

FDA PREEMPTION OF DRUG AND DEVICE LABELING: WHO SHOULD DECIDE WHAT GOES ON A DRUG LABEL?

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ABSTRACT

The Supreme Court decided an issue that is critical to consumer health and safety last year. In April 2009, the Supreme Court held that extensive FDA regulation of drugs did **not** preempt a state law claim that an additional warning on the label was necessary to make the drug reasonably safe for use. Thus, states—and even courts and juries—are now free to cast their vote on what a drug label should say. This is in direct contrast to medical devices, where the federal statute regulating medical devices expressly provides that state regulations are preempted. This Article discusses basic preemption principles and drugs, and explores the policy ramifications of pro- and anti-preemption policy in the healthcare industry.

INTRODUCTION

In *Wyeth v. Levine*,¹ the Supreme Court held that state tort failure-to-warn claims for pharmaceuticals are **not** preempted by federal labeling requirements, but, in *Riegel v. Medtronic, Inc.*,² the Court held that regulatory approval of medical devices **does** preempt state tort law on labeling and warnings. On the one hand, the result is easily predicted since the statute governing medical devices has an express

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¹ *Wyeth v. Levine*, 129 S. Ct. 1187 (2009).

² *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 321-330 (2008).

preemption clause, whereas the statute relating to drugs does not. However, given the similarity of the two types of medical products, it is difficult to posit a rational basis for treating them differently.

Was *Wyeth's* outcome predicted by limited federal requirements, while *Riegel's* is the result of a more extensive approval process for medical devices? That distinction requires some metric for determining how extensive a regulatory process is, but at first blush, most practitioners would agree that drug regulation is at least as extensive—if not more so—than medical device regulation. Indeed, the regulatory regimes are roughly analogous—at least for the riskiest Class III devices.

If the differing regulatory regimes do not provide an answer, then perhaps the nature of the state claim that was found preempted will suggest a rationale. However, because similar state labeling laws—failure to warn—and similar monetary remedies were at issue in each case, the state claim does not offer much promise for explaining the different outcomes. Thus, developing a useful analytic framework for deciding which regulatory regime **should** be preempted poses a challenge.

This Article responds to this challenge by drawing on the framework of comparative institutional analysis, a process that identifies those who are in the best position to make a particular legal decision. A simple example of comparative institutional analysis arises from the question of whether to allow the judge or the jury to determine a particular issue. The line between judge and jury is drawn based upon identifying certain questions as that of law and certain questions as that of fact. More deeply, the judge/jury distinction rests on identifying a legal issue as one requiring a stable, deductive answer to a question (e.g., a legal question needing a legal answer) and one requiring a particularized determination based on the specific record (e.g., a factual question needing an individual factual analysis). Other examples of comparative institutional analysis are provided by constitutional law with such doctrines as political question and standing. These legal issues effectively depend on whether it is more desirable for a court, or a legislature, to resolve a specific dispute. Comparative institutional analysis thus addresses how to structure the answer to a legal problem by looking to see who is in the best position to decide given differences in expertise as well as the social, political, and economic constraints that face the actors.

Comparative institutional analysis is particularly relevant to preemption because the **choice** of decision maker is at the heart of the question of whether state law is—or should be—trumped by federal law. In the area of health and safety, the central question is whether an administrative agency is in a better position to resolve a specific issue

than a state court and its body of jurors. Drawing on the comparative institutional analysis framework, we propose a simple and readily applicable method for answering the question. If the issue involves technical questions requiring scientific expertise and a careful balancing of competing interests, then federal law should preempt. However, if there is a non-technical question raising issues of standard of care and liability in an individual case, then there should not be preemption.

