violated a state-law duty to warn.

In asserting preemption, Wyeth claims (at 28) that FDA makes "particularized judgments about the relative risks and benefits" of drugs and their labeling. Contrary to that rhetoric, Wyeth produced no evidence below showing that it ever submitted for FDA consideration, or that the agency performed on its own, a balancing of particularized risks and benefits of IV-push injection versus other forms of administration. Wyeth's claim of conflict preemption, therefore, rests not on any specific conflict between a particular conclusion reached in reviewing the Phenergan labeling and state-law duties to warn, but rather on the mere fact that FDA approved the Phenergan labeling and authorized Wyeth to market the drug. If accepted by this Court, that position would radically change the traditional state-law remedial process that has developed over the past century with congressional acceptance.

In an about-face from the position it had taken since the FDCA's enactment, FDA unconvincingly supports preemption in this case. It offers a never-before-advanced approach to preemption (which Wyeth itself does not advocate), suggesting that failure-to-warn claims should be preempted where FDA has received information about the general risks at issue. That approach, however, would inoculate manufacturers from liability when they advise FDA of side effects without informing physicians of the

significantly greater risks of causing those effects by administering the drug one way instead of through other, safer methods.

This case does not involve a life-saving, but risky, drug made available following full weighing of risks and benefits by FDA and full disclosure to health-care professionals. Rather, it concerns whether a drug manufacturer may be held liable under state law for inadequately warning that one method of administering an anti-nausea drug causes unacceptable risks of amputation. When neither Wyeth nor FDA performed any risk-benefit analysis of different ways of administering Phenergan, preemption simply provides a windfall for the drug maker. It decreases manufacturers' incentives to improve safety and to inform FDA of risks, impedes FDA's ability to protect consumers, and denies compensation to victims of dangerous drugs for catastrophic but avoidable injuries.

STATEMENT

A. Statutory and Regulatory Background

1. In the nineteenth and early twentieth centuries, centralized markets for food and drugs developed to serve growing urban centers. *See* Peter Barton Hutt et al., *Food and Drug Law* 7 (3d ed. 2007) ("*Food and Drug Law*"). Courts routinely recognized failure-to-warn claims and other causes of action for consumers injured by dangerous drugs.[1] Such actions had their roots in cases from "the early days of the common law," when "those engaged in the business of selling

---

[1] *See, e.g.*, *Halloran v. Parke, Davis & Co.*, 280 N.Y.S. 58, 59 (App. Div. 1935) (per curiam); *Blood Balm Co. v. Cooper*, 10 S.E. 118, 119 (Ga. 1889); *Fisher v. Golladay*, 38 Mo. App. 531, 1889 WL 174, at *3-*6 (1889); *Thomas v. Winchester*, 6 N.Y. 397, 407-10 (1852); *Fleet v. Hollenkemp*, 52 Ky. 219, 1852 WL 1716, at *5-*6 (1852).

food intended for human consumption" were first "held to a high degree of responsibility for their products." *Restatement (Second) of Torts* § 402A cmt. b (1965).

Against that backdrop of common-law liability, Congress in 1938 enacted the FDCA "for the purposes of safeguarding the public health [and] preventing deceit upon the purchasing public." H.R. Rep. No. 75-2139, at 3 (1938). The Act's "high purpose" was "to protect consumers." *Kordel v. United States*, 335 U.S. 345, 349 (1948); *see also United States v. Dotterweich*, 320 U.S. 277, 280, 282 (1943) (FDCA protects the health and safety of consumers, which, "in the circumstances of modern industrialism, are largely beyond self-protection"). It required manufacturers for the first time to submit to federal safety review before marketing drugs. *See* FDCA § 505, 52 Stat. 1052-53.

A fundamental provision of the FDCA – then, as now – prohibits selling misbranded or adulterated products in interstate commerce. *See id.* §§ 301(a)-(c), 501-502, 52 Stat. 1042, 1049-51 (codified as amended at 21 U.S.C. §§ 331(a)-(c), 351-352). An early version of the bill that became the FDCA included a federal private right of action for injured consumers. *See* H.R. 6110, 73d Cong. § 25 (1933). Witnesses testified that the provision was unnecessary because long-standing state-law remedies protected consumers,[2] and Congress omitted it from the enacted legislation.

---

[2] *See, e.g.*, *Food, Drugs, and Cosmetics: Hearings on S. 1944 Before a Subcomm. of the S. Comm. on Commerce*, 73d Cong. 400 (1933) (statement of W.A. Hines) (recommending federal right of action "be stricken from the bill on the ground that it is unnecessary" because "common-law right of action exists"); *id.* at 403 (statement of J.A. Ladds) ("This act should not attempt

2. When Wyeth's application to market Phenergan became effective in 1955 (JA267), the FDCA prohibited selling in interstate commerce a "new drug" – one not generally recognized by experts as safe for its intended use, *see* 21 U.S.C. § 321(p) (1952) – unless "an application" filed under the Act was "effective with respect to such drug." *Id.* § 355(a). Applicants had to submit reports of investigations and other materials "to show whether or not such drug is safe for use," as well as "specimens of the labeling proposed to be used for such drug." *Id.* § 355(b). FDA could "issue an order refusing to permit the application to become effective" only if the drug had not been shown to be "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." *Id.* § 355(d).

If FDA failed to act, the application typically became effective 60 days after filing. *Id.* § 355(c). Subsequently, FDA could suspend the application's effectiveness if it found the drug unsafe or the application contained a material misstatement. *Id.* § 355(e). The FDCA provided for judicial review of an FDA order "refusing to permit [an] application to become effective, or suspending the effectiveness of the application," but not where FDA permitted an application to become effective. *Id.* § 355(h). Indeed, Congress has never authorized judicial review of FDA approval of a new-drug application. By contrast, in 1976, Congress provided for judicial review of the approval of an application to market a medical device. *Compare id. with* 21 U.S.C. § 360g(a)(4).

When Congress passed the Drug Amendments of 1962 ("1962 Amendments"), it required for the first

---

to modify or restate the common law with respect to personal injuries.").

time that "new drugs meet an additional test of 'effectiveness' in addition to the existing test of 'safety.'" S. Rep. No. 87-1744, at 9-10 (1962). Whereas the 1938 Act permitted applications to take effect upon FDA inaction, the 1962 Amendments required FDA to "approve" a new-drug application. *Compare* FDCA § 505(c), 52 Stat. 1052, *with* 1962 Amendments § 104(b), 76 Stat. 784.

Even as the 1962 Amendments strengthened FDA's premarket-review authority, Congress made clear that

> [n]othing in the amendments made by this Act to the [FDCA] shall be construed as invalidating any provision of State law which would be valid in the absence of such amendments unless there is a direct and positive conflict between such amendments and such provision of State law.

1962 Amendments § 202, 76 Stat. 793.

State-law actions against drug manufacturers continued after the FDCA's enactment,[3] with courts rejecting arguments that the FDCA preempted such claims in the rare instances in which manufacturers raised that defense.[4]

---

[3] *See*, *e.g.*, *McEwen v. Ortho Pharm. Corp.*, 528 P.2d 522, 528 (Or. 1974) ("well settled" that drug maker "bears [a] duty of making timely and adequate warnings"); *see also Riegel*, 128 S. Ct. at 1017 & n.11 (Ginsburg, J., dissenting) (collecting cases); W. Page Keeton, *Prosser and Keeton on the Law of Torts* 688 (5th ed. 1984); Janet Fairchild, Annotation, *Liability of Manufacturer or Seller for Injury or Death Allegedly Caused by Failure To Warn Regarding the Danger in Use of Vaccine or Prescription Drug*, 94 A.L.R.3d 748 (1979).

[4] "Courts that have considered the question have overwhelmingly held that FDA approval of a new drug application does not preempt state tort suits." *Riegel*, 128 S. Ct. at 1018-19

3. To further the FDCA's purpose of ensuring accurate labeling bearing adequate warnings and instructions, *see* 21 U.S.C. §§ 331(a)-(c), 352(a), (f), FDA regulations have long permitted and encouraged drug manufacturers to update their labels to provide physicians with the most current information about the risks of their products, *see*, *e.g.*, 21 C.F.R. § 1.110(d) (1955) (authorizing "supplemental application" proposing changes in "labeling").

In 1965, FDA determined that certain important safety-based labeling changes should be implemented "at the earliest possible time." 30 Fed. Reg. 993, 993 (1965). Under FDA's amended rule, a manufacturer could augment the labeling with an "additional warning, contraindication, side-effect, and precaution information" when it submitted a supplemental application covering the change, without waiting for FDA's approval. *Id.* at 993-94 (promulgating 21 C.F.R. § 130.9(d)(1), (e) (1965)).

Consistent with Congress's purpose in the FDCA to protect consumers and the public health by prohibiting false and misleading labels, that regulation today provides that a drug manufacturer can make "[c]hanges [in] labeling" – *without* prior FDA approval – "[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 product." 21 C.F.R. § 314.70(c)(6)(iii)(A), (C). Under § 314.70(c)(6) – known as the "changes being effected" ("CBE") regulation – such labeling changes can be implemented when FDA receives the supplemental application reflecting the change

---

(Ginsburg, J., dissenting) (collecting cases, *see id.* at 1017-19 & nn.11, 16).

and before FDA acts on that application. *See id.* § 314.70(c)(6).

Further, FDA has long required manufacturers to revise drug labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." *Id.* § 201.80(e). As FDA explained when promulgating that regulation, "it is *essential* to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it"; "the act requires labeling to include warnings about both *potential* and verified hazards"; and the agency "believes that practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." 44 Fed. Reg. 37,434, 37,443, 37,447 (1979) (emphases added).[5]

4. FDA has consistently encouraged manufacturers voluntarily to update their labeling because, at all times relevant to this case, it lacked the power to compel manufacturers to make specific labeling changes. As a senior FDA official testified to Congress in 2005, if FDA believed that a labeling change was necessary, it had to "negotiate" with the manufacturer because it did not have "the authority to tell a company, this is how your label has to look."[6] FDA's only recourse if a manufacturer refused to implement a labeling change was to withdraw its

---

[5] *See also Werner v. Upjohn Co.*, 628 F.2d 848, 860 (4th Cir. 1980) ("FDA's regulations and policies encourage early unilateral action by the drug companies to improve their warnings").

[6] *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the S. Comm. on Health, Education, Labor, and Pensions*, 109th Cong. 23 (2005) (testimony of Sandra Kweder, M.D., Deputy Director, Office of New Drugs, FDA).

approval of the application under § 355(e)[7] or to initiate a misbranding action in federal court, with the misbranding question typically decided by a federal jury, *see* 21 U.S.C. §§ 331(a), 332, 333(a), 334(a)-(b).[8]

B. FDA Regulation of Phenergan

1. Phenergan is an anti-nausea drug prescribed and administered by physicians. JA38, 85, 390-91. It has a dangerous side effect: when exposed to arterial blood, Phenergan causes swift and irreversible gangrene. JA239 (Finding of Fact ("FOF") 1); JA57-59, 72-73.

In accordance with the labeling in effect at the time of Diana Levine's injury, Phenergan can be administered through an injection into the patient's muscle – intramuscular (IM) injection – or it can be introduced into the patient's vein. JA391.[9] Intravenous (IV) administration can be performed in two ways. In the first – "IV drip" – the medication is placed into a stream of saline flowing from a hanging IV bag into a vein in the patient's arm. JA49-51, 66-68, 239-40 (FOF 2). In the second – "IV push" – a medical practitioner injects the medication directly into the patient's vein using a syringe. JA46-47, 52-53, 88, 92.

---

[7] FDA took that step only once, more than 30 years ago, in a case concerning a lethal side effect, not a labeling issue. *See* U.S. Gov't Accountability Office, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process* 10 n.19 (Mar. 2006) ("GAO Drug Safety Report").

[8] The Food and Drug Administration Amendments Act of 2007 ("2007 Amendments") provided FDA with limited authority to order labeling changes after first negotiating with the manufacturer. *See* Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 924-26 (codified at 21 U.S.C. § 355(*o*)(4)).

[9] A vein carries blood back to the heart; an artery carries blood from the heart to the capillaries of organs and tissue.

With IV push, Phenergan can be exposed to arterial blood inadvertently if the medical professional either punctures an artery directly or pierces the other side of the vein, causing the medication to "extravasate" – or exude from the vein – into the surrounding tissue and bathe an artery. JA67, 71, 240 (FOF 3). Even an experienced clinician exercising due care will, on occasion, inadvertently expose the medication to the patient's artery, rather than injecting it entirely into the vein. JA73, 75-76. Some patients have so-called "aberrant" arteries near the veins in their arms, thus heightening the risk of inadvertent arterial exposure from IV-push administration of Phenergan. JA54-55, 75-76, 78.

The IV-drip technique works differently. An IV drip is started with saline, which will not flow properly if the catheter is not entirely within the vein. Back-pressure from an artery will prevent the fluid from flowing into an artery; if the fluid is flowing into the tissue surrounding the vein, it fills the available space and has nowhere to go. Thus, at the outset of the IV-drip procedure, before any medication is introduced, the medical professional can readily determine whether the saline is flowing into the vein or escaping into an artery or surrounding tissue. JA49-51, 60, 66-68, 74-75, 108-09, 240 (FOF 4).

2. In 1967, Wyeth reported to FDA an adverse reaction evidently caused by exposure of Phenergan to blood in a patient's artery through a method of intravenous administration Wyeth did not identify to FDA and does not here assert to have been IV push (Br. 12). Although Phenergan's "direction circular" at that time warned against intra-arterial injection, a physician administering the drug intravenously nonetheless inadvertently caused the drug to enter

the patient's artery, causing "gangrene of the arm and subsequent amputation." JA268-69.

In 1973, Wyeth submitted a supplemental application for Phenergan that included revised labeling. JA270. FDA "recommend[ed]" a series of changes to Wyeth's proposed package insert. JA271. One was to change the "Warnings" section to note that the "intravenous use of" Phenergan "is not without hazard." *Id.* That suggestion duplicated the statement in the "Dosage and Administration" section that "proper intravenous administration of promethazine hydrochloride is well tolerated, but use of this route is not without some hazard." JA277.

In 1975, Wyeth submitted another supplemental application containing revised labeling for Phenergan. JA280. FDA again wrote Wyeth with revisions that "should" be made to the proposed label. *Id.* Most did not pertain to the risk of arterial exposure. JA280-86. FDA suggested that a warning, in capital letters, about arterial exposure be included in the "Cardiovascular Effects" section. JA283. FDA also recommended an addition to the Warnings section to clarify that medical practitioners cannot rely on the color of the blood drawn back into an intravenous setup to determine whether it is venous (dark red) or arterial (bright red) blood, because Phenergan discolors arterial blood. JA282. Consistent with FDA's lack of authority to require label changes for previously authorized drugs, *see supra* p. 8, Wyeth declined to implement many of FDA's recommendations. *Compare* JA281 (FDA recommending a warning to reduce dosages for elderly patients) *with* JA290 (noting that Wyeth "disagree[d]" with that recommendation).

In 1976, an FDA advisory committee met to discuss a number of topics, including revisions to the proposed Phenergan package insert that FDA had suggested and Wyeth had rejected. JA287-95.[10] Disagreeing with FDA, the committee "had no objections" to Wyeth's proposal to continue to contraindicate – that is, recommend against – arterial injection of Phenergan (FDA evidently had opposed the contraindication as unnecessary, because "arterial injection is not an acceptable means of administering drugs"). JA289. The committee also recommended warning practitioners to inject the drug "into a satisfactorily functioning intravenous set." JA294. Nothing in the advisory committee's minutes indicates that it considered (or was asked to consider) whether to include a specific warning about IV-push injection or to recommend against IV-push injection entirely.

In 1979, FDA promulgated a rule to standardize the formatting of prescription drug labeling. Although FDA required manufacturers to submit reformatted labeling for approval, it made clear that the rule did not supersede provisions allowing manufacturers to change labeling to add or strengthen a warning.[11] FDA also specified that it did not "inten[d]" "to influence the civil tort liability of the manufacturer," 44 Fed. Reg. at 37,437, and cited approvingly a state appellate decision upholding a plaintiff's verdict in a

---

[10] FDA uses advisory committees of outside experts to advise it on a variety of issues. *See generally Food and Drug Law* 1573-88.

[11] *See* 44 Fed. Reg. at 37,438 ("Labeling revisions that may be placed into effect without FDA approval, such as the addition of a warning," would not require "the revision of the labeling to comply with these final regulations in advance of the scheduled revision date for the drug.").

failure-to-warn case, *see id.* at 37,447 (citing *McEwen v. Ortho Pharm. Corp.*, *supra*).

In 1981, Wyeth filed a supplemental application proposing revised Phenergan labeling to comply with the 1979 rule. JA297-306. In 1987, FDA recommended revisions to, among other things, the proposed warning on intra-arterial injection. JA311-15. Neither Wyeth's proposal nor FDA's recommended revisions restricted use of IV-push administration. *Compare* JA300-06 *with* JA310-19. In 1988, Wyeth submitted revised labeling incorporating FDA's requested revisions, along with additional changes of its own. *Compare* JA325-26, 328-30, 334-35, 339-41 *with* JA311-15.

In 1996, FDA requested from Wyeth the package insert then in use for Phenergan. JA347. In 1997, FDA informed Wyeth that its proposed labeling revisions were "approvable" subject to certain further revisions. JA355-56. Relevant here, FDA did not endorse its 1987 proposed revisions (JA311-15) to the warning on inadvertent intra-arterial injection. It stated – without further explanation – that Wyeth instead should "[r]etain verbiage in current label," meaning the version of the label Wyeth submitted at FDA's request in 1996. JA350, 359. The government here explains that statement as follows: "it appears that FDA viewed the change" Wyeth submitted in 1988 at FDA's request "as non-substantive and rejected it for formatting reasons." U.S. Br. 25. Subsequently, in 1998, Wyeth submitted revised labeling incorporating FDA's comments, along with further modifications of its own. JA366-80. Later that year, FDA completed its "review" of Wyeth's 1981 supplemental application. JA382.

