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

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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.

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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

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[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.

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[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

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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]

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[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

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(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

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[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.

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[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

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[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

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[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,

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[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.

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[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-

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[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

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[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,

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[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

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[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

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[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,

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[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

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[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

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[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

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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

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[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.*

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[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.*,

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[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,

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[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

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[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.

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[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]

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[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]

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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

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[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.

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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,

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ADDENDUM

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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.

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[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.

* * *