Based on this analysis, we suggest that litigation is **not** an appropriate venue for deciding what the package insert for a drug or medical device should say. In litigation, only the injured plaintiff is represented—no one represents the patients that benefit from a given medical product. Thus, there will always be a tendency towards false positives—a jury will usually be biased in favor of the injured plaintiff in the court room, and the warnings on a package insert can become **too** strong as a result. Further, over-warning is not merely a theoretical concern—there now are examples where overly strong warnings have deterred use of a medical product—and thus increased the overall harm to the public. In contrast, the FDA, together with advisory committees and the manufacturer, crafts a label that reflects a **balancing** of risks and benefits, and thus is a better mechanism for determining label content.

At the same time, preemption would eliminate much litigation against medical product companies. Historically, litigation has helped to supplement the FDA's ability to gather information and has helped to ensure that medical product companies act in compliance with the law. However, Congress recently amended the law and medical product companies are now required to publish **all** clinical trials and summaries of adverse events, even for trials that are **discontinued**. Therefore, as these changes are fully implemented, there will be less need to supplement the FDA's information gathering with private litigation because the FDA and the general public will be aware of adverse events that led to discontinued trials.

The importance of litigation as a tool to ensure medical company compliance with FDA regulations is also on the decline. Although strongly criticized for under-enforcement, recent data indicates that enforcement activities **are** increasing. Further, the ready availability of the expanded clinical trial data to the general public will allow watchdog groups to supplement agency enforcement activities via citizen's petitions. Thus, many of the criticisms leveled against the FDA are being addressed, indicating that the agency may be the better mechanism for deciding the content of package inserts.

Given these facts and trends, the authors suggest that Congress should consider providing an express preemption clause in the Food

Drug and Cosmetic Act. This clause should be drafted to prevent failure-to-warn litigation regarding package inserts, but provide exceptions for the misrepresentation of data or delays in its presentation. Thus, the careful balancing of risks and benefits will be placed back in the hands of the medical experts at the FDA and its non-employee Advisory Committees, but the threat of litigation will remain available to deter misconduct.

This Article develops this policy argument for legislatively changing the *Wyeth* outcome. We emphasize from the outset that our concern lies with “package inserts”—the detailed instructions for use of a medical device or drug that is **pre**-approved by the FDA before the drug or device can enter the market. The content of the package insert reflects a careful balancing of product risks and benefits and contains highly technical information to allow medical professionals to evaluate the risks and benefits of each product before prescribing it to a patient.³ As such, it is our proposal that the package insert should not be subject to state-by-state jury decisions regarding content.

We are **not**, however, concerned herein with **other** types of consumer communications, such as direct-to-consumer television or magazine advertisements or web sites for specific products. Such advertisements, while subject to FDA regulation,⁴ are **not** pre-approved before deployment and do not reflect the same risk benefit balancing efforts. Instead, such ads are highly simplified and serve to provide consumers some information about a product, while referring them to the package insert for complete information. Further, when a medical product company bypasses the medical expert, omits safety information and advertises directly to consumers, it incurs a greater risk of misleading patients. Thus, direct-to-consumer advertising lies outside the scope of our comparative institutional analysis.

Section One presents a general discussion of the goals of the preemption doctrine and its doctrinal outline. Section Two describes the regulatory framework for both drugs and medical devices. Sections Three and Four present discussions and analyses of the *Riegel* and *Wyeth* cases. Section Five presents the broader discussion of who

³ Christine H. Kim, *The Case for Preemption of Prescription Drug Failure-to-Warn Claims*, 62 FOOD & DRUG L.J. 399, 405 (2007) (“The centerpiece of risk management for prescription drugs’ is its labeling” (citation omitted)).

⁴ See, e.g., 37 C.F.R. § 202.1 (2010). For information on the FDA’s current thinking on direct-to-consumer advertising, see FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PRESENTING RISK INFORMATION IN PRESCRIPTION DRUG AND MEDICAL DEVICE PROMOTION (2009), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM155480.pdf>.

should decide the salient issue in each of these cases. It is in Section Five that we examine the ramifications of over-warning.