As Wyeth and the government here do not dispute, the correspondence between Wyeth and FDA provides no indication that the agency considered (at Wyeth's request or on its own) whether Phenergan's labeling should bear a specific warning on or prohibition of IV-push injection.

C. Ms. Levine's Injury

On April 7, 2000, Diana Levine went to a clinic near Marshfield, Vermont to treat a migraine headache. She received an intramuscular injection of Demerol (for her headache), along with Phenergan (for nausea, which is associated with a migraine headache and is a common side effect of Demerol). JA38, 237-38; Pet. App. 2a. After Ms. Levine's migraine recurred later that day, she returned to the clinic, where she received a second Demerol-Phenergan combination. In accordance with the instructions in Phenergan's package insert, the physician's assistant administered this dose of Phenergan through an IV-push injection into Ms. Levine's right arm. JA52-53, 88, 92, 104-06, 109-10, 191, 199, 210; Pet. App. 2a.

During the IV-push injection, the Phenergan penetrated one of Ms. Levine's arteries. JA240 (FOF 3); JA58. In the ensuing weeks, the tissue in her right forearm died and she experienced extreme pain. JA55-57, 127, 133-35, 154-55, 162-63, 165-68, 178-79; JA166 (expert testimony that the pain was "a ten" on a "[p]ain scale[]" of "one to ten"). Her fingers slowly turned black as they lost all blood circulation.[12]

Doctors initially amputated Ms. Levine's hand. JA163. After several days, during which the gangrene

---

[12] *See* JA386-89 (before-and-after-injury photographs of Ms. Levine's arm).

spread down her forearm and Ms. Levine continued to experience excruciating pain, she underwent a second operation to amputate what was left of her forearm below her elbow. JA163-64. After her amputations, Ms. Levine has continued to experience physical and "phantom pain" in her right arm and tendonitis from over-using her left arm, while enduring emotional trauma and depression. JA156-57, 159-62, 169-72.

Before her injury, Ms. Levine was a professional musician who developed musical programs to perform with children. JA117-26, 130-32, 136-37, 386. She also performed live concerts and recorded her music for sale. JA118-19, 122-23, 132. After her arm was amputated, Ms. Levine could no longer play her guitar – her profession and lifelong passion. JA120. She struggles to perform daily tasks and household chores, and can no longer participate in outdoor activities she once enjoyed. JA123-24, 128-29, 137-54, 157-58, 168-69. She lost her livelihood and incurred hundreds of thousands of dollars in medical bills. JA173-76.

D. Proceedings Below

1. In Vermont Superior Court, Ms. Levine asserted state-law negligence and products-liability claims premised on Wyeth's failure to provide proper warnings and instructions regarding the foreseeable risks of IV-push injection of Phenergan. JA227-32. The amended complaint alleged that Phenergan was defective because, among other things, the company failed to instruct clinicians to administer the drug intravenously using the IV-drip technique. JA14 (¶ 5). Ms. Levine sought only damages, not an injunction requiring any labeling change. JA17.

The trial evidence, which the Court views in the light most favorable to Ms. Levine's verdict,[13] demonstrated that inadvertent arterial exposure – causing gangrene requiring amputation – can result from IV-push administration, even when performed by an experienced clinician. JA73, 75-76. Administering Phenergan using the IV-drip technique, by contrast, "almost precludes" inadvertent arterial contact. JA67; *see* JA49-51, 60, 66-68, 74-75, 108-09, JA240 (FOF 4). Further, the only benefit of IV-push administration, as compared to IV drip, is marginally faster relief from nausea. JA104, 106. Experts testified at trial that any such benefit would never justify a significantly increased risk of gangrene and that, if Phenergan is used intravenously, it should be injected only through a hanging IV bag and Wyeth's package insert should have precluded IV-push administration. JA59, 77-80, 96, 108-09; *see also* JA112 ("It's nausea. . . . [T]his isn't a heart attack, this is somebody who's sick to their stomach.").

A Wyeth expert testified that he could "conceive of" a circumstance in which IV-push injection of Phenergan might "theoretically" be medically appropriate – namely, if the patient had "been vomiting to the point of severe hypobulimia, fluid depletion, veins are very tough to get into." JA195. That expert also acknowledged, however, that he would hesitate to use IV-push injection in non-life-threatening situations and that he would have written the label to instruct that Phenergan be administered intravenously only through the IV-drip method. JA192-94. Another Wyeth expert, who neither treated migraines nor prescribed anti-nausea medications,

---

[13] *E.g.*, *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 213 (1993).

testified that the benefits of intravenous administration of Phenergan outweighed its risks in some circumstances, but he did not offer that opinion with respect to *IV-push* injection. JA200-01, 207-10.[14] (Wyeth offered no evidence it ever submitted or FDA considered analyses of such facts in making any labeling judgments concerning Phenergan.)

Wyeth also contended that the physician's assistant who administered the IV-push injection of Phenergan, not Wyeth, bore sole responsibility for Ms. Levine's injury (an argument Wyeth reiterates here, Br. 19-20 & n.10). Specifically, Wyeth alleged that the physician's assistant negligently administered the drug by continuing the injection after Ms. Levine cried out in pain and by exceeding the recommended dosage.

Ms. Levine's evidence rebutted Wyeth's attempt to blame the physician's assistant. The physician's assistant testified that, although Ms. Levine said that the medicine "burned," she completed the injection because the injection site looked fine, the Phenergan was flowing normally, and Ms. Levine's complaints of discomfort were not unusual. JA111, 116; *see also* JA185 (testimony of Ms. Levine that she did not scream). Testimony also established that stopping the injection when Ms. Levine expressed discomfort would not have prevented her injury. JA57-59, 239 (FOF 1); *see also* JA72-73, 80. In addition, an expert testified that, although the label stated that the "usual" dose for nausea was 12.5 to 25 milligrams (JA391), a 50-milligram dose was appropriate under the circumstances. JA41; *see also* JA105.

---

[14] *Compare* JA84 (testimony of Dr. Harold Green that he could not recall a case in which a patient needed immediate relief of nausea).

2. The trial judge instructed the jury that "the disputed issue is whether the warning and instructions provided by Wyeth were adequate concerning the risks of injection of [Phenergan]. The warning must reasonably advise of the risks and provide adequate instructions to the medical professionals for its safe use." JA231-32. The judge also instructed the jury on Wyeth's regulatory-compliance defense, explaining that the jury could "consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning." JA227. The instructions explained that FDA's CBE regulation permits drug makers to change their labels without prior FDA approval to add or strengthen a warning. JA228. Wyeth did not object to those instructions, although it objected to others. JA223.

In the summation, Ms. Levine's counsel told the jury, "You will make the decision" whether Wyeth adequately warned against arterial exposure during IV-push injection of Phenergan. JA211. That statement accurately reflected the trial record: because Wyeth introduced no evidence that FDA ever considered (or was asked to consider) the relative benefit of relieving nausea a few minutes faster versus the risk of losing a limb – or the associated risks of IV push versus other methods of administration – the decision whether Wyeth adequately warned of IV-push injection risks was for the properly instructed jury to make.

In its verdict, the jury specifically rejected Wyeth's contention that unforeseeable negligence of the physician's assistant, rather than Wyeth's failure to warn, caused Ms. Levine's injury. JA233-35; *see also* JA230-32, 252 (intervening-cause issue "raises factual issues which were argued to the jury and

resolved in plaintiff's favor at trial"). The jury awarded damages to compensate Ms. Levine's economic and non-economic losses – including past and future medical expenses and the loss of her ability to earn a living (evidence Wyeth did not dispute, *see* JA259). The trial judge found Ms. Levine's injuries to be "tragic," "horrific," and "as bad an injury case as any court is likely to see." JA258-59.

The trial court denied Wyeth's post-judgment motion asserting preemption. The court recognized that Wyeth could comply with both Vermont law and federal law, because FDA's CBE regulation permitted Wyeth to change its labeling to prohibit IV-push administration or strengthen the warnings about IV push without prior FDA approval. JA250-51. (Wyeth never asserted at trial that the CBE regulation applied only to labeling changes based on "new" information.)

The court also held that its judgment posed no obstacle to Congress's purposes in the FDCA. It found "no evidence in this record that either the FDA or the manufacturer gave more than passing attention" to whether the label should preclude IV-push injection. JA249. It further explained that this case posed little or no risk that an unwarranted warning might deter beneficial uses of a drug, because Ms. Levine's claim related "only to the method of administration, not to the decision to use Phenergan." JA250. That made this case "different from cases involving proposed warnings of remote side effects [that] might dissuade physicians from using the drug to the detriment of the patient population." *Id.*

3. The Vermont Supreme Court affirmed, concluding that Wyeth had shown no "actual[] conflict[]" between the trial court's judgment and federal law.

Pet. App. 8a (internal quotation marks omitted). The court explained that compliance with both federal law and a state-law duty to warn is possible, because FDA's regulations "allow[], and arguably encourage[], manufacturers to add and strengthen warnings that, despite FDA approval, are insufficient to protect consumers." *Id.* at 11a (citing 21 C.F.R. § 314.70(c)); *see id.* at 17a. "State tort claims," the court explained, "simply give these manufacturers a concrete incentive to take this action as quickly as possible." *Id.* at 11a.

The court further found that the "record lacks any evidence" that FDA would have "prohibited the use of a stronger warning with respect to IV-push administration of Phenergan." *Id.* at 16a. As the court reasoned, "[n]either the letters [Wyeth and FDA exchanged] nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan." *Id.* at 17a; *see also id.* at 18a n.2.

The court also rejected Wyeth's argument that the trial court's judgment posed an obstacle to Congress's objectives in the FDCA. *See id.* at 15a, 19a. It explained that "there is no conflict between federal objectives and Vermont common law," because "FDA and the state share the purpose of encouraging pharmaceutical companies to alter their drug labels when they are inadequate to protect consumers." *Id.* Chief Justice Reiber dissented. *Id.* at 35a-48a.

SUMMARY OF ARGUMENT

I. Because this Court presumes that Congress "does not cavalierly pre-empt state-law causes of action," *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996), Wyeth must demonstrate clear congressional intent to preempt Ms. Levine's claims. Wyeth cannot do so.

When Congress enacted the FDCA, a well-established body of state-law remedies existed for patients injured by defective drugs – including drugs lacking adequate warnings and instructions. Against that backdrop, Congress in the FDCA neither provided a federal right of action nor expressed any intent to preempt state-law actions. In the 70 years since the FDCA was enacted, courts have continued to adjudicate state-law failure-to-warn claims, and Congress has amended the statute on numerous occasions. Although it chose expressly to preempt claims against device manufacturers, it never passed a similar provision for drug makers. Moreover, Congress took other actions that would have been meaningless if the FDCA already had immunized drug manufacturers from lawsuits. That statutory history reinforces that Congress never intended the FDCA to preempt state-law claims.

II. Ms. Levine's state-law claim is not impliedly preempted on the ground that it is "impossible" to comply with both state and federal law.

A. The FDCA does not preclude drug manufacturers from adding or strengthening warnings or instructions regarding their products. Wyeth could have added a stronger warning against IV-push injection at the inception of its FDA approval process or after the drug was approved, through a labeling change.

Without any textual support for its conflict preemption argument, Wyeth erroneously contends that it would be liable for misbranding or distributing an unauthorized new drug if it complied with the state-law duty to warn of IV-push risks. A drug is not misbranded if it contains true and accurate information about the risks associated with a particular method of administration. There is no credible claim that a court would have rejected a stronger warning or instruction regarding IV-push injection. And Wyeth's criticisms of juries are misdirected, because federal juries decide allegations of misbranding. Nor would adding or strengthening a warning or instruction regarding IV push have transformed Phenergan into an unauthorized new drug. Its use would have been for the same purpose; the only changes would warn of significantly greater risks from IV-push injection versus other forms of administration.

B. Federal law did not prohibit Wyeth from providing a stronger warning or instruction regarding IV-push injection. Wyeth could have strengthened the Phenergan labeling initially or changed it after FDA approval consistent with FDA regulations. FDA seeks all relevant risk information prior to a drug's approval, and the CBE regulation, 21 C.F.R. § 314.70(c)(6), permits manufacturers to change drug labeling to add or strengthen a warning or instruction. Wyeth and the government argue that the CBE regulation does not apply here because CBE supplements must be based on newly discovered risk information. But the regulation's text contains no such limitation. And the government cannot claim deference for its a-textual interpretation of the CBE regulation, both because the regulation's language contains no ambiguity and because courts do not

defer to agency efforts to re-write regulations through purported interpretation. In any event, FDA has interpreted its CBE rule to permit labeling changes based on re-analysis of existing information, which Wyeth should have done with Phenergan.

C. Because Ms. Levine did not seek (and was not awarded) injunctive relief, Wyeth could comply with the judgment below by paying the damages awarded to Ms. Levine for her injuries. The incidental regulatory consequences of tort judgments do not create impossibility conflicts with the federal regime, which still permits Wyeth to sell its drug and enables the manufacturer to conduct its own cost-benefit analysis of compliance with state-law duties of due care in particular factual circumstances.

III. The Vermont judgment poses no obstacle to Congress's purposes in the FDCA. On the contrary, state and federal law impose complementary duties. Both Vermont law and the FDCA require drug manufacturers to provide adequate warnings and instructions regarding their products. As this Court's cases recognize, state-law claims promote federal labeling rules by encouraging manufacturers to discover and to disseminate the most current information about the risks of their products. Vermont law also follows the general rule permitting manufacturers to present evidence of compliance with the FDCA and FDA regulations in defending failure-to-warn suits. Through the regulatory-compliance defense, state law supports the federal regulatory scheme by providing a compensatory mechanism federal law lacks and an additional incentive for manufacturers to use due care in providing appropriate warnings.

Wyeth argues, however, that the Vermont judgment poses an obstacle to the federal regime because

FDA balanced the relevant risks and benefits and determined that the Phenergan labeling regarding IV-push injection was appropriate. But, as the Vermont courts found, the record contains no evidence that FDA ever weighed the risks and benefits of *IV-push* administration of Phenergan or made a judgment that some benefit of IV-push injection in treating nausea justified its increased risks of gangrene requiring amputation. Thus, the Vermont courts' determination that Phenergan's labeling inadequately warned of the risks of IV-push injection did not contradict any deliberate federal judgment.

The government asserts that a state-law claim is preempted so long as the agency knew the relevant risk – broadly defined – when it approved the labeling. That new and overly broad position would eliminate state-law remedies without requiring proof that FDA made a judgment conflicting with the state-law duty in question. Here, the issue is not knowledge that arterial exposure to Phenergan causes gangrene; rather, it is knowledge that the IV-push administration method poses significantly higher risks of that adverse effect without any countervailing benefit. Because FDA took no action on IV push from any Wyeth submission or on its own, conflict preemption is inapplicable.

Finally, the Court should give no weight to the government's view that the FDCA preempts state-law claims. As the government concedes, any weight given to its views would be determined in accordance with *Skidmore v. Swift & Co.*, 323 U.S. 134 (1944). But even *Skidmore* consideration must take into account the inconsistency and current unpersuasiveness of FDA's positions. FDA's assertion now that the FDCA generally preempts state-law failure-to-

warn claims represents a policy reversal – not a law-based change – when for many decades FDA viewed common-law claims as complementary to its regulatory efforts.

ARGUMENT

Preemption "fundamentally is a question of congressional intent." *English v. General Elec. Co.*, 496 U.S. 72, 78-79 (1990); *see Puerto Rico Dep't of Consumer Affairs v. Isla Petroleum Corp.*, 485 U.S. 495, 503 (1988) ("There is no federal pre-emption *in vacuo*, without a constitutional text or a federal statute to assert it."). Accordingly, the "purpose of Congress is the ultimate touchstone of pre-emption analysis." *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504, 516 (1992) (internal quotation marks omitted).

Because Congress included no express preemption provision in the FDCA and because Wyeth concedes (at 52-53) that the FDCA does not preempt the field of drug labeling,[15] Wyeth can prevail only by demonstrating that Vermont law "actually conflicts" with federal law. *English*, 496 U.S. at 79. An "actual conflict" exists when "it is impossible for a private party to comply with both state and federal requirements, or where state law stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress." *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002) (citations and internal quotation marks omitted). Conflict-

---

[15] *See also* JA261-62 (Wyeth counsel oral argument, Vermont Supreme Court) ("Wyeth is not contending for a field preemption, for the ouster of Vermont law, tort law, not at issue here. . . . [N]or are we arguing that the mere compliance with the federal labeling requirements in and of itself creates a conflict preemption[.]"); Pet. App. 8a (noting Wyeth's "conce[ssion]" on this point).

preemption analysis is not, however, a "'freewheeling judicial inquiry into whether a state statute is in tension with federal objectives,' but an inquiry into whether the ordinary meanings of state and federal law conflict." *Bates v. Dow AgroSciences LLC*, 544 U.S. 431, 459 (2005) (Thomas, J., concurring in the judgment in part and dissenting in part) (quoting *Gade v. National Solid Wastes Mgmt. Ass'n*, 505 U.S. 88, 111 (1992) (Kennedy, J., concurring in part and concurring in the judgment)) (citation omitted). Ms. Levine's state-law claims readily survive implied conflict preemption.

I. CONGRESS'S LONG ACCEPTANCE OF STATE-LAW FAILURE-TO-WARN CLAIMS AGAINST DRUG MANUFACTURERS DECISIVELY UNDERMINES WYETH'S IMPLIED PREEMPTION ARGUMENT

In the FDCA, Congress emphasized consumer safety as a paramount goal. To that end, it established that:

- Introduction of any "misbranded" drug would be "prohibited," 21 U.S.C. § 331(a);
- A drug label would be "misbranded" if "false or misleading in any particular," *id.* § 352(a); and
- Such labeling would be misbranded if it lacked "adequate warnings . . . against unsafe dosage or methods or duration of administration or application," *id.* § 352(f).

Under Vermont law, as in states generally, a failure-to-warn claim imposes on drug companies "a duty to take reasonable steps to notify users of the product – in this case the medical community – of the risks and dangers of the product and to provide adequate instructions about how to use the product

safely." JA228 (jury instructions). Such claims directly parallel federal misbranding requirements. *Cf.* 21 U.S.C. § 352(f).

The long history of state-law failure-to-warn claims against pharmaceutical manufacturers, *see supra* notes 1 & 3, and Congress's consistent acceptance of such actions, undermine Wyeth's assertion that state-law claims conflict with federal law. In evaluating preemption of longstanding state-law remedies, this Court's decisions require a "clear[]" indication of Congress's intent. *Bates*, 544 U.S. at 449.[16]

A. In The FDCA And Its Amendments, Congress Expressed No Intent To Preempt State-Law Failure-To-Warn Claims Against Drug Manufacturers

Congress has never enacted a prescription-drug preemption provision, despite numerous opportunities to do so. Its enactment of a preemption provision for medical devices, but not drugs, strongly signals its intent to preserve state-law remedies against pharmaceutical manufacturers. *See Riegel*, 128 S. Ct. at 1009 ("Congress could have applied the pre-emption clause" in the Medical Device Amendments of 1976 "to the entire FDCA," but it "instead wrote a pre-emption clause that applies only to medical devices"); *see also id.* at 1017 (Ginsburg, J., dissenting) ("Nothing in the FDCA's text or legislative history suggested that FDA preclearance would immunize drug manufacturers from common-law tort suits."). In fact, Congress demonstrated its intent to preserve state-law claims by declining to include in the 1938

---

[16] *See Lohr*, 518 U.S. at 485; *Silkwood v. Kerr-McGee Corp.*, 464 U.S. 238, 251 (1984); *see also Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166-67 (1989).

Act a federal private right of action against drug makers based on testimony that state-law remedies were sufficient. *See supra* p. 4 & n.2.

Against that backdrop of existing common-law claims and precedent rejecting assertions of preemption, subsequent congressional actions bolster the inference that Congress has not intended to preempt state-law damages suits against drug manufacturers.[17] In 1997, for example, Congress added provisions pre-empting some state statutory and regulatory requirements for over-the-counter drugs. *See* Food and Drug Administration Modernization Act of 1997 ("1997 Act"), Pub. L. No. 105-115, § 412(a), 111 Stat. 2296, 2373-75 (codified at 21 U.S.C. § 379r(a)-(d)). The new section expressly disclaimed any effect on "the liability of any person under the product liability law of any State." *Id.* at 2375 (codified at 21 U.S.C. § 379r(e)).[18] And, in 1995, the House passed a bill to eliminate punitive, but not compensatory, damages recoverable against drug manufacturers where FDA approved the drug's "labeling." H.R. 956, 104th Cong. § 201(f) (1995) (as passed by House, Mar. 10,

---

[17] *Cf. FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 143-59 (2000); *Albemarle Paper Co. v. Moody*, 422 U.S. 405, 414 n.8 (1975); *cf. also Branch v. Smith*, 538 U.S. 254, 280-81 (2003) (plurality opinion).

[18] *See* S. Rep. No. 105-43, at 66 (1997) ("[T]he legislation explicitly provides that it shall not be construed to modify or otherwise affect the traditional product liability law of any State. Tort liability rules and requirements would remain unchanged and unaffected."); *see also* 1997 Act § 131, 111 Stat. 2332 (requiring manufacturers of life-saving drugs to provide FDA six months' notice before discontinuing manufacture of such a drug and reducing period if "a *liability problem* may exist for the manufacturer if the manufacturing is continued") (emphasis added) (codified at 21 U.S.C. § 356c(b)(3)).

1995). That bill also would have limited non-economic damages to $250,000 in "any health care liability action," defined to include actions against "the manufacturer" of "a medical product." *Id.* § 203(a), (c)(3).[19]

The 1995 and 1997 bills would have been largely meaningless if state tort suits against drug manufacturers – the vast majority of which were failure-to-warn claims[20] – had already been preempted.

B. The Statutory History Supports A Presumption Against Preemption

The absence of any FDCA preemption clause for prescription drugs, combined with subsequent congressional actions that make sense only against the backdrop of state-law liability, confirms the importance of applying this Court's longstanding presumption against preemption. The Court has "never assumed lightly that Congress has derogated state regulation, but instead ha[s] addressed claims of pre-emption with the starting presumption that Congress does not intend to supplant state law." *New York State Conference of Blue Cross & Blue Shield Plans v. Travelers Ins. Co.*, 514 U.S. 645, 654-55 (1995). That presumption against preemption "provides assurance that the federal-state balance will not be disturbed unintentionally by Congress or unnecessarily by the courts." *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (citation and internal

---

[19] A subsequent version of the legislation passed both houses of Congress, but was vetoed. *See* 32 Weekly Comp. Pres. Doc. 780 (May 2, 1996).

[20] *See Restatement (Third) of Torts: Products Liability* § 6 cmt. d (1998) ("[f]ailure to instruct or warn is the major basis of liability for manufacturers of prescription drugs").

quotation marks omitted); *see also Lohr*, 518 U.S. at 485.[21] Wyeth therefore must show a conflict between the FDCA and the Vermont judgment "that is strong enough to overcome the presumption that state and local regulation of health and safety matters can constitutionally coexist with federal regulation." *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 716 (1985).[22]

Wyeth cannot meet that burden. The broad theory of preemption advanced by Wyeth and its *amici* posits that FDA's approval of a drug's labeling constitutes both a "floor" and a "ceiling" and preempts any state law that might affect the labeling in any way. Wyeth Br. 45; U.S. Br. 19. Congress's history of acquiescence in, and this Court's precedents recognizing the presumptive validity of, traditional

---

[21] *See* Brief for the United States as Amicus Curiae Supporting Petitioner at 17, *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001) (No. 98-1768) ("claims of . . . negligent failure to warn . . . implicate[] core areas of traditional state concern").

[22] Wyeth asserts (at 51 n.23) that the presumption against preemption does not apply here because federal statutes have regulated the drug industry for a number of years. But, in *Bates* and *Lohr*, federal regulation had existed since 1910 and 1938, respectively, *see Bates*, 544 U.S. at 437; *Lohr*, 518 U.S. at 475, and this Court nonetheless applied its presumption against preemption. Wyeth cites cases involving areas of traditional, longstanding, and nearly exclusive *federal* concern. *See United States v. Locke*, 529 U.S. 89, 108 (2000) ("national and international maritime commerce," in which, "from the earliest days of the Republic," "Congress has legislated"); *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 347 (2001) ("[p]olicing fraud against federal agencies"). The presumption against preemption applies with special force where, as here, preemption is asserted for federal regulatory action to override state law in the absence of a federal statute expressing an intent to displace state law, and federal law does not provide any private right of action.

state-law remedies against drug manufacturers rebut that claim. Nothing in the FDCA's history suggests that Congress either viewed state-law claims intended to promote public safety and compensate injured patients as conflicting with the federal scheme or intended to allow FDA to immunize drug manufacturers from such claims.

II. IT IS NOT IMPOSSIBLE FOR WYETH TO COMPLY WITH FEDERAL LAW AND THE STATE-COURT JUDGMENT

This Court has said on many occasions that federal law preempts state law when "compliance with both federal and state regulations is a *physical impossibility*." *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963) (emphasis added). But that rarely met test does not require preemption so long as compliance with federal and state law is "theoretically possible." *California Fed. Sav. & Loan Ass'n v. Guerra*, 479 U.S. 272, 291 (1987) (internal quotation marks omitted).

Wyeth can comply with both a damages judgment in a failure-to-warn case and the FDCA, which does not expressly preempt state law. Vermont law duties are consistent with federal law, because nothing in the statute or FDA's regulations prohibits manufacturers from proposing stronger warnings or later strengthening them to promote the drug's safe use. Independently, Wyeth could have complied with the Vermont judgment without changing its label.

A. The FDCA Did Not Compel The Specific Warning Found Inadequate In This Case And Permits Drug Manufacturers To Strengthen Warnings

Federal law did not compel the particular warning Wyeth used. Either in the initial proposed labeling for Phenergan before FDA approved the drug or after FDA approval, Wyeth could have warned of the special hazards of IV-push injection consistent with the FDCA. Congress recognized that pharmaceutical manufacturers have access to far greater information than FDA, which is why drug makers have always had the responsibility for drafting the warnings in prescription drug labeling. Insofar as Wyeth contends that, once FDA approves drug labeling, the FDCA bars a manufacturer from changing that labeling, that broad assertion finds no support in the FDCA's text. Wyeth's argument also cannot be squared with a prominent FDA regulation, 21 C.F.R. § 314.70(c)(6), that expressly permits such changes to strengthen inadequate warnings. Although the parties dispute the reach of that regulation, *see infra* Part II.B.3, under some circumstances the regulation unquestionably allows a manufacturer to implement stronger warnings while seeking FDA approval. If the FDCA barred *all* unapproved labeling revisions, that regulation necessarily would be facially invalid, a conclusion neither Wyeth nor FDA supports. Indeed, the government acknowledges (at 3 n.1) that the FDCA does not preclude a manufacturer from changing the labeling submitted with an approved new-drug application.

Wyeth seeks to evade the absence of textual support for its argument by asserting (at 30-31) that, if it had changed the Phenergan package insert to

comply with Vermont's duty of due care, it would have violated the FDCA's prohibitions on "misbranding" and "unauthorized distribution." Neither contention has merit.

1. Changing the Phenergan labeling to add a warning about IV push would not have caused the drug to be misbranded under the FDCA, 21 U.S.C. § 331(a). Indeed, the state-law duty runs parallel to the federal misbranding standard. A drug is "misbranded" if, among other things, its labeling is "false or misleading" or fails to include "such adequate warnings . . . where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." *Id.* § 352(a), (f). The Act nowhere provides that a drug is misbranded simply because the manufacturer changes the labeling submitted to FDA during the pre-market review process under § 355. *See id.* § 352. And Wyeth's supposition that federal law would prohibit a drug maker from enhancing warnings when one method of administering the drug significantly increases the risk of traumatic injury is directly contradicted by § 352(f)'s plain text, in which Congress sought to protect public health by insisting on adequate warnings.

Moreover, the congressional misbranding scheme does not confer exclusive authority on FDA to make misbranding determinations. Rather, Congress explicitly envisioned that, in any misbranding enforcement action, the question whether a drug's labeling is "false or misleading" or fails to contain adequate warnings would be decided in federal court – typically with a *jury* resolving FDA's allegations of misbranding. *See id.* §§ 332, 333(a), 334(a)-(b); *see also Lewis v. United States*, 518 U.S. 322, 326 (1996). "[L]ay juries," therefore, "are in no sense anathema to" the

FDCA's scheme. *Bates*, 544 U.S. at 452 (rejecting pro-preemption argument based on mistrust of juries because, in prosecutions under federal pesticide law, "juries necessarily pass on allegations of misbranding").

Wyeth's argument thus boils down to a dubious hypothetical: if Wyeth had changed its labeling after FDA approval, FDA would have decided to bring a misbranding action against it, and a federal jury or judge would have found that a stronger warning or instruction regarding IV-push injection would have rendered the labeling "false or misleading" or otherwise inadequate under the statute. That "hypothetical" possibility "is insufficient to warrant the pre-emption." *Rice v. Norman Williams Co.*, 458 U.S. 654, 659 (1982); *see also English*, 496 U.S. at 90 ("The teaching of this Court's decisions . . . enjoin[s] seeking out conflicts between state and federal regulation where none clearly exists.") (internal quotation marks omitted, alterations in original). The notion that an increased warning about IV-push injection would cause Wyeth to be liable for misbranding is particularly farfetched considering the overwhelming record evidence that IV-push injection's risks far outweigh any supposed benefits.

Notably, the government does not even suggest (as it has in other failure-to-warn cases) that it would have instituted a misbranding prosecution if Wyeth had used a stronger IV-push warning. *Compare*, *e.g.*, Brief of the United States as Amicus Curiae in Support of Defendants-Appellees at 16, *Colacicco v. Apotex, Inc.*, 521 F.3d 253 (3d Cir. 2008) (No. 06-3107) (asserting that the warning the plaintiff sought would have misbranded the drug), *with* U.S. Br. 21. Nor has Wyeth or the government identified any

case in which the government pursued a misbranding action against a drug manufacturer for strengthening its labeling. Indeed, in 2008, FDA responded to a congressional inquiry by identifying *no* instances in which it had concluded that a stronger warning implemented through a CBE supplement would harm public health.[23]

2. Wyeth also incorrectly asserts (at 30) – without explanation or authority – that a change in Phenergan's labeling regarding IV-push injection, without more, would have subjected it to liability for "unauthorized distribution." (The government does not make that argument.) The FDCA prohibits the introduction into interstate commerce of "any new drug" unless "an approval of an application" under § 355 "is effective with respect to such drug." 21 U.S.C. § 355(a); *see also id.* § 331(d). Wyeth's "unauthorized distribution" argument assumes that any change in an approved drug's labeling renders it a "new drug" "with respect to" which "an approval of an application" under § 355 is not "effective." *Id.* § 355(a).

That assumption is unfounded. With exceptions not relevant here, the FDCA defines a "new drug" as a drug that is "not generally recognized" by experts "as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof." *Id.* § 321(p)(1). Under that definition,

---

[23] *See* Letter from Stephen Mason, FDA, to Hon. Henry Waxman 3-4 (Mar. 7, 2008). That letter identified only four instances since 2004 in which FDA did not approve a CBE supplement seeking to add or strengthen a contraindication, warning, precaution, or adverse reaction. In three of those cases, FDA determined that a *stronger* warning was necessary; in the other case, the warning was approved after the manufacturer submitted additional data.

if a manufacturer were to add a "condition[]" for "use" to a drug's label, the drug conceivably would be different from the "new drug" covered by the approved application. Had Wyeth changed its package insert to market Phenergan as a cancer-treating drug, that labeling might have made Phenergan a "new drug" within the meaning of § 321(p)(1). But adding or strengthening the warning on arterial exposure to address the greater risks with IV-push injection versus IV drip, or to preclude IV-push injection altogether, would not have added any new condition for use.[24] Therefore, Wyeth would have faced no liability under § 355(a) if its warning complied with Vermont's legal duties.

B. FDA Regulations Encourage And Permit Changes In Labeling To Increase Safety

Wyeth erroneously claims that any labeling different from the package insert used in Ms. Levine's case would have violated FDA regulations. That assertion is incorrect in three respects.

1. It is not impossible to comply with a state-law failure-to-warn judgment and FDA's initial approval of a drug. FDA approval signifies federal acceptance of a drug for marketing based on risk information presented to FDA. A state-law negligence judgment does not negate federal approval of a drug. A manufacturer may still market the drug, although the

---

[24] Under an FDA regulation, the *addition* to the label of "a dosage, or method or duration of administration or application, or other condition of use," "may" cause the agency to conclude that it is a "new drug" under the FDCA. 21 C.F.R. § 310.3(h)(5). But that regulation does not support the conclusion that the agency would consider the *removal* of a method of administration – or the addition of a stronger warning regarding that method – to render a drug "new."

incident giving rise to the plaintiff's injury may trigger federal regulatory obligations for adverse-event reporting and the updating of warnings. *See* 21 C.F.R. §§ 201.80(e), 314.80. A manufacturer can readily comply with those additional reporting requirements while also adhering to state-law duties of due care in providing adequate warnings.

2. Wyeth also could have complied with Vermont state-law standards and federal regulations by submitting a supplemental application for FDA approval to strengthen its label to address IV-push injection risks. *See* 21 C.F.R. § 314.70(c)(6). Neither Vermont law nor the other hundreds of damages judgments against drug manufacturers over the years required labeling changes *without* seeking FDA's approval. And it is not impossible now for Wyeth to comply with the judgment below while seeking FDA approval of a labeling change. Because FDA cannot stop a manufacturer from withdrawing a drug from the market, it is illogical to suppose that FDA can prohibit a drug manufacturer from taking the lesser step of withdrawing a method of administering that drug. In any event, Wyeth cannot prevail on a conflict preemption claim when it never sought (or was denied) FDA approval for an enhanced warning on IV-push injection.

3. a. In the circumstances here, Wyeth can comply with the state-law duty by changing its label even *without* FDA's prior approval, as the very regulation Wyeth claims as conflicting provided. The CBE regulation provides, in pertinent part:

> The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribu-

> tion of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:
>
> . . .
>
> (iii) Changes in the labeling . . . to accomplish any of the following:
>
> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;
>
> . . .
>
> (C) To 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).

In 2007, Congress explicitly approved of FDA's CBE regulation, which permitted labeling changes to be made pending applications for approval. Section 901(a) of the 2007 Amendments, which gave FDA limited authority to order labeling changes after first negotiating with the manufacturer, *see supra* note 8, contains a "rule of construction" stating that the amendment "shall not be construed to affect the responsibility of" the drug company "to maintain its label in accordance with existing requirements, including subpart B of Part 201 and sections *314.70* and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 121 Stat. 925-26 (emphasis added) (codified at 21 U.S.C. § 355(*o*)(4)(I)). That provision reflects Congress's intent that manufacturers possess the authority (and responsibility) to modify their labeling as needed to promote safety. And it undermines Wyeth's claim (at 35) that

manufacturer-initiated labeling changes are somehow contrary to the FDCA scheme.[25]

b. Wyeth and the government wrongly contend that the CBE regulation would not have permitted Wyeth to change its label to comply with a state-law duty to warn of IV-push injection risks or to instruct against IV-push injection. They assert that the CBE regulation applies only when the information motivating the labeling change is "new" or was not "previously available to the agency." U.S. Br. 24. That new argument – which Wyeth never raised at trial and the government apparently discovered only recently, after Ms. Levine's injury – cannot be squared with the regulation's unambiguous text, which contains no "new information" limitation.

The government claims the Court should defer to its a-textual interpretation of the CBE regulation under *Auer v. Robbins*, 519 U.S. 452 (1997). But "*Auer* deference is warranted only when the language of the regulation is ambiguous." *Christensen v. Harris County*, 529 U.S. 576, 588 (2000). The CBE regulation unambiguously permits labeling changes without requiring them to be based on "new" information. This Court therefore owes no deference to, and must reject, the government's effort to import a new-information limitation into the regulation through "interpretation."[26] A contrary approach

---

[25] The government misses the point in disputing (at 32) whether that provision indicates congressional intent to preserve state-law remedies. The clause plainly evidences Congress's belief that drug manufacturers should "maintain" their labeling in accordance with the CBE regulation – which refutes Wyeth's claim that manufacturers cannot change their labeling to strengthen a warning in light of a state-law duty or judgment.