I. GENERAL PREEMPTION PRINCIPLES

In any system of law with different tiers of regulation, such as country, state or municipality, there exist legal principles to ensure that the various regulations do not conflict, and, where they do conflict, there are principles in place for resolving the inconsistency. “Preemption” refers generally to the displacement of a lower jurisdiction’s laws when they conflict with those of a higher jurisdiction. In the United States in particular, federal preemption refers to the displacement of state law by federal law.

Our preemption doctrine stems directly from the Supremacy Clause of the United States Constitution, which states:

This Constitution, and the Laws of the United States which shall be made in Pursuance thereof; and all Treaties made, or which shall be made, under the Authority of the United States, shall be the supreme Law of the Land; and the Judges in every State shall be bound thereby, any Thing in the Constitution or Laws of any State to the Contrary notwithstanding.⁵

Thus, the Supremacy Clause provides that federal laws are supreme over state laws and when the two directly conflict, the Constitution dictates that federal law controls and the state law is unenforceable.⁶

However, the framers of the U.S. Constitution envisioned a political system that avoided the concentration of power in a small number of individuals. Thus, power is dispersed between the three branches of the federal government and also between the state and federal governments.⁷ Federal power is thus limited under our Constitution, and the Tenth Amendment reflects a bias towards maintaining state powers to regulate: “The powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively, or to the people.”⁸

⁵ U.S. CONST. art. VI, cl. 2.

⁶ *Gibbons v. Ogden*, 22 U.S. (9 Wheat.) 1, 129 (1824) (“In case of collision, therefore, the State laws must yield to the superior authority of the United States.”).

⁷ *United States v. Lopez*, 514 U.S. 549, 561 n.3 (1995) (holding that the Constitution ensures state legislative authority by delegating specific powers to the federal government and limiting the exercise of federal legislative authority to these delegated powers).

⁸ U.S. CONST. amend. X.

In keeping with this principle of limited federal powers, the courts are guided by a presumption against preemption.⁹ This presumption holds that the “historic police powers of the States [are] not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.”¹⁰ The presumption against preemption applies with “particular force when Congress has legislated in a field traditionally occupied by the States,”¹¹ and this is particularly true in health and safety, where the states have historically regulated.¹² Thus, preemption is not the preferred choice, and if two laws can exist side-by-side, they will each be allowed to stand.

In deciding preemption cases, the courts have long recognized two types of preemption—express preemption and implied preemption. Express preemption “occurs when a federal statute includes a preemption clause explicitly withdrawing specified powers from the states.”¹³ In enacting legislation Congress can expressly dictate that

⁹ *California v. FERC*, 495 U.S. 490, 497 (1990) (“This interpretation would accord with the ‘presumption against finding pre-emption of state law in areas traditionally regulated by the States’ and ‘with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress.’” (citations omitted)); *Jones v. Rath Packing Co.*, 430 U.S. 519, 525 (1977) (discussing the normal presumption against finding preemption).

¹⁰ *Altria Group, Inc. v. Good*, 129 S. Ct. 538, 543 (2008) (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)).

¹¹ *Id.*; *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996) (holding that the preemption clause in the medical device statute did not preempt common law causes of action for negligent design and labeling of a 501(k) medical device and stating “we used a ‘presumption against the pre-emption of state police power regulations’ to support a narrow interpretation of such an express command in *Cipollone*. That approach is consistent with both federalism concerns and the historic primacy of state regulation of matters of health and safety.” (citation omitted)); *see also Lorillard Tobacco Co. v. Reilly*, 533 U.S. 525, 541-42 (2001) (applying the federal preemption standard to advertising because advertising is a field of traditional state regulation). *But see Geier v. American Honda Motor Co.*, 529 U.S. 861, 871 (2000) (not applying a presumption or ‘special burden’ against preemption where there was both a preemption clause and a savings clause for common law liability because “Congress [would] have wanted ordinary pre-emption principles to apply where an actual conflict with a federal objective is at stake[.]”).