[26] *See also Norfolk Southern Ry. Co. v. Shanklin*, 529 U.S. 344, 356 (2000) (agency's interpretation must be rejected when

would permit the agency functionally to amend its regulations without complying with Administrative Procedure Act ("APA") notice-and-comment procedures. *See Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 100 (1995) (noting that an "APA rulemaking" would be required if an interpretive rule "adopted a new position inconsistent with" any "existing regulations"). Indeed, FDA's lack of confidence in its litigating position is reflected in the recent issuance of notice-and-comment rulemaking to implement its new view that CBE supplements can be based only on "new information." *See* 73 Fed. Reg. 2848 (2008).

Furthermore, to the extent Wyeth argues that a CBE supplement must be based on information about a *newly discovered risk* – as opposed to a manufacturer's reevaluation or analysis of existing risk information – that position conflicts with the FDA's own proposal to codify its "new information" limitation on the CBE regulation. The proposed rule defines "newly acquired information" to include "new analyses of *previously submitted* data." *Id.* at 2853 (emphasis added). Thus, even under FDA's proposed rule (which the government asserts reflects FDA's view of the meaning of the current CBE regulation), Wyeth could have re-analyzed data on the safety of IV-push injection and used the CBE regulation to implement a stronger warning or instruction.

Congress's recent amendments to the FDCA comport with that understanding of what information

---

it is "inconsistent with the text" of the regulation). Courts of appeals have repeatedly refused to adopt agency interpretations that, like FDA's new interpretation of the CBE regulation, clash with the rule's text. *See*, *e.g.*, *United States v. Hoyts Cinemas Corp.*, 380 F.3d 558, 569 (1st Cir. 2004); *Fina Oil & Chem. Co. v. Norton*, 332 F.3d 672, 676 (D.C. Cir. 2003); *Dithiocarbamate Task Force v. EPA*, 98 F.3d 1394, 1399 (D.C. Cir. 1996).

can be considered "new" in the context of a labeling change. The 2007 Amendments provide FDA with limited authority to order labeling changes based on "new safety information," § 901(a), 121 Stat. 924 (codified at 21 U.S.C. § 355(*o*)(4)(A)), which is defined to include "scientific data" about "a serious risk or an unexpected serious risk associated with use of the drug that the Secretary has become aware of *(that may be based on a new analysis of existing information)* since the drug was approved," § 901(b), 121 Stat. 927-28 (emphasis added) (codified at 21 U.S.C. § 355-1(b)(3)(A)). Thus, Congress too has recognized that, because risk information about a drug builds up over time, it makes no sense to limit labeling changes to those based wholly on information not available when the agency last considered the labeling. *See* Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J.A.M.A. 2215, 2218-19 (May 1, 2002) (providing examples of drugs that were withdrawn from the market based on adverse effects that had appeared in pre-market trials).

In revising the CBE regulation in 1985, FDA recognized that reevaluation of existing data can support a CBE supplement. In 1982, FDA had proposed revising the CBE regulation to remove the clause allowing manufacturers to "delete false, misleading, or unsupported indications for use or claims for effectiveness" through a CBE supplement. In response, a commenter "urged" FDA to continue to permit applicants "to delete, without prior approval, any indication for use or claim for effectiveness considered by the applicant to be unsupportable *as a result of the applicant's reconsideration of the data* or considered by the applicant to present an unacceptable

safety to efficacy ratio." 50 Fed. Reg. 7452, 7469 (1985) (emphasis added). In the 1985 final rule, FDA stated that it "agree[d] with" that comment and revised the final rule accordingly. *Id.*

Further, in the same 1982 document on which Wyeth (at 37) and the government (at 22) rely, FDA proposed a number of provisions containing an explicit "new information" limitation.[27] Those proposals demonstrate that FDA knew how to limit the effect of its regulations to cases of new information when it wanted to.[28] Finally, despite its newfound interpretation of the regulation, the government provides no indication that FDA has ever rejected

---

[27] *See* 47 Fed. Reg. 46,622, 46,652 (1982) (proposing a requirement that drug companies submit an annual report containing, among other things, a "brief summary of significant *new information* from the previous year that might affect the safety, effectiveness, or labeling of the drug product") (proposed 21 C.F.R. § 314.80(c)(4)(i)) (emphasis added); *id.* at 46,657 (proposing provision that FDA would notify drug company that it intended to withdraw approval of drug if it found, in part on "basis of *new information* before FDA," that drug no longer meets criteria for approval) (proposed 21 C.F.R. § 314.150(a)(2)(iii)) (emphasis added); *id.* (proposed 21 C.F.R. § 314.150(b)(2)) (same); *id.* (proposed 21 C.F.R. § 314.150(b)(3)) (same). Although, as Wyeth and the government note, FDA there indicated that one use for the CBE regulation would be to add warnings about new information, it did not say the regulation applied *only* to changes based on such information. *See id.* at 46,623, 46,635.

[28] Although Wyeth also argues (at 35) that FDA lacks statutory authority to promulgate a rule permitting drug manufacturers to alter their labels without prior FDA approval based on anything other than newly discovered information, the government does not adopt that argument and, instead, observes (at 3 n.1) that the statute is silent on changes to the labeling in an approved new-drug application.

CBE supplements for failing to comply with the "new information" requirement it now posits.[29]

C. Wyeth Can Comply With The Vermont Judgment Without Changing Its Label

Ms. Levine did not seek or obtain an injunction. Wyeth could pay her damages award without changing Phenergan's labeling. Its violation of state-law duties might induce, but does not mandate, future corrective action, and such inducement does not create an actual conflict with federal law. *Cf. Bates*, 544 U.S. at 445 (explaining that "an event, such as a jury verdict, that merely motivates an optional decision is not a requirement").

This Court's cases show that, for preemption purposes, common law is distinct from statutory and regulatory law because it fulfills primarily a compensatory function, rather than a regulatory one. As the Court recognized in *Sprietsma*, "common-law claims" – "unlike most administrative and legislative regulations" – "necessarily perform an important remedial role in compensating accident victims." 537 U.S. at 64. And, in *Goodyear Atomic Corp. v. Miller*, 486 U.S. 174 (1988), the Court explained that a workers' compensation award has only "incidental regulatory effects" that are "significantly" less "intrusive" than "direct state regulation," such as a state statute. *Id.*

---

[29] Wyeth, which bore the burden of establishing its preemption defense, never argued at trial that the CBE regulation applied only to changes based on "new information"; nor did it object to a jury instruction lacking any mention of that limitation. JA223, 228. Before preemption could definitively be found, therefore, a remand would be required to determine whether Wyeth waived or forfeited that argument under state law and, if not, whether the evidence supports a CBE supplement under the new standard.

at 185; *see also Silkwood*, 464 U.S. at 249, 256 (while federal law occupies field of nuclear-safety regulation, state tort law can provide damages remedy for those injured in nuclear incidents).[30]

This Court has recognized, but not resolved, the question whether the incidental regulatory effects of state tort judgments create preemptive "obstacles" to the accomplishment of federal purposes. *See Geier*, 529 U.S. at 882. There can be no doubt, however, that there is no physical impossibility, because Wyeth could pay the judgment to Ms. Levine and not otherwise alter its conduct.

Wyeth relies heavily on *Riegel*'s statement that "common-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." 128 S. Ct. at 1008 (internal quotation marks omitted). But *Riegel* did not say that, to comply with a state-law judgment, the defendant needed to do more than pay damages. Rather, it held that Congress intended the term "requirements" to encompass those state-law duties that, when violated, lead to damages claims. Significantly, by creating clarity for Congress's future usage of the term "requirements" in express preemption provisions, *id.*,

---

[30] The other cases on which Wyeth relies (at 33) are inapposite. *Geier v. American Honda Motor Co.*, 529 U.S. 861 (2000), did not involve the physical-impossibility test, but rather addressed whether a state tort suit posed an "obstacle" to a "deliberately imposed" federal requirement. *Id.* at 881. *Buckman* involved "[s]tate-law fraud-on-the-FDA claims." 531 U.S. at 350. Wyeth does not assert that the claims here fall into that category. The Court emphasized that the fraud claims in *Buckman* arose "solely from the violation of FDCA requirements" and distinguished cases (like this one) based on "traditional state tort law principles." *Id.* at 352-53.

Riegel did not purport to announce a rule for *implied* preemption cases. It would be anomalous to suppose that *implied* preemption operates the same way as when Congress enacts an *express* preemption provision using the term "requirements." Yet that is the logical import of Wyeth's argument.

III. THE VERMONT JUDGMENT POSES NO OBSTACLE TO THE FEDERAL REGIME

A. Vermont Law Complements The Federal Regime

1. Vermont law imposes a duty to warn on drug manufacturers that complements and parallels the FDCA's duties. Under Vermont law, drug companies must "provide adequate instructions about how to use the product safely." JA228. *See also Restatement (Third) of Torts: Products Liability* § 6(a), (b)(3), (d)(2). That duty requires courts to assess "the seriousness of the risk to patients" and "the likelihood or incidence of injury," JA229, using a similar standard as the federal misbranding provision, 21 U.S.C. § 352(f).[31] *See supra* pp. 26-27.

Thus, both state and federal law require drug manufacturers to provide physicians with information about the known risks of their products. As recently as 1998, FDA recognized the complementary nature of those duties, stating that it "does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations." 63 Fed. Reg. 66,378, 66,384 (1998). In both *Bates* and *Lohr*, the Court held that the existence of federal labeling rules did not, without more, deny states "'the right to provide a traditional damages remedy for violations of

[31] Wyeth did not object to these jury instructions. JA223.

common-law duties'" that "'parallel federal requirements.'" *Bates*, 544 U.S. at 447 (quoting *Lohr*, 518 U.S. at 495). Although "the threat of a damages remedy will give manufacturers an additional cause to comply" with federal rules, that does not make such suits obstacles to federal purposes. *Id.* at 448.

On the contrary, Vermont law furthers the FDCA's "high purpose" of "protect[ing] consumers," *Kordel*, 335 U.S. at 349, by holding drug companies liable when they fail to provide physicians with adequate information about their products' risks. In carrying out its paramount mission of "protect[ing] the public health by ensuring that . . . drugs are safe and effective," 21 U.S.C. § 393(b)(2)(B), FDA requires drug companies to revise inadequate labeling (which may include seeking agency approval of labeling changes even in the absence of an agency demand). Under FDA regulations, drug companies must revise drug labeling to include a warning "*as soon as* there is *reasonable evidence* of an association of a serious hazard with a drug; *a causal relationship need not have been proved*." 21 C.F.R. § 201.80(e) (emphases added).

Thus, like the federal scheme at issue in *Bates*, the FDCA, as implemented by FDA, "contemplates that [drug] labels will evolve over time, as manufacturers gain more information about their products' performance in diverse settings." 544 U.S. at 451. As *Bates* recognized, "tort suits can serve as a catalyst in this process," because such actions "'may provide manufacturers with added dynamic incentives to continue to keep abreast of all possible injuries stemming from use of their product'" and thereby prompt necessary labeling changes. *Id.* (quoting *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1541-42 (D.C. Cir. 1984)).

The common-law regulatory-compliance defense, which permits manufacturers to present evidence of compliance with federal law in defending against failure-to-warn suits, presents another way in which tort law complements the federal regulatory scheme. Here, the trial court instructed the jury – without objection – that it could "consider evidence of compliance by Wyeth with FDA requirements in obtaining approval for the Phenergan warning." JA227. *See also Restatement (Third) of Torts: Products Liability* § 4(b).

In this case, Wyeth not only presented a vigorous regulatory-compliance defense, but also attempted to bolster that defense with evidence showing the benefits of IV-push injection of Phenergan. That evidence, however, amounted to nothing more than speculation that IV-push administration might theoretically be medically appropriate in some rare and dire circumstance. *See supra* p. 16. Neither Wyeth nor its *amici* suggest in this Court any benefits of IV-push injection of Phenergan that Wyeth neglected to introduce at trial. Nor do they assert that such a benefit, if one existed, could outweigh the grave risk of gangrene and amputation they concede may result from IV-push injection. For any rational person, a greatly increased risk of amputation for minutes-faster relief from nausea is never a risk worth taking. Wyeth's failure to prevail below thus cannot be blamed on the trial court's ignorance either of FDA's regulation of Phenergan's labeling or of any (hypothetical) "'patients who reaped [the] benefits'" of IV-push injection of Phenergan. Wyeth Br. 46 (quoting *Riegel*, 128 S. Ct. at 1008). Rather, the jury properly determined that FDA never considered (and could not have concluded) that IV push would benefit any

actual patient, as compared to IV drip, which the record showed had a significantly lower risk of causing gangrene.[32]

2. Failure-to-warn suits augment the FDCA regime by encouraging manufacturers to provide FDA with data and analyses on risks of drugs.

Manufacturers conduct relatively limited clinical trials to support applications to market new drugs; FDA does not test drugs.[33] Because the participants are healthy adults, the trials do not reveal adverse reactions affecting, for example, pregnant, elderly, or sick patients, and, because of their relatively brief durations, the studies also do not uncover side effects with long latency periods. *See* Institute of Medicine Report 37-38. Unsurprisingly, a 1990 GAO report found that serious post-approval risks surfaced in more than half of the drugs FDA approved between 1976 and 1985.[34]

After FDA has approved a drug with manufacturer-proposed labeling, the manufacturer bears primary responsibility for analyzing safety information and evaluating needed labeling modifications in response to that information. *See* 21 C.F.R. §§ 201.80(e), 314.80(b). FDA's post-approval authority is limited,

---

[32] Wyeth presented no evidence at trial and makes no argument in this Court that Ms. Levine's medical condition was so dire as to warrant the risks she incurred.

[33] Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* 34-38, 152 (2007) ("Institute of Medicine Report").

[34] U.S. General Accounting Office, Report to the Chairman, Subcomm. on Human Resources and Intergovernmental Relations, Comm. on Government Operations, House of Representatives, *FDA Drug Review: Postapproval Risks 1976-85*, at 3 (Apr. 1990).

however – particularly prior to 2007, when FDA could not force a manufacturer to make a labeling change. Instead, the agency "negotiated" such changes with the manufacturer, as the record here shows occurred with Wyeth. *See supra* p. 8. Although most risks of a drug will become known or fully appreciated only *after* FDA approves the drug, the post-approval period is when FDA's regulatory powers are most limited. State-law actions therefore induce manufacturers to evaluate and act on risk information they receive.

Throughout FDA's history, well-respected independent observers have recognized that the agency lacks the resources and tools to serve as the sole protector of public health. In 1955, the year FDA allowed Wyeth to market Phenergan, an FDA advisory committee found that the "budget and staff of [FDA] are inadequate to permit the discharge of its existing responsibilities for the protection of the American public."[35] Three recent studies have expressed similar doubts about FDA's abilities and performance. In 2007, an FDA Science Board subcommittee "concluded that science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities."[36] "FDA's inability to keep up with scientific advances," the report explained, "means that *American lives are at risk*." FDA Science Board Report 3 (emphasis added). The National

---

[35] Citizens Advisory Committee on the Food and Drug Administration, Report to the Secretary of Health, Education and Welfare, H.R. Doc. No. 84-227, at 53 (1955).

[36] FDA Science Board, *Report of the Subcommittee on Science and Technology: FDA Science and Mission at Risk* 2 (Nov. 2007) ("FDA Science Board Report").

Academy of Sciences' Institute of Medicine and the Government Accountability Office issued reports, in 2007 and 2006, respectively, finding that deficiencies in the drug safety system directly affected the quality of risk information provided to the public. *See* Institute of Medicine Report 4; GAO Drug Safety Report 5. Those recent studies further undermine the notion that state-law remedial suits pose an obstacle to FDA's efforts to regulate the pharmaceutical industry.

B. Wyeth's Obstacle-Preemption Arguments Have No Merit

Despite the parallel objectives of federal and state law and the long history of litigation against drug manufacturers, Wyeth and the government contend that the Vermont judgment poses an obstacle to the federal scheme. They claim FDA comprehensively regulates the content of a drug's labeling and carefully balances risks and benefits in determining what information should appear on that labeling and how the information should be expressed. Wyeth further asserts that FDA performed a careful and complete balancing with respect to the risk at issue in this case, while the government claims it is irrelevant whether such balancing took place, so long as the agency was aware of the "relevant risk," broadly defined – that is, the general risk of arterial exposure to Phenergan, not the risk of IV-push administration specifically. Those contentions caricature the federal scheme, overlook the complementary role state tort law has long played in that regime, and ignore that the record and findings of the Vermont courts below establish that FDA never performed a balancing of the risks and supposed benefits of IV-push administration of Phenergan.

1. The assertion that FDA "balances" what warnings and instructions should appear in a drug's labeling is incorrect. Like Vermont law, federal law requires manufacturers to warn of *all* known risks of a drug. *See* 21 U.S.C. § 352(f); 21 C.F.R. § 201.80(e). As FDA has explained, "it is essential to the safe use of a drug for the physician to know *all* adverse reactions that are likely to occur with it," and "the act requires labeling to include warnings about both potential and verified hazards." 44 Fed. Reg. at 37,443, 37,447 (emphasis added). In FDA's view, "practicing physicians will welcome such information so that they can make their best informed medical judgments in the care of their patients." *Id.* Thus, nothing in the statute or regulations empowers FDA to permit a manufacturer to withhold information about a substantiated risk (such as the greatly increased risk of inadvertent arterial exposure leading to gangrene through IV-push injection of Phenergan) on the ground that providing such information might deter beneficial uses of the drug.

2. In any event, there is no evidence that FDA determined that Wyeth adequately informed medical practitioners of the specific risks of IV-push injection of Phenergan. The Vermont Supreme Court found that the "record lacks any evidence" that FDA would have "prohibited the use of a stronger warning with respect to IV-push administration of Phenergan." Pet. App. 16a. "Neither the letters [Wyeth and FDA exchanged] nor any other evidence presented to the jury indicated that the FDA wished to preserve the use of IV push as a method of administering Phenergan." *Id.* at 17a; *see also id.* at 18a n.2;

JA249.[37] Thus, this case does not involve a claim that Wyeth failed to include in labeling "a statement that FDA has considered and found scientifically unsubstantiated," 71 Fed. Reg. 3922, 3935 (2006), as the government implicitly concedes.

Wyeth argues (at 43-45), however, that FDA's 1997 letter to Wyeth embodies a conscious resolution of the issue in this case. But that letter, which came approximately 16 years after Wyeth submitted the supplemental application in question, contains no indication that FDA considered whether the risks of IV-push injection of Phenergan merited a stronger warning or an instruction precluding that method of administration. Indeed, FDA's letter did not insist on revised warnings regarding the risks of arterial exposure that FDA itself originally had suggested, apparently because it "viewed the change as non-substantive and rejected it for formatting reasons." U.S. Br. 25. FDA's 1997 letter therefore is a far cry from "an expert judgment" (Wyeth Br. 46) that any benefit of IV-push injection outweighs its risks or that a stronger warning would deter beneficial IV-push injections.

---

[37] Although Wyeth's obstacle claim focuses on FDA's purported decision to permit "IV administration of Phenergan," Wyeth Br. 40, 46, the state-law duty imposed by Vermont's highest court on review here is premised on the label's failure to have proper warnings or instructions regarding *IV-push* administration. *See*, *e.g.*, Pet. App. 3a. That understanding controls here. *See Perez v. Campbell*, 402 U.S. 637, 644 (1971) (in determining conflict preemption, the Court is "bound by" the state's highest court's interpretation of state law); *see also Riley v. Kennedy*, 128 S. Ct. 1970, 1985 (2008) ("A State's highest court is unquestionably 'the ultimate exposito[r] of state law.'") (quoting *Mullaney v. Wilbur*, 421 U.S. 684, 691 (1975)) (alteration in original).

This case is therefore quite unlike *Geier*, on which Wyeth (at 47-49) and the government (at 18) rely. There, the Court found that a suit premised on an automaker's failure to install airbags actually conflicted with a federal regulation that did not require airbags in all circumstances. *See* 529 U.S. at 874-81. Unlike in this case, the agency in *Geier* specifically "had *rejected*" a proposed "'all airbag' standard" and instead imposed a standard that "deliberately" sought "a mix of several different passive restraint systems." *Id.* at 878-79.[38]

This case more closely resembles *Sprietsma*. There, a damages action premised on a boat manufacturer's failure to install a propeller guard was not preempted where the federal agency considered whether to require such guards but ultimately took no action on the topic. *See* 537 U.S. at 60-62, 65-67. Indeed, this case presents an even weaker argument for conflict preemption than *Sprietsma*, because FDA did not even consider, let alone reject or take no action on, stronger warnings or instructions regarding IV-push injection.[39]

---

[38] *See also Lohr*, 518 U.S. at 501 (distinguishing case in which "the Federal Government has weighed the competing interests relevant to the particular requirement in question, reached an unambiguous conclusion about how those competing considerations should be resolved in a particular case or set of cases, and implemented that conclusion via a specific mandate on" manufacturer).

[39] Because FDA made no judgment on the labeling deficiency at issue in this case, the Court can reject Wyeth's preemption claim without considering whether FDA action on a manufacturer's labeling proposal in a supplemental application – which is not explained in a written order and generally is not subject to judicial review – should ever be given preemptive effect. (The administrative orders at issue in *Geier* and *Riegel*, by contrast,

For its part, the government asserts that state-law claims are preempted so long as the manufacturer informed the agency of the "relevant risk," which the government describes as inadvertent arterial exposure causing gangrene. U.S. Br. 25. But that overly broad position would abolish any form of compensation for nearly all patients injured by FDA-approved drugs because it would support preemption whenever the manufacturer can point to some bit of data regarding the risk in its submissions to the agency, without any showing that FDA considered or made a judgment about what the labeling should say regarding the risk. The government's new position also ignores that the labeling deficiency demonstrated at trial was not a failure to warn that inadvertent arterial exposure would cause gangrene. Rather, Wyeth failed either to warn that IV-push injection has a far greater risk of inadvertent arterial exposure or to preclude that method of administration altogether. It cannot be enough to inform the agency of a side effect, without also disclosing that the side effect occurs much more frequently with one method of administration than another.[40]

---

were subject to judicial review. *See* 15 U.S.C. § 1392(b) (1982) (authorizing judicial review of "orders establishing, amending, or revoking a Federal motor vehicle safety standard"); 21 U.S.C. § 360g(a)(4) (providing for judicial review of an order approving an application to market a medical device).)

[40] Because the Vermont judgment in this case poses no obstacle to the federal regime, the Court need not address Wyeth's criticisms of the Vermont Supreme Court's discussion of the effect of § 202 of the 1962 Amendments.

C. FDA's Inconsistent Position Is Entitled To No Weight

This Court should give no weight to FDA's opinion, expressed in a regulatory preamble and an *amicus* brief in this case, that federal law generally preempts state failure-to-warn claims. "It is not certain that an agency regulation determining the preemptive effect of *any* federal statute is entitled to deference," *Lohr*, 518 U.S. at 512 (O'Connor, J., concurring in part and dissenting in part), much less agency pronouncements of the types presented here. Even assuming it is, the extent of that consideration would depend on the persuasiveness of the agency's views and their consistency with past agency positions (as the government concedes (at 26)). *See Skidmore*, 323 U.S. at 140; *see also United States v. Mead Corp.*, 533 U.S. 218, 228 (2001); *Good Samaritan Hosp. v. Shalala*, 508 U.S. 402, 417 (1993); *cf. Riegel*, 128 S. Ct. at 1009. This is particularly true where the agency takes inconsistent positions on the preemptive effect of a federal regime. *See Bates*, 544 U.S. at 449 (describing government's preemption argument as "particularly dubious" given agency's change in position).

FDA's position is not consistent, grounded in any statutory change, or persuasive. Rather, "FDA's current view of the preemptive effect of its labeling regulations is a 180-degree reversal of its prior position." *In re Bextra and Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. M:05-1699 CRB, 2006 WL 2374742, at *8 (N.D. Cal. Aug. 16, 2006).[41] For

---

[41] *Accord* Entry on Pl.'s Mot. To Reconsider at 13, *Tucker v. SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL (S.D. Ind. July 18, 2008) ("FDA's current position on preemption is not long standing but is in fact a 180-degree reversal from its

example, contrary to FDA's current view that its labeling regulations impose a "ceiling" on the amount of information the public should receive, when it established requirements for patient labeling for selected prescription drugs in 1998, FDA stated that its "regulations establish the *minimal standards* necessary, but were not intended to preclude the states from imposing additional labeling requirements." 63 Fed. Reg. at 66,384 (emphasis added). Congress enacted no intervening statute to justify that shift. And, when FDA proposed the revised labeling rule (to which it later appended its preamble advocating preemption), the agency stated that the "proposed rule does not preempt State law." 65 Fed. Reg. 81,082, 81,103 (2000). On numerous occasions, "FDA [has] recognize[d] that product liability plays an important role in consumer protection." 59 Fed. Reg. 3944, 3948 (1994).[42] Its current policy, which represents a reversal of that longstanding position, has no basis in any change in law.

* * *

---

earlier stance.") (internal quotation marks omitted); *see also* 2 James T. O'Reilly, *Food and Drug Administration* § 26.56 (3d ed. 2007) (describing FDA's change in position).

[42] *See also*, *e.g.*, Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (FDA's then-Chief Counsel explained that, if the Medical Device Amendments were interpreted to preempt state-law claims, "FDA's regulation of devices would have been accorded an entirely different weight in private tort litigation than its counterpart regulation of drugs and biologics").

Diana Levine needlessly lost her arm and her livelihood from an unnecessarily dangerous method of administering a drug intended to relieve nausea. Wyeth never made FDA aware that IV-push injection greatly increased the risks of gangrene, and its Phenergan labeling similarly omitted any warning of those risks. Vermont's duty to warn of such risks is perfectly consistent with federal law and promotes Congress's paramount interest in ensuring safe use of drugs.

CONCLUSION

The judgment of the Vermont Supreme Court should be affirmed.

Respectfully submitted,

RICHARD I. RUBIN
RUBIN, KIDNEY, MYER & DEWOLFE
237 North Main Street
Barre, Vermont 05641
(802) 479-2514

DAVID C. FREDERICK
Counsel of Record
SCOTT H. ANGSTREICH
SCOTT K. ATTAWAY
BRENDAN J. CRIMMINS
KELLOGG, HUBER, HANSEN, TODD, EVANS & FIGEL, P.L.L.C.
1615 M Street, N.W.
Suite 400
Washington, D.C. 20036
(202) 326-7900

August 7, 2008

ADDENDUM

TABLE OF CONTENTS

Page

21 U.S.C. § 321. Definitions; generally

For the purposes of this chapter—

* * *

(p) The term "new drug" means—

(1) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof, except that such a drug not so recognized shall not be deemed to be a "new drug" if at any time prior to June 25, 1938, it was subject to the Food and Drugs Act of June 30, 1906, as amended, and if at such time its labeling contained the same representations concerning the conditions of its use; or

(2) Any drug (except a new animal drug or an animal feed bearing or containing a new animal drug) the composition of which is such that such drug, as a result of investigations to determine its safety and effectiveness for use under such conditions, has become so recognized, but which has not, otherwise than in such investigations, been used to a material extent or for a material time under such conditions.

* * *

21 U.S.C. § 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 355, or 360bbb-3 of this title.

* * *

21 U.S.C. § 332. Injunction proceedings

(a) Jurisdiction of courts

The district courts of the United States and the United States courts of the Territories shall have jurisdiction, for cause shown[1] to restrain violations of section 331 of this title, except paragraphs (h), (i), and (j).

(b) Violation of injunction

In case of violation of an injunction or restraining order issued under this section, which also constitutes a violation of this chapter, trial shall be by the court, or, upon demand of the accused, by a jury.

---

[1] So in original. Probably should have a comma.

21 U.S.C. § 333. Penalties

(a) Violation of section 331 of this title; second violation; intent to defraud or mislead

(1) Any person who violates a provision of section 331 of this title shall be imprisoned for not more than one year or fined not more than $1,000, or both.

(2) Notwithstanding the provisions of paragraph (1), if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.

*** * ***

21 U.S.C. § 334. Seizure

(a) Grounds and jurisdiction

(1) Any article of food, drug, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce or while held for sale (whether or not the first sale) after shipment in interstate commerce, or which may not, under the provisions of section 331(*ll*), 344, or 355 of this title, be introduced into interstate commerce, shall be liable to be proceeded against while in interstate commerce, or at any time thereafter, on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which the article is found. No libel for condemnation shall be instituted under this chapter, for any alleged misbranding if there

is pending in any court a libel for condemnation proceeding under this chapter based upon the same alleged misbranding, and not more than one such proceeding shall be instituted if no such proceeding is so pending, except that such limitations shall not apply (A) when such misbranding has been the basis of a prior judgment in favor of the United States, in a criminal, injunction, or libel for condemnation proceeding under this chapter, or (B) when the Secretary has probable cause to believe from facts found, without hearing, by him or any officer or employee of the Department that the misbranded article is dangerous to health, or that the labeling of the misbranded article is fraudulent, or would be in a material respect misleading to the injury or damage of the purchaser or consumer. In any case where the number of libel for condemnation proceedings is limited as above provided the proceeding pending or instituted shall, on application of the claimant, seasonably made, be removed for trial to any district agreed upon by stipulation between the parties, or, in case of failure to so stipulate within a reasonable time, the claimant may apply to the court of the district in which the seizure has been made, and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, to which the case shall be removed for trial.

(2) The following shall be liable to be proceeded against at any time on libel of information and condemned in any district court of the United States or United States court of a Territory within the jurisdiction of which they are found: (A) Any drug that

is a counterfeit drug, (B) Any container of a counterfeit drug, (C) Any punch, die, plate, stone, labeling, container, or other thing used or designed for use in making a counterfeit drug or drugs, and (D) Any adulterated or misbranded device.

(3)(A) Except as provided in subparagraph (B), no libel for condemnation may be instituted under paragraph (1) or (2) against any food which—

(i) is misbranded under section 343(a)(2) of this title because of its advertising, and

(ii) is being held for sale to the ultimate consumer in an establishment other than an establishment owned or operated by a manufacturer, packer, or distributor of the food.

(B) A libel for condemnation may be instituted under paragraph (1) or (2) against a food described in subparagraph (A) if—

(i)(I) the food's advertising which resulted in the food being misbranded under section 343(a)(2) of this title was disseminated in the establishment in which the food is being held for sale to the ultimate consumer,

(II) such advertising was disseminated by, or under the direction of, the owner or operator of such establishment, or

(III) all or part of the cost of such advertising was paid by such owner or operator; and

(ii) the owner or operator of such establishment used such advertising in the establishment to promote the sale of the food.

(b) Procedure; multiplicity of pending proceedings

The article, equipment, or other thing proceeded against shall be liable to seizure by process pursuant to the libel, and the procedure in cases under this section shall conform, as nearly as may be, to the procedure in admiralty; except that on demand of either party any issue of fact joined in any such case shall be tried by jury. When libel for condemnation proceedings under this section, involving the same claimant and the same issues of adulteration or misbranding, are pending in two or more jurisdictions, such pending proceedings, upon application of the claimant seasonably made to the court of one such jurisdiction, shall be consolidated for trial by order of such court, and tried in (1) any district selected by the claimant where one of such proceedings is pending; or (2) a district agreed upon by stipulation between the parties. If no order for consolidation is so made within a reasonable time, the claimant may apply to the court of one such jurisdiction and such court (after giving the United States attorney for such district reasonable notice and opportunity to be heard) shall by order, unless good cause to the contrary is shown, specify a district of reasonable proximity to the claimant's principal place of business, in which all such pending proceedings shall be consolidated for trial and tried. Such order of consolidation shall not apply so as to require the removal of any case the date for trial of which has been fixed. The court granting such order shall give prompt notification thereof to the other courts having jurisdiction of the cases covered thereby.

* * *

21 U.S.C. § 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbranded—

(a) False or misleading label

If its labeling is false or misleading in any particular. Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 355 or under section 262(a) of Title 42 for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 355(a) of this title or in section 262(a) of Title 42 shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term "health care economic information" means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention.

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement. Required labeling for prescription devices intended for use in health care facilities or by a health care professional and required labeling for in vitro diagnostic devices intended for use by health care professionals or in blood establishments may be made available solely by electronic means, provided that the labeling complies with all applicable requirements of law, and that the manufacturer affords such users the opportunity to request the labeling in paper form, and after such request, promptly provides the requested information without additional cost.

* * *

21 U.S.C. § 355. New drugs

(a) Necessity of effective approval of application

No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) of this section is effective with respect to such drug.

(b) Filing application; contents

(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a) of this section. Such person shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. If an application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing

date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by clause (A), and (G) any assessments required under section 355c of this title.

* * *

(c) Period for approval of application; period for, notice, and expedition of hearing; period for issuance of order

(1) Within one hundred and eighty days after the filing of an application under subsection (b) of this section, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) Approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) of this section applies, or

(B) Give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) of this section on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any

such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

* * *

(d) Grounds for refusing application; approval of application; "substantial evidence" defined

If the Secretary finds, after due notice to the applicant in accordance with subsection (c) of this section and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b) of this section, do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented

to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b) of this section; or (7) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e) of this section, the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence.

(e) Withdrawal of approval; grounds; immediate suspension upon finding imminent hazard to public health

The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this

section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) of this section was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: *Provided*, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application

shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) of this section with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) of this section or to comply with the notice requirements of section 360(k)(2) of this title, or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the

approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 355-1(g)(2)(D) of this title.

(f) Revocation of order refusing, withdrawing or suspending approval of application

Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) of this section refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Service of orders

Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) Appeal from order

An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of

the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of Title 28. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of Title 28. The commencement of proceedings under this subsection shall not,

unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

* * *

21 U.S.C. § 393. Food and Drug Administration

(a) In general

There is established in the Department of Health and Human Services the Food and Drug Administration (hereinafter in this section referred to as the "Administration").

(b) Mission

The Administration shall—

(1) promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;

(2) with respect to such products, protect the public health by ensuring that—

(A) foods are safe, wholesome, sanitary, and properly labeled;

(B) human and veterinary drugs are safe and effective;

(C) there is reasonable assurance of the safety and effectiveness of devices intended for human use;

(D) cosmetics are safe and properly labeled; and

(E) public health and safety are protected from electronic product radiation;

(3) participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements; and

(4) as determined to be appropriate by the Secretary, carry out paragraphs (1) through (3) in consultation with experts in science, medicine, and public health, and in cooperation with consumers, users, manufacturers, importers, packers, distributors, and retailers of regulated products.

*** * ***

21 C.F.R. § 201.80. Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

* * *

(e) *Warnings*. Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved. A specific warning relating to a use not provided for under the "Indications and Usage" section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard. Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. If a boxed warning is required, its location will be specified by the Food and Drug Administration. The frequency of these serious adverse reactions and, if known, the approxi-

mate mortality and morbidity rates for patients sustaining the reaction, which are important to safe and effective use of the drug, shall be expressed as provided under the "Adverse Reactions" section of the labeling.

* * *

21 C.F.R. § 314.70. Supplements and other changes to an approved application.

* * *

(c) *Changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes).* (1) A supplement must be submitted for any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included.

(2) These changes include, but are not limited to:

(i) A change in the container closure system that does not affect the quality of the drug product, except those described in paragraphs (b) and (d) of this section; and

(ii) Changes solely affecting a natural protein, a recombinant DNA-derived protein/polypeptide or a complex or conjugate of a drug substance with a monoclonal antibody, including:

(A) An increase or decrease in production scale during finishing steps that involves different equipment; and

(B) Replacement of equipment with that of a different design that does not affect the process methodology or process operating parameters.

(iii) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

(3) A supplement submitted under paragraph (c)(1) of this section is required to give a full explanation of the basis for the change and identify the date on which the change is to be made. The supplement must be labeled "Supplement—Changes Being Effected in 30 Days" or, if applicable under paragraph (c)(6) of this section, "Supplement—Changes Being Effected."

(4) Pending approval of the supplement by FDA, except as provided in paragraph (c)(6) of this section, distribution of the drug product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) of this section must be contained in the supplement.

(5) The applicant must not distribute the drug product made using the change if within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either:

(i) The change requires approval prior to distribution of the drug product in accordance with paragraph (b) of this section; or

(ii) Any of the information required under paragraph (c)(4) of this section is missing; the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information.

(6) The agency may designate a category of changes for the purpose of providing that, in the case of a change in such category, the holder of an approved application may commence distribution of the drug product involved upon receipt by the agency of a supplement for the change. These changes include, but are not limited to:

(i) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess;

(ii) A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of drug product or from one container closure system to another;

(iii) Changes in the labeling, except for changes to the information required in § 201.57(a) of this chapter (which must be made pursuant to paragraph (b)(2)(v)(C) of this section), to accomplish any of the following:

(A) To add or strengthen a contraindication, warning, precaution, or adverse reaction;

(B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;

(C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;

(D) To delete false, misleading, or unsupported indications for use or claims for effectiveness; or

(E) Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision.

(7) If the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug product(s) made with the manufacturing change.

* * *

No. 06-1249

In the Supreme Court of the United States

WYETH, PETITIONER

v.

DIANA LEVINE

ON WRIT OF CERTIORARI TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

PAUL D. CLEMENT
Solicitor General
Counsel of Record

GREGORY G. KATSAS
Acting Assistant Attorney General

EDWIN S. KNEEDLER
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
PETER R. MAIER
Attorneys

Department of Justice
Washington, D.C. 20530-0001
(202) 514-2217

THOMAS R. BARKER
Acting General Counsel

GERALD F. MASOUDI
Associate General Counsel

WENDY S. VICENTE
Attorney
Department of Health and Human Services
Washington, D.C. 20201

QUESTION PRESENTED

Whether the prescription drug labeling judgments imposed on manufacturers by the Food and Drug Administration (FDA) pursuant to FDA's comprehensive safety and efficacy authority under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*, preempt state law product liability claims premised on the theory that different labeling judgments were necessary to make drugs reasonably safe for use.

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases:

Cases—Continued: Page

Cases—Continued: Page

Constitution, statutes and regulations:

Statutes and regulations—Continued: Page

Regulations—Continued: Page

Miscellaneous: Page

Miscellaneous—Continued: Page

Miscellaneous—Continued: Page

In the Supreme Court of the United States

No. 06-1249

WYETH, PETITIONER

v.

DIANA LEVINE

ON WRIT OF CERTIORARI
TO THE SUPREME COURT OF VERMONT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING PETITIONER

INTEREST OF THE UNITED STATES

This case concerns the extent to which state law may hold a drug manufacturer liable for using labeling approved by the federal Food and Drug Administration (FDA). FDA administers the approval process for new drugs and monitors the safety of approved drugs after they have been marketed. At the Court's invitation, the United States filed a brief as amicus curiae at the petition stage of this case.

STATEMENT

1. Under the Federal Food, Drug, and Cosmetic Act (FDCA or Act), 21 U.S.C. 301 *et seq.*, a drug manufacturer may not market a new drug unless it has submitted a new drug application to the Food and Drug Administration (FDA) and received the agency's approval. 21

U.S.C. 355(a). An application must contain, among other things, "the labeling proposed to be used for such drug," 21 U.S.C. 355(b)(1)(F) (Supp. V 2005); see 21 C.F.R. 314.50(c)(2)(i) and (e)(2)(ii); "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use," 21 U.S.C. 355(b)(1)(A) (Supp. V 2005); and "a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling," 21 C.F.R. 314.50(d)(5)(viii); see 21 C.F.R. 314.50(c)(2)(ix).

The FDCA also requires that drugs not be misbranded. 21 U.S.C. 331(a) and (b). A drug is misbranded if, among other things, its "labeling is false or misleading in any particular;" the labeling does not provide "adequate directions for use" or certain "adequate warnings;" or the drug "is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof." 21 U.S.C. 352(a), (f) and (j). FDA has established specific requirements for drug labeling. 21 C.F.R. Pt. 201.

FDA will approve a new drug application only if it finds, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d).

After a drug has been approved and marketed, the manufacturer must investigate and report to FDA any adverse events associated with the use of the drug in

humans, 21 C.F.R. 314.80, and must periodically submit any new information that may affect FDA's previous conclusions about the safety, effectiveness, or labeling of the drug, 21 C.F.R. 314.81. See 21 U.S.C. 355(k); Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, § 901, 121 Stat. 922 (enhancing FDA's authority to require postmarket clinical studies, clinical trials, and surveillance). FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

Following FDA's approval of an application, the manufacturer generally may not make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to FDA and securing the agency's prior approval for the change. 21 C.F.R. 314.70(b)(2)(v)(A). A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug." 21 C.F.R. 201.57(c)(6). "An applicant may ask FDA to expedite its review of a supplement for public health reasons." 21 C.F.R. 314.70(b)(4). A manufacturer may, however, change a drug's labeling after its supplemental application is received by FDA, without waiting for the agency's approval of the change, if, among other things, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C).[1]

[1] The FDCA itself does not directly address changes to a drug's labeling after a new drug application has been approved. That subject is instead left to FDA to address by regulation. Compare 21

FDA interprets that regulation to permit changes without prior approval only to address "newly discovered risks" for which there is sufficient evidence of causal association with the drug. See 47 Fed. Reg. 46,623 (1982); 73 Fed. Reg. 2848 (2008) (proposing to codify that interpretation). If a manufacturer makes such a change before receiving FDA's approval, the agency may later disapprove the change and order the manufacturer to cease distribution of the changed product. 21 C.F.R. 314.70(c)(7).

2. After FDA approved petitioner's new drug application for the anti-nausea drug Phenergan, petitioner informed FDA of adverse events in which Phenergan apparently was inadvertently injected intra-arterially, resulting in gangrene and amputation. See, *e.g.*, Pet. App. 139a-140a (1967 report). Over the ensuing years, FDA and petitioner engaged in back-and-forth communications concerning the appropriate labeling to address the risks presented by inadvertent intra-arterial injection. See, *e.g.*, *id.* at 141a-166a. As part of its deliberations, FDA convened an expert advisory committee to consider that question. *Id.* at 144a, 147a-148a. FDA was thus fully aware of the risk of an inadvertent intra-arterial injection, and the labeling or revised labeling it approved uniformly contained warnings to address that risk. See, *e.g.*, *id.* at 142a-143a, 151a-154a, 162a, 165a; J.A. 271, 276, 277, 282, 283, 311-312, 356, 359, 374, 382, 390-391.

As of 2000 (when the events giving rise to this suit occurred), the FDA-approved labeling stated, in part, that "[u]nder no circumstances should Phenergan Injec-

---

U.S.C. 360e(d)(6) (addressing certain changes to an approved medical device).

tion be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene." Pet. App. 167a. The labeling went on to explain that the "preferred" method of administering the drug is "by deep intramuscular injection," because intravenous administration can result, in some circumstances, in inadvertent intra-arterial injection. *Ibid.* For circumstances in which the drug is injected intravenously, the labeling described in detail how such injection should be done, in order "to avoid * * * inadvertent intra-arterial injection." *Ibid.*; see *id.* at 4a-5a n.1.

3. In April 2000, respondent sought treatment at a health center for headache and nausea. Pet. App. 2a. The health center's staff first administered Phenergan to respondent by intra-muscular injection. *Ibid.* When respondent's nausea continued, the staff administered an additional dose of Phenergan later the same day by intravenous injection into her arm. *Ibid.* The intravenous injection was made by a procedure the parties refer to as IV push, whereby the staff did not drip the Phenergan solution through a free-flowing bag into a tube already inserted into respondent's arm, but instead sought to inject it directly into a vein in her arm. See *id.* at 2a, 52a. The IV push apparently resulted in inadvertent arterial injection, which caused gangrene and required amputation of respondent's hand and forearm. *Id.* at 2a.

Respondent brought and settled an action against the health center where she had received the injection of Phenergan. Pet. App. 50a. She also sued petitioner in a Vermont state court, asserting negligence and failure-to-warn claims premised on alleged inadequacies in the drug's labeling. *Id.* at 3a. Respondent asserted that "the label should not have allowed IV push as a means of

administration, as it was safer to use other available options, such as intramuscular injection or administration through the tubing of a hanging IV bag." *Ibid.* After the trial court rejected petitioner's preemption defense, *id.* at 51a-65a, the jury found in respondent's favor, and the trial court entered judgment in the amount of $6,774,000, *id.* at 3a.

4. a. The Supreme Court of Vermont affirmed. Pet. App. 1a-34a. It interpreted 21 C.F.R. 314.70(c) "to allow unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." *Id.* at 13a. The court viewed that section as crucial to its preemption analysis: "While specific federal labeling requirements and state common-law duties might otherwise leave drug manufacturers with conflicting obligations, [Section] 314.70(c) allows manufacturers to avoid state failure-to-warn claims without violating federal law" by making unilateral changes to FDA-approved labeling. *Id.* at 11a.

The Vermont Supreme Court also relied on a provision in the 1962 amendments to the FDCA that states that "[n]othing in the amendments * * * shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law." Drug Amendments of 1962, Pub. L. No. 87-781, § 202, 76 Stat. 793. The court construed that provision to limit preemption to circumstances in which it would be physically impossible for a manufacturer to comply with both federal and state law. Pet. App. 21a. Here, the court determined, there was no such impossibility because the record did not affirmatively show that FDA would have rejected a supplemental application seeking to strengthen the warning. *Id.* at 17a.

b. Chief Judge Reiber dissented. Pet. App. 35a-48a. He explained that respondent's state-law claims conflict with federal law because, while "FDA concluded that the drug—with its approved methods of administration and as labeled—was both safe and effective," the "jury concluded that the same drug—with its approved methods of administration and as labeled—was 'unreasonably dangerous.'" *Id.* at 35a (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)). Supporting that conclusion, in the Chief Judge's view, was the fact that FDA does not merely establish minimum safety standards, but instead "balances its assessment of a drug's safety against concerns for the drug's efficacy, taking into account that a safer but less effective drug is not necessarily best for the public health overall." *Id.* at 47a. With respect to drug labels, the Chief Judge explained, "FDA considers not only what information to include, but also what to exclude," in part because overwarning can do more harm than good. *Ibid.*

The Chief Judge also took issue with the majority's understanding of Section 314.70(c). Pet. App. 39a-41a. He explained that the regulation "allow[s] manufacturers to address newly-discovered risks," but "does not allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." *Id.* at 40a.

SUMMARY OF ARGUMENT

Respondent's claims are preempted because they challenge labeling that FDA approved after being informed of the relevant risk.

A. FDA approves new drugs based on a thorough evaluation of their safety, efficacy, and labeling. The

agency's consideration of safety and effectiveness is directly tied to its consideration of proposed labeling, because a drug's safety and effectiveness depend on the conditions under which it is used (such as its dosage, method of administration, and intended use). Many drugs can be dangerous if not used as directed, and labeling can help ameliorate risks of misuse. As part of the new-drug approval process, FDA considers and approves specific labeling for a drug, and the drug manufacturer is generally barred from making unilateral changes to the FDA-approved labeling.

In deciding whether to approve a drug, FDA does not merely establish minimum standards of safety. Instead, as with the Class III medical devices at issue in *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008), FDA weighs a drug's health benefits against its health risks, and "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979). FDA also balances the health benefits and detriments of particular labeling, in part because labeling must strike a balance between notifying users of potential dangers and not unnecessarily deterring beneficial uses through overwarning. If FDA concludes that a drug's benefits outweigh its risks only under certain conditions, the agency may require appropriate labeling to reflect that determination.

B. Because FDA's approval strikes a balance between competing considerations, state laws that strike a different balance conflict with FDA's determination and are impliedly preempted. In *Riegel*, this Court determined that "[s]tate tort law that requires a manufacturer's [devices] to be safer, but hence less effective, than the model the FDA has approved disrupts the fed-

eral scheme." 128 S. Ct. at 1008. So too here, state tort law that required a manufacturer to use different labeling than that approved by FDA would disrupt the agency's balancing of health risks and benefits. The FDA-approved labeling gives specific instructions on how to inject Phenergan intravenously; respondent, in contrast, would impose further limits on such injection—limits that might harm some patients' health by restricting their physicians' treatment options. If a state regulatory agency directed drug manufacturers not to use FDA-approved labeling, the conflict with federal law would be manifest. As in *Riegel*, the fact that juries instead of an expert agency would second-guess FDA's judgments in individual cases only exacerbates the conflict.

C. The Vermont Supreme Court opined that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes [the changes] will make the product safer." Pet. App. 13a. That interpretation of the regulation is wrong, because Section 314.70(c) permits manufacturers to make changes to the labeling, subject to FDA's subsequent review and approval, based *only* on newly available information, not based on information that was previously submitted to FDA—let alone whenever the manufacturer believes a different label "will make the product safer." If manufacturers were free to make unilateral changes to labeling the day after FDA's approval, based on information that was previously available to FDA, the approval process would be undermined and the agency's careful balancing of risks and benefits as reflected in the labeling would be thwarted. Here, there is no question that petitioner informed FDA of the relevant risk, and FDA determined that Phenergan was safe

and effective under the conditions set forth in the labeling, including intravenous administration.

D. The Vermont Supreme Court also erred in concluding that normal conflict-preemption principles do not apply to the FDCA. The 1962 amendments to the FDCA provide that they should not "be construed as invalidating any provision of State law * * * unless there is a direct and positive *conflict* between such amendments and such provision of State law." Pub. L. No. 87-781, § 202, 76 Stat. 793 (emphasis added). That provision means that the relevant amendments do not give rise to *field* preemption; it does not express any intent to preserve state laws that *conflict* with federal law, as Vermont tort law does in this case.

ARGUMENT

THE FDCA PREEMPTS TORT CLAIMS THAT WOULD IMPOSE LIABILITY FOR THE USE OF LABELING THAT THE FOOD AND DRUG ADMINISTRATION APPROVED AFTER BEING INFORMED OF THE RELEVANT RISK

Federal law preempts state laws that conflict with federal law, including state laws that either "make it 'impossible' for private parties to comply with both state and federal law," *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 873 (2000), or that "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines* v. *Davidowitz*, 312 U.S. 52, 67 (1941). Because respondent's claims challenge labeling that FDA approved after being informed of the relevant risk (and that petitioner was not free to change in the manner urged by respondent without FDA's prior approval), they conflict with FDA's approval of the labeling and are preempted.

A. FDA's Approval Of A Drug, Including Its Labeling, Reflects The Agency's Expert Weighing Of The Health Risks And Benefits Of The Drug As Labeled

1. FDA may approve a new drug application only if it determines, among other things, that (i) the drug is "safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof," (ii) there is "substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof," and (iii) the proposed labeling is not "false or misleading in any particular." 21 U.S.C. 355(d). The agency's consideration of safety and effectiveness is directly tied to its consideration of "the proposed labeling," *ibid.*, because a drug's safety and effectiveness usually depend on the conditions under which it is used (such as its dosage, its method of administration, and its intended use). Thus, "[d]rug labeling serves as the standard under which FDA determines whether a product is safe and effective." 50 Fed. Reg. 7470 (1985). Labeling is "[t]he centerpiece of risk management," as it "communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively." 71 Fed. Reg. 3934 (2006); cf. *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1004 (2008) ("FDA evaluates safety and effectiveness [of Class III medical devices] under the conditions of use set forth on the label.").

FDA's review of a new drug application is similar to its premarket approval process for Class III medical devices, see 60 Fed. Reg. 39,180 (1995), which this Court has described as "rigorous," *Riegel*, 128 S. Ct. at 1004;

see *id.* at 1018 (Ginsburg, J., dissenting); *Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 477 (1996). "Under the FDCA, a drugmaker must submit research data to FDA at two general stages of new-drug development." *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193, 196 (2005). A manufacturer first submits an investigational new drug application seeking authorization to conduct clinical trials (*i.e.*, trials on humans) in order to investigate the safety and effectiveness of the drug. See 21 U.S.C. 355(i) (2000 & Supp. V 2005); 21 C.F.R. 312.20. In determining whether to permit clinical trials to proceed, FDA considers whether "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). The investigational new drug application must be supported by pre-clinical research regarding the safety and efficacy of the drug, including "pharmacological and toxicological studies of the drug involving laboratory animals or in vitro." 21 C.F.R. 312.23(a)(8); see generally 21 C.F.R. 312.23(a).

If clinical trials demonstrate safety and efficacy, a manufacturer may submit a new drug application seeking approval to market the drug. See 21 U.S.C. 355(b) (2000 & Supp. V 2005). The applicant must submit "the labeling proposed to be used for such drug," 21 U.S.C. 355(b)(1)(F) (Supp. V 2005), as well as extensive information about the composition, manufacture, and specification of the drug, the pre-clinical and clinical studies, and "any other data or information relevant to an evaluation of the safety and effectiveness of the drug product obtained or otherwise received by the applicant from any source." 21 C.F.R. 314.50(d)(5)(iv); see 21 U.S.C. 355(b)(1)(A) (Supp. V 2005). FDA has issued numerous guidance documents that describe, in detail, how to pre-

pare a new drug application. See FDA, *Drug Applications, New Drug Application (NDA) Process* (last modified Dec. 28, 2007) <http://www.fda.gov/cder/regulatory/applications/NDA.htm> (listing the guidance documents).

FDA must deny any application that does not "include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." 21 U.S.C. 355(d)(1). There must also be "substantial evidence" of the drug's effectiveness, with "substantial evidence" defined to be "adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have." 21 U.S.C. 355(d).

FDA's "rigorous evaluation process * * * scrutinizes everything about the drug—from the design of clinical trials to the severity of side effects to the conditions under which the drug is manufactured." FDA, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (*Review Process*) (visited June 2, 2008) <http://www.fda.gov/fdac/special/testtubetopatient/drugreview.html>. "[A]n FDA review team—medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts—evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use." *Ibid.* In order to ensure that FDA has all the information it needs, the agency "usually communicates often with sponsors about scientific, medical, and procedural issues that arise dur-

ing the review process." FDA, *The CDER Handbook* 24 (1998) <http://www.fda.gov/cder/handbook/handbook.pdf>; see 21 C.F.R. 314.50(f)(4), 314.102(a), (c), (d), and (e). FDA may also consult with independent panels of scientific experts. 21 U.S.C. 355(n). FDA is more likely to consult with such an independent advisory committee if a drug is the first in its class. *Review Process, supra*.

After a drug is approved, the manufacturer must investigate and report adverse events to FDA. 21 C.F.R. 314.80. If such an event is serious and unexpected, the report must be made "as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant." 21 C.F.R. 314.80(c)(1)(i). Certain other information must be submitted to FDA within three working days. 21 C.F.R. 314.81(b)(1). A variety of other postmarketing reports are filed periodically, including quarterly and annual reports analyzing adverse events, 21 C.F.R. 314.80(c)(2), 314.81, and annual reports disclosing, among other things, all "significant new information * * * that might affect the safety, effectiveness, or labeling of the drug," including any new studies and data, 21 C.F.R. 314.81(b)(2)(i), (v), (vi). FDA also receives reports from health professionals and members of the public. FDA, *Postmarketing Surveillance Programs* (last modified Apr. 9, 2004) <http://www.fda.gov/cder/regulatory/applications/Postmarketing/surveillancepost.htm>.

Following its approval of a drug, FDA "monitors adverse events" from various reports, and "uses this information to update drug labeling." *Postmarketing Surveillance Programs*, *supra*. In addition, FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under

the conditions of use specified in the drug's labeling. 21 U.S.C. 355(e).

2. In determining whether to grant or continue its approval of a new drug application, FDA does not merely impose minimum standards of safety, as the Vermont Supreme Court concluded. See Pet. App. 19a. "No drug is absolutely safe; all drugs have side effects." *Review Process, supra*; see *FDA* v. *Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 142 (2000) ("[V]irtually every drug or device poses dangers under certain conditions."). Thus, FDA weighs health benefits against health risks. See 71 Fed. Reg. at 3934; 60 Fed. Reg. at 39,180; 47 Fed. Reg. 39,149 (1982). And FDA "generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use." *United States* v. *Rutherford*, 442 U.S. 544, 555 (1979); accord *Brown & Williamson*, 529 U.S. at 140; *Review Process, supra*. The agency has, for example, approved cancer treatments that are highly toxic and thus not "safe" as that term is ordinarily used, but that are nonetheless safe in the relevant sense because the potential benefits to the health of cancer patients outweigh the risks. 61 Fed. Reg. 44,413 (1996); see *Brown & Williamson*, 529 U.S. at 142.

FDA's balancing of a drug's risks and benefits is similar to the balancing it undertakes in the analogous context of Class III medical devices. As this Court recently explained, FDA weighs the benefits of a Class III device against its risks, and FDA "may * * * approve devices that present great risks if they nonetheless offer great benefits in light of available alternatives." *Riegel*, 128 S. Ct. at 1004. So too with drugs. FDA's risk-benefit balancing looks in part to the availability of more effective or less risky alternatives. If similar, safer products

are already on the market, the agency may require a heightened health benefit to justify the heightened risk. For example, FDA determined in 2005 that a drug product called Bextra should be withdrawn from the market because it presented greater safety risks than other drugs for the same indication with comparable efficacy, and the manufacturer withdrew it. See FDA, *Alert for Healthcare Professionals, Valdecoxib (marketed as Bextra)* (Apr. 7, 2005) <http://www.fda.gov/cder/drug/InfoSheets/HCP/valdecoxibHCP.pdf>; Memorandum from John K. Jenkins & Paul J. Seligman through Steven Galson to NDA files 20-998, 21-156, 21-341, 21-042 at 17 (Apr. 6, 2005) <http://www.fda.gov/cder/drug/infopage/COX2/NSAIDdecisionMemo.pdf>. Similarly, FDA withdrew its approval of terfenadine when a safer alternative became available because the drug's risks no longer outweighed its benefits in light of the alternative. See 62 Fed. Reg. 1889 (1997); 63 Fed. Reg. 53,444 (1998). On the other hand, FDA decided *not* to withdraw its approval of erythromycin estolate despite the availability of alternatives with lower risks, because the drug's higher risks were "offset by" its greater efficacy in certain circumstances. 47 Fed. Reg. at 22,547-22,548.

3. In the course of weighing health risks and benefits, FDA considers the overall health consequences of including particular instructions or warnings in a drug's labeling. As explained above, a drug's safety and effectiveness are not determined in the abstract, divorced from its labeling. See 71 Fed. Reg. at 3934. Rather, FDA requires each new drug application to contain "a discussion of why the benefits exceed the risks *under the conditions stated in the labeling*." 21 C.F.R. 314.50(d)(5)(viii) (emphasis added); see 21 U.S.C. 355(d); 21 C.F.R. 314.50(c)(2)(ix). When FDA concludes that a

drug's benefits outweigh its risks only under certain conditions, the agency requires appropriate labeling to reflect that determination. See, *e.g.*, 21 C.F.R. 314.110(a).

Moreover, labeling must strike a balance between notifying users of potential dangers and not unnecessarily deterring beneficial uses through overwarning. 71 Fed. Reg. at 3935. "Exaggeration of risk could discourage appropriate use of a beneficial drug," and thereby harm the public health. *Ibid.* In addition, excessive warnings can cause more meaningful risk information to "lose its significance." 44 Fed. Reg. 37,447 (1979); accord 71 Fed. Reg. at 3935; 65 Fed. Reg. 81,083 (2000). "Warnings about dangers with less basis in science or fewer hazards could take attention away from those that present confirmed, higher risks." *Brooks* v. *Howmedica, Inc.*, 273 F.3d 785, 796 (8th Cir. 2001), cert. denied, 535 U.S. 1056 (2002). Thus, as the dissent in the Vermont Supreme Court explained, there are "a number of sound reasons why the FDA may prefer to limit warnings on product labels." Pet. App. 47a (quoting *Brooks*, 273 F.3d at 796).

B. FDA's Approval Of A Drug Preempts Claims Challenging The FDA-Approved Design Or Labeling When FDA Has Been Made Aware Of The Relevant Risk

Respondent's claims are preempted because they challenge labeling that FDA approved after being informed of the relevant risk.

1. When federal law merely seeks to impose minimum safety standards, state laws that impose more stringent safety standards ordinarily are not preempted because such standards do not ordinarily frustrate the federal government's objective to ensure minimum lev-

els of safety. See, *e.g.*, *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 57 n.6, 64-68 (2002); cf. *Lohr*, 518 U.S. at 501 (emphasizing, in holding that FDA's substantial-equivalence determination for a grandfathered medical device did not expressly preempt state tort claims, that FDA had *not* "weighed the competing interests relevant to the particular requirement in question").

Where, however, federal regulation is designed to strike a *balance* between competing considerations, state laws that strike a different balance are impliedly preempted because they interfere with the federal balancing. *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 152 (1989); *Chicago & N.W. Transp. Co.* v. *Kalo Brick & Tile Co.*, 450 U.S. 311, 321, 326-327, 330 (1981). In *Geier*, for example, an agency did not merely impose minimum safety standards. 529 U.S. at 874-875. Instead, it determined that, in light of competing considerations, public safety was best served by affording manufacturers the choice to install a variety of different passive restraint systems in their vehicles. *Id.* at 881. The Court held that a state suit seeking to impose liability for a manufacturer's decision not to use a particular type of restraint system would stand as an obstacle to the federal agency's decision. *Id.* at 881-883; see also, *e.g.*, *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001) (fraud-on-FDA claim preempted because it would interfere with FDA's ability to strike "a somewhat delicate balance of statutory objectives"); *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987) (state nuisance law preempted because it would "upset[] the balance of public and private interests so carefully addressed by" the federal permitting regime for water pollution).

2. So too here, the jury's imposition of liability based on petitioner's use of FDA-approved labeling would interfere with FDA's expert weighing of risks and benefits. As discussed above, FDA approves labeling for a new drug based on its determination that the labeling strikes the appropriate balance between health risks and benefits. See pp. 16-17, *supra*. Overwarning can both deter beneficial uses of a drug and "limit physician appreciation of potentially far more significant" risks. 71 Fed. Reg. at 3935; see 65 Fed. Reg. at 81,083. Accordingly, FDA's approval of a new drug under the FDCA and its implementing regulations "establish[es] both a 'floor' and a 'ceiling'" with respect to drug labeling. 71 Fed. Reg. at 3935.

That conclusion is confirmed by the fact that liability under state law turns on whether a drug, as labeled, is "unreasonably dangerous." Pet. App. 35a (Rieber, C.J., dissenting) (quoting *Town of Bridport* v. *Sterling Clark Lurton Corp.*, 693 A.2d 701, 704 (Vt. 1997)); J.A. 15 (respondent's complaint); J.A. 219 (jury instructions). Any such finding would directly conflict with FDA's determination that the drug *is* safe and effective under the conditions prescribed, recommended, or suggested in the labeling. Pet. App. 35a-36a. Indeed, respondent specifically urged the jury to second-guess FDA and reject the agency's expert judgment. See J.A. 82, 85, 98, 211, 212, 249.

If a state regulatory agency directed manufacturers not to use FDA-approved labeling, but instead to provide different or additional warnings, the conflict with federal law would be manifest. As in *Riegel*, the conflict is exacerbated, rather than ameliorated, by the fact that juries would make those determinations in individual tort suits. As the *Riegel* Court explained, a jury tends

to focus on the risk of a particular design or labeling that arguably contributed to a particular plaintiff's injury, not on the overall benefits of that design or labeling; "the patients who reaped those benefits are not represented in court." 128 S. Ct. at 1008. In contrast, FDA's drug-approval determinations consider the interests of *all* potential users of a drug, including "those who would suffer without new medical [products]" if juries in all 50 States were free to second-guess FDA's expert determinations. *Id.* at 1009; see Pet. App. 48a (Reiber, C.J., dissenting).

Thus, just as "[s]tate tort law that requires a manufacturer's [Class III medical devices] to be safer, but hence less effective, than the model FDA has approved disrupts the federal scheme," *Riegel*, 128 S. Ct. at 1008, state tort law that requires a manufacturer to use different labeling than that approved by FDA would disrupt the federal balance.

Here, there is no question that FDA was presented with extensive information about the dangers of accidental intra-arterial injection from intravenous administration of the drug. Indeed, the agency approved labeling that explained how to inject the drug intravenously so as "to avoid * * * inadvertent intra-arterial injection," and thereby ensured that the drug was safe and effective under the stated conditions of use. Pet. App. 167a; see pp. 4-5, *supra.* Nor did the Vermont Supreme Court point to any marked change in the number or type of reported cases of accidental intra-arterial injection from intravenous administration establishing that the risk was of a distinct type or substantially greater magnitude than the risks of which FDA had been made aware. Thus, the state supreme court's decision sanctioned

what amounts to a frontal assault on FDA's approval of the labeling in question.

C. Federal Law Does Not Permit Manufacturers To Make Unilateral Changes To FDA-Approved Labeling Based On Previously Available Information

In holding that respondent's claims are not preempted, the Vermont Supreme Court relied in large part on its view that an FDA regulation, 21 C.F.R. 314.70(c), "allow[s] unilateral changes to drug labels whenever the manufacturer believes it will make the product safer." Pet. App. 13a. That is incorrect. Petitioner was not free to disregard FDA's judgment concerning previously known risks.

1. As discussed above, the FDCA requires a manufacturer to receive FDA's approval for a new drug's labeling. 21 U.S.C. 355(a) and (d). Because FDA's approval strikes an important balance between, among other things, warning of risks and not overdeterring beneficial uses, manufacturers ordinarily may *not* modify designs or labeling approved by FDA without first obtaining FDA's approval for the change. See 21 C.F.R. 314.70; cf. *Riegel*, 128 S. Ct. at 1005, 1007 (discussing similar requirement for Class III devices). Here, for example, FDA instructed petitioner that the "final printed labeling * * * must be identical" to the approved labeling. Pet. App. 165a. Indeed, a unilateral modification of the labeling, absent special circumstances, can open a manufacturer to liability for misbranding the drug. See 21 U.S.C. 352(a); 21 U.S.C. 352(f) (Supp. V 2005); 21 C.F.R. 201.100(c)(1) and (d); see also 21 U.S.C. 355(a). If manufacturers were free to make unilateral changes to labeling the day after FDA's approval based on information that was previously available to

the agency, the approval process would be greatly undermined and the agency's careful balancing of risks and benefits thwarted. The Vermont Supreme Court's view that "FDA approval of a drug label" is nothing more than "a first step," *id.* at 15a, is therefore a fundamental misconception of the federal regulatory framework.

Under FDA's regulations, a manufacturer ordinarily must submit a supplemental application before making any changes to an approved drug, including changes in labeling. 21 C.F.R. 314.70(b)(2)(v). As a general rule, the manufacturer must obtain prior approval by FDA before making such changes. Section 314.70(c)(6), on which the court below relied, provides only a *limited* exception to that rule permitting "the holder of an approved [new drug] application [to] commence distribution of the [changed] drug product involved upon receipt by the agency of a supplement for the change" if, among other requirements, the change "add[s] or strengthen[s]" a warning or a statement about administration of the drug in order to promote safety. 21 C.F.R. 314.70(c)(6)(iii)(A) and (C). And even that limited exception requires submission of a supplemental new drug application to, albeit not prior approval by, the agency.

As FDA explained when it proposed that regulation in 1982, however, substantive changes may be made without prior FDA approval only "to correct concerns about *newly discovered* risks from the use of the drug." 47 Fed. Reg. at 46,623 (emphasis added). FDA determined that, "[a]lthough most changes in labeling would require the applicant to submit a supplement and obtain FDA approval before making a change," some changes that "would make available *important new information* about the safe use of a drug product" could be made upon submission of a supplemental application. *Id*. at

46,635 (emphasis added); see also FDA, *Guidance for Industry, Changes to an Approved NDA or ANDA* 25 (Nov. 1999) <http://www.fda.gov/cder/guidance/2766fnl.pdf> (explaining that changes may be made without prior FDA approval to add "a precaution arising out of a *postmarketing* study") (emphasis added).

In a proposed rule issued in January 2008, FDA confirmed that interpretation of Section 314.70(c). 73 Fed. Reg. 2848 (2008). The proposed rule would "reaffirm [FDA's] longstanding position that a supplemental application * * * is appropriate to amend the labeling for an approved product *only to reflect newly acquired information*," and may "add or strengthen a contraindication, warning, precaution, or adverse reaction only if there is sufficient evidence of a causal association with the drug, biologic, or device." *Ibid.* (emphasis added). FDA explained that "[a]llowing sponsors to unilaterally amend the labeling for approved products without limitation—even if done to add new warnings—would undermine the FDA approval process required by Congress" and "disrupt FDA's careful balancing of how the risks and benefits of the product should be communicated." *Id.* at 2849. Thus, the supplemental-application process is "primarily designed to provide information to FDA so that the agency," not the manufacturer, "can decide when safety information should be included in the labeling for a product." *Ibid.*

Even when a manufacturer may make a change prior to FDA's approval under Section 314.70(c), the supplemental application must "give a full explanation of the basis for the change." 21 C.F.R. 314.70(c)(3). The agency may then reject the change based on its own balancing of the relevant health risks and benefits. See 21 C.F.R. 314.70(c)(7). If FDA rejects the change, it may

order the manufacturer to cease further distribution of the changed product. *Ibid.* Thus, whether to authorize a change remains "squarely and solely FDA's" decision. 71 Fed. Reg. at 3934. Moreover, products distributed with a unilaterally changed label "remain[] subject to enforcement action" if FDA finds that the unilateral change rendered "the labeling false or misleading." *Ibid.*; see 21 U.S.C. 352 (2000 & Supp. V 2005). In practice, therefore, manufacturers typically consult with FDA before making any labeling changes. See 73 Fed. Reg. at 2849; 71 Fed. Reg. at 3934.

As the dissent in the Vermont Supreme Court correctly explained, Section 314.70(c) does not "allow manufacturers to simply reassess and draw different conclusions regarding the same risks and benefits already balanced by the FDA." Pet. App. 40a. Instead, any changes to a drug's labeling without prior FDA approval must be the subject of a supplemental application, which FDA can approve or reject, and must be based on new information establishing that risks arising from use of the drug are of a different type or greater severity than the risks of which FDA had previously been made aware—not cumulative new information that does not add to the information that was previously available to the agency. FDA's interpretation of its own regulation is entitled to significant deference. See, *e.g.*, *Auer* v. *Robbins*, 519 U.S. 452, 461 (1997).

For that reason, a state law premising liability on petitioner's failure to depart from the FDA-approved labeling concerning intravenous injection of the drug would not only "stand[] as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress," *Hines*, 312 U.S. at 67, it would also "make it 'impossible' for private parties to comply with both

state and federal law," *Geier*, 529 U.S. at 873. See 73 Fed. Reg. at 2853. Under respondent's theory, petitioner would have had to change the FDA-approved labeling, but petitioner could not have done so without prior FDA approval.

2. The parties have disputed whether FDA expressly rejected the precise warning that respondent asserts should have been included in the labeling. See, *e.g.*, Br. in Opp. 15-17. That factual dispute is irrelevant, because it is FDA's approval decision—which, in this case, followed the disclosure of the relevant risk—not the specifics of the agency's deliberations or speculation about whether the agency might have modified the label in some manner not expressly proposed at the time of the approval, that gives rise to preemption. Any state-law liability would be premised on a re-weighing of the same risks and benefits that FDA already considered in deciding to approve the precise labeling at issue, and federal law would preclude the applicant from making the state-mandated change without prior FDA approval. The agency could not reasonably be expected to *expressly* reject every possible variant of approved labeling as part of its decisional process. Indeed, it would underestimate the post hoc imagination of lawyers to think such an exhaustion of potential variants by the manufacturer or the agency is even possible. More to the point, such express rejection of a precise proposal is not necessary for preemption.

Moreover, any inquiry into the specifics of FDA's decisionmaking process would pose serious practical concerns. Here, FDA expressly rejected one particular labeling change proposed by petitioner, see Pet. App. 17a-18a, but it appears that FDA viewed the change as non-substantive and rejected it for formatting reasons,

cf. *id.* at 18a. With the passage of time, however, it would be increasingly difficult to reconstruct the agency's decisionmaking process. If preemption turned on the details of the agency's deliberations, preemption analysis would devolve into an intrusive, and potentially inconclusive, second-guessing of the agency's decisional process. Such an intrusion could also impose unreasonable discovery demands on the agency to explain the details of its deliberative process. Cf. U.S. Br. at 21-23, *Warner-Lambert* v. *Kent,* 128 S. Ct. 1168 (2008); U.S. Br. at 28-30, *Buckman*, *supra*.

3. As in *Riegel*, this Court need not rely on deference to FDA's views to conclude that respondent's claims challenging FDA's weighing of health risks and benefits are preempted. See *Riegel*, 128 S. Ct. at 1009. But FDA's interpretation of its own regulations is entitled to significant deference. See *Auer*, 519 U.S. at 461. And FDA's further views on preemption are also entitled to some weight under *Skidmore* v. *Swift & Co.*, 323 U.S. 134 (1944). Cf. *Riegel*, 128 S. Ct. at 1009. FDA's role in administering its own drug approval process makes it "uniquely qualified to determine whether a particular form of state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" *Lohr*, 518 U.S. at 495-496 (quoting *Hines*, 312 U.S. at 67); see *Geier*, 529 U.S. at 883 (explaining that an agency has a "thorough understanding of its own regulation and its objectives and is 'uniquely qualified' to comprehend the likely impact of state requirements") (quoting *Lohr*, 518 U.S. at 496).

In the preamble to a January 2006 rule concerning the labeling of drugs, FDA explained that the government's "long standing view[]" is that "FDA approval of labeling under the [FDCA] * * * preempts conflicting

or contrary State law," especially considering that "FDA interprets the [FDCA] to establish both a 'floor' and a 'ceiling'" for labeling. 71 Fed. Reg. at 3934, 3935. The agency also "recognize[d] that FDA's regulation of drug labeling will not preempt all State law actions." *Id.* at 3936. FDA then provided some specific examples of circumstances in which state laws are preempted, though it did not attempt to exhaust such circumstances. See *id.* at 3935-3936 (noting that "at least" those examples would be preempted). In this brief, the government has articulated a more generally applicable rule of decision, consistent with those examples, based on the preamble's explanation that (i) the labeling requirements are not a mere minimum safety standard, but rather strike a balance between risks and benefits, and (ii) FDA's regulations permit changes in labeling without prior approval only in narrow circumstances. See *id.* at 3934-3935; see also 73 Fed. Reg. at 2853; *Testimony of Deputy FDA Commissioner Randall Lutter Before The House Comm. on Oversight and Government Reform* 1-2 (May 14, 2008) <http://oversight.house.gov/documents/20080514142253.pdf>.[2]

Respondent suggests (Supp. Pet. Stage Br. 2 n.1; Br. in Opp. 19 n.6) that the government took a different position in a district court filing in *Perry* v. *Novartis*, Civ. No. 05-5350 (E.D. Pa. Sept. 21, 2005). The *Perry* brief

---

[2] Respondent's reliance (Br. in Opp. 8, 28) on snippets from various earlier Federal Register notices is misplaced because those notices did not squarely address the preemption question here. See 65 Fed. Reg. at 81,103 (stating that proposed *changes* to existing labeling rules would not have federalism implications); 63 Fed. Reg. at 66,384 (response to comments concerning Medication Guides for "a small number of products," *id.* at 66,379); 44 Fed. Reg. at 37,437 (responding to comment that FDA should use different administrative procedures).

argued, however, that failure-to-warn claims "premised on scientific information known to and considered by FDA as part of the approval process, would * * * be preempted." U.S. Br. at 12, *Perry*, *supra*. Respondent quotes (Br. in Opp. 19 n.6) a portion of the brief stating that FDA approval does not preempt *all* state-law labeling claims, because manufacturers may make labeling changes without prior FDA approval in some circumstances. The brief went on to explain, however, that such changes may "be made to warn of *new* hazards or cautions." U.S. Br. at 11, *Perry*, *supra* (emphasis added). Thus, the *Perry* brief is one of several amicus filings in which the government addressed FDCA preemption issues on a more fact-specific basis, without articulating a more general rule of decision.

D. Neither The 1962 Nor The 2007 Amendments To The FDCA Displaced The Operation Of Ordinary Conflict-Preemption Principles

1. The Vermont Supreme Court mistakenly thought that Section 202 of the 1962 amendments to the FDCA precludes the application of ordinary preemption principles. See Pet. App. 21a-23a. That provision states as follows:

> Nothing in the amendments made by this Act to the Federal Food, Drug, and Cosmetic Act shall be construed as invalidating any provision of State law * * * unless there is a direct and positive conflict between such amendments and such provision of State law.

76 Stat. 793.

At the outset, it is not clear to what extent Section 202 applies here. It is limited to "the amendments made by" the 1962 legislation. § 202, 76 Stat. 793. While those

amendments broadened the scope of FDA's new drug approval process by requiring the agency to consider the efficacy as well as the safety of a drug, see § 102(b), 76 Stat. 781, FDA's new drug approval process predated the amendments, see 21 U.S.C. 355(a) and (d) (1958). Indeed, FDA approved Phenergan before 1962. See Pet. 6; Br. in Opp. 23 n.8.

Assuming *arguendo* that Section 202 is relevant in this case, that provision means only that the 1962 amendments do not preempt *the field* of drug regulation; it does not manifest an intent to displace ordinary principles of conflict preemption. 71 Fed. Reg. at 3935 n.8. To the contrary, Section 202 expressly contemplates preemption in circumstances involving "a direct and positive conflict." 76 Stat. 793. The Vermont Supreme Court read that phrase to refer only to situations in which it would be impossible to comply with both federal and state law, as distinguished from situations in which state law would frustrate the purpose of the federal scheme. Pet. App. 21a-23a. Any such distinction is irrelevant here because, as discussed above, the impossibility standard is satisfied in this case. See pp. 21-25, *supra*.

In any event, at the time of the 1962 amendments, the phrase "direct and positive conflict" had long been understood to refer to conflict preemption generally, not to a mere subset of such preemption. See, *e.g.*, *United Constr. Workers* v. *Laburnum Constr. Corp.*, 347 U.S. 656, 663 n.5 (1954); *Sinnot* v. *Davenport*, 63 U.S. (22 How.) 227, 243 (1859). This Court has long contrasted "direct and positive" conflict preemption with "field" preemption, rather than using it as a byword for the impossibility variant of conflict preemption. *E.g., Kelly* v. *Washington ex rel. Foss Co.*, 302 U.S. 1, 9-10 (1937).

Indeed, the Court found a "direct and positive conflict" in circumstances analogous to this one, where federal law imposed some conditions and state law purported to impose an *additional* one that would frustrate Congress's objective. *Sinnot*, 63 U.S. (22 How.) at 241-243. More generally, this Court has never "driven a legal wedge—only a terminological one—between 'conflicts' that prevent or frustrate the accomplishment of a federal objective and 'conflicts' that make it 'impossible' for private parties to comply with both state and federal law." *Geier*, 529 U.S. at 873. A sponsor of Section 202 confirmed that the phrase "direct and positive conflict" takes its ordinary meaning by explaining that the amendment "would merely say that this Food and Drug Act shall not be construed as the intent of Congress to abolish *all* State laws on the same subject *where they are not in conflict with the Federal law*." 108 Cong. Rec. 21,083 (1962) (emphases added).

Not surprisingly then, "[t]he Court has * * * refused to read general 'saving' provisions to tolerate actual conflict both in cases involving impossibility *and* in 'frustration-of-purpose' cases." *Geier*, 529 U.S. at 873-874 (citation omitted). Especially considering that the Constitution itself, via the Supremacy Clause (U.S. Const. Art. VI, Cl. 2), subordinates state law to federal law, the courts should not lightly assume that federal law is so self-negating as to authorize state law to frustrate its objectives. Thus, even when a statute contained a savings clause providing that "[c]ompliance with" a federal safety standard "does not exempt any person from any liability under common law," 15 U.S.C. 1397(k) (1988), this Court held that the clause did not preclude the application of ordinary conflict preemption principles, including frustration-of-purpose principles. *Geier*,

529 U.S. at 868, 873-874. The savings clause here, which expressly provides for conflict preemption, likewise does not displace ordinary conflict preemption principles.

Nor is it material that the FDCA lacks an express preemption provision for drugs like the one at issue in *Riegel*. When Congress enacted a premarket approval process for Class III medical devices in 1976, it expressly preempted state requirements that are "different from, or in addition to," certain federal requirements (21 U.S.C. 360k(a); see *Riegel*, 128 S. Ct. at 1003)—*i.e.*, state-law provisions that conflict most directly with the federal regime. The enactment of that provision in 1976 does not suggest that FDA's new drug approval process has any less preemptive effect, because the device amendments were enacted years later by a subsequent Congress. See *Gomez-Perez* v. *Potter*, No. 06-1321, slip op. 10 (May 27, 2008); *California Div. of Labor Standards Enforcement* v. *Dillingham Constr., N.A., Inc.*, 519 U.S. 316, 331 n.8 (1997). Rather, the presence of an express preemption provision for devices but not drugs is explained by the fact that Congress legislated in 1976 against the backdrop of a then-existing state premarket approval requirement for devices, whereas States do not appear to have had similar requirements for drugs in 1938, when the FDCA was enacted. See *Riegel*, 128 S. Ct. at 1017-1018 (Ginsburg, J., dissenting); see also H.R. Rep. No. 853, 94th Cong., 2d Sess. 45 (1976). Moreover, this Court has looked to conflict preemption principles in determining whether a federal requirement applicable to a device is different from, or in addition to, a state requirement, and thus expressly preempted by Section 360k(a). See *Riegel*, 128 S. Ct. at 1008; *Lohr*, 518 U.S. at 500; *id.* at 508 (Breyer, J., concurring in part and in the judgment).

2. Respondent has suggested (Supp. Pet. Stage Br. 8-9) that recent amendments to the FDCA bear on the question presented. But those amendments do not reflect any intent to limit the FDCA's preemptive effect. In 2007, Congress enacted Section 901(a) of the FDAAA, Pub. L. No. 110-85, 121 Stat. 922, to enhance FDA's authority to require applicants to undertake postmarketing actions, including additional clinical studies, clinical trials, and safety labeling changes. That provision specifies that it "shall not be construed to affect the responsibility of the responsible person or the holder of the approved application * * * to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)." 121 Stat. 925-926 (to be codified at 21 U.S.C. 355(o)(4)(I) (Supp. I 2007)). That simply means that the relevant amendments do not affect obligations under other *federal* laws. It does not manifest any intent to depart from the application of ordinary principles governing the preemption of conflicting *state* laws.

Respondent selectively quotes floor statements of some individual legislators suggesting that, in their view, the FDCA does not preempt state-law claims. Supp. Pet. Stage Br. 8-9. At least as many other legislators, however, opined that the FDCA would continue to have broad preemptive effect. See, *e.g.*, 153 Cong. Rec. S11,940 (daily ed. Sept. 21, 2007) (Sen. Gregg); *id.* at S11,839-S11,840 (Sen. Coburn); *id.* at S11,939 (Sen. Enzi); *id.* at S12,050 (daily ed. Sept. 25, 2007) (Sen. Alexander). And as noted, the text of the rule of construction that Congress actually enacted, which is limited to the effect of Section 901, itself preserves *complemen-*

tary federal requirements without evincing any intent to protect *conflicting state* laws.

CONCLUSION

The judgment of the Supreme Court of Vermont should be reversed and the case remanded for further proceedings.

Respectfully submitted.

PAUL D. CLEMENT
Solicitor General

GREGORY G. KATSAS
Acting Assistant Attorney General

EDWIN S. KNEEDLER
Deputy Solicitor General

DARYL JOSEFFER
Assistant to the Solicitor General

DOUGLAS N. LETTER
PETER R. MAIER
Attorneys

THOMAS R. BARKER
Acting General Counsel

GERALD F. MASOUDI
Associate General Counsel

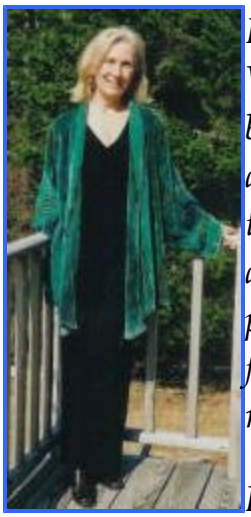
WENDY S. VICENTE
Attorney
Department of Health and Human Services

JUNE 2008

Pharmalot.com

Preemption And Amputation: Diana Fights Wyeth

By Ed Silverman // February 20th, 2008 // 1:00 pm 23 Comments



Eight years ago, Diana Levine entered the emergency room of a Vermont hospital because of a severe migraine. This had happened before and, as on other occasions, she was given a painkiller and another med to treat the nausea brought on by the first drug. One thing, however, was unusual about this visit - the nausea med was administered differently. And the incident eventually caused Levine, a professional musician, to lose her right arm below the elbow. She later filed a lawsuit against Wyeth, which sells the injectable Phenergan nausea med.

Levine successfully argued that, even though Phenergan labeling complied with FDA requirements, the adequacy of the warning still wasn't established. This referred to a particular method for administering Phenergan known as IV push. Moreover, Levine's attorneys contended Wyeth wasn't prevented from adding or strengthening the warning on the label, even though the FDA rejected a proposed change. Levine was awarded more than $6 million and, despite appeals, the Vermont Supreme Court sided with her. But Wyeth has appealed again and now the US Supreme Court agreed to review the case.

Why? At issue is preemption - a legal notion that FDA approval of a drug supercedes state law claims challenging safety, efficacy, or labeling. Drugmakers and the FDA argue that preemption exists by maintaining the agency's actions are the final word on safety and effectiveness. The court's decision, therefore, is being closely watched because its ruling will determine whether patients can sue a drugmaker through state law when a product has already been approved by the FDA. We chatted with Levine, 62, about her plight and the legal battle. This is an excerpt…

Pharmalot: Before this episode, you were a professional musician. What did you do?
Levine: Back in 1989, my husband and I started a label, called Rebop Records,

which I did to combine my passion for music and songwriting, and my love for kids. I played bass, guitar and piano. Sometimes, I'd play with my sister, who lives nearby, or my husband in local bands. The label was designed to provide rock and roll that kids and parents could enjoy together.

Pharmalot: But in 2000, you went to the hospital and Phenergan was administered. What happened?
Levine: I have a history of these migraines and, normally, I can manage them, but on occasion, they could be excruciating and debilitating, and I'd get hauled off to the emergency room. Normally, I'd get Demerol for the pain and then Phenergan, because the Demerol would make me nauseous. And it would be intramuscular administration, which was normally a shot in the butt. This time, they gave me a push IV and that's what caused the problem When I woke up, I was still in pain.

Pharmalot: At what point was your arm in jeopardy?
Levine: This went on for two or three weeks. It's a bit of blur now. But I was taking bloodthinners and morphine and painkillers. The doctors tried desperately to keep my hand. I'd never been in such pain. There were two procedures, though. The first was to amputate the hand. But it became obvious that the skin (below the elbow) wasn't going to regenerate and get healthy. The gangrene was still there. So I told them to take as little (of the arm) as you have to. The trauma seemed insurmountable. The best I could say was that I hadn't died.

Pharmalot: What did this do to your life, and your music?
Levine: Well, it stripped me of my career and my business and my ability to do what mattered most. I had to start from scratch. I'm left-handed and it was my right arm that was affected, so in a way, it was a blessing. Although I tried to do too much and developed over-use syndrome. Anyway, I was eventually outfitted with a prosthesis. And now I can hold a guitar pick and strum and make a chord. I still work with kids, but I can't tell you how many times they ask what happened. I tell them one is my soft hand and the other is my hard hand.

Pharmalot: What's your view of Wyeth and its actions?
Levine: They should've taken responsibility for changing the label…

…It's not a bad drug. It's a good drug, for what it is. But I'd much rather throw up than lose my arm. I think they should've come out and said that, under no circumstances should the drug be administered under push IV. They didn't protect me and ensure my safety…They have strong economic incentives and, sometimes,

those things take precedent…They say the FDA is their first line of defense, but if a drug company recognizes there's something that could hurt the public, they have an obligation to do something.

Pharmalot: What do you think about the Supreme Court agreeing to review your case?
Levine: Well, those nine judges aren't supposed to be influenced by whatever goes on between industry and the administration (which back preemption). I just have to have faith…If people like me are denied the ability to sue a drug company, well, a drug company has a mind of its own. They know when something is dangerous and they can change it. Think of all the little clinics and emergency rooms that may know as a result of my case. But it's Wyeth's responsiblity to let them know, not mine.

I can understand why (Wyeth) is doing this. It's probably because of all the frivolous case. But don't punish me or change a sytem that, right now, helps keep people safe. The only way I look at it is that now I have an opportunity to talk to people. Millions are now paying attention to the situation. I'm up on my soapbox and I'm going to create awareness. Hopefully, that'll lead to change. It's a shame we have to take this upon ourselves. Why should I have to be the savior? It's astonishing to me that the Supreme Court took this, but I'm going to make the best of it.

Comments

Laurie
February 20th, 2008
1:15 pm

"Levine: They should've taken responsibility for changing the label…"

This is the key phrase. While the FDA is touted as the "final word" on safety, it is the drug manufacturer who has the data and has to openly provide that data to the FDA for review. The FDA then takes years to "review" the data and act. This is the catch 22 that is created, while the public is at risk.

Nathan
February 20th, 2008
1:39 pm

Levine: They should've taken responsibility for changing the label… I think they should've come out and said that,