¹² *Medtronic*, 518 U.S. at 475 (“Throughout our history the several States have exercised their police powers to protect the health and safety of their citizens. Because these are ‘primarily, and historically . . . matter[s] of local concern,’ the ‘States traditionally have had great latitude under their police powers to legislate as to the protection of the lives, limbs, health, comfort, and quiet of all persons.’” (citations omitted)).

¹³ Caleb Nelson, *Preemption*, 86 VA. L. REV. 225, 226 (2000); *see also Jones v. Rath Packing Co.*, 430 U.S. at 532 (holding that the Federal Meat Inspection Act (FMIA) preempted a California statute, used to evaluate the average weight or measure of any commodity, as applied to packed meat).

state laws are preempted,¹⁴ and Congress often does so. However, even where a federal law contains an express preemption clause, the **scope** of the preemption and whether a state law lies within that scope still must be determined, leading to considerable variation in the judicial interpretations of a simple preemption clause.¹⁵ For example, many statutes expressly preempt any state “requirements” that conflict with the federal requirements. Most would agree that the word “requirements” should apply to any contradictory state laws or regulations, but there can be considerable disagreement as to whether common law tort causes of action are also preempted.¹⁶

Implied preemption may manifest itself in several ways. The Supreme Court has often found that Congress enacted a statute that was “so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it.”¹⁷ Similarly, the Supreme

¹⁴ *English v. General Elec. Co.*, 496 U.S. 72, 78-79 (1990).

¹⁵ *Altria Group*, 129 S. Ct. at 543 (“If a federal law contains an express preemption clause, it does not immediately end the inquiry because the question of the substance and scope of Congress’ displacement of state law still remains.”).

¹⁶ *E.g.*, *Medtronic*, 518 U.S. at 485 (applying a presumption against preemption in deciding the *scope* of an express preemption clause in the area of health and safety and holding that no preemption of common law tort claims exists for medical devices that are *not* PMA approved and stating “‘in a field which the States have traditionally occupied,’ we ‘start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress . . . Although dissenting Justices have argued that this assumption should apply only to the question whether Congress intended any preemption at all, as opposed to questions concerning the scope of its intended invalidation of state law . . . That approach is consistent with both federalism concerns and the historic primacy of state regulation of matters of health and safety.’”) (emphasis added) (citations omitted); *cf.* *Cipollone v. Liggett Grp., Inc.*, 505 U.S. 504, 545, 548 (1992) (Scalia, J., dissenting) (“First, [the opinion] says that express pre-emption provisions must be given the narrowest possible construction. This is in its view the consequence of our oft repeated assumption that, absent convincing evidence of statutory intent to pre-empt, ‘the historic police powers of the States [are] not to be superseded.’ But it seems to me that assumption dissolves once there is conclusive evidence of intent to pre-empt in the express words of the statute itself, and the only remaining question is what the scope of that pre-emption is meant to be” and concluding that where “the pre-emption provision was intended to sweep broadly, our construction must sweep broadly as well.” (citation omitted)); *see also* *Geier, v. American Honda Motor Co.*, 529 U.S. at 867-68, 870 (holding that the preemption clause coupled with a saving clause that did not “exempt any person from any liability under common law” allowed state tort claims, but holding that the claim action at issue nonetheless provided an actual conflict with the law and was nevertheless preempted) (quoting 15 U.S.C. § 1397(k) (1988)).

¹⁷ *English*, 496 U.S. at 79 (quoting *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947)); *see* *Pennsylvania R. Co. v. Public Service Comm’n*, 250 U.S. 566, 569 (1919) (striking down a Pennsylvania statute as being preempted by federal regulations concerning the size and structure of mail cars located at the end of trains);

Court has also found that when an act of Congress touches “a field in which the federal interest is so dominant that the federal system will be assumed to preclude enforcement of state laws on the same subject.”¹⁸ This is generally known as “field preemption.”

Implied preemption can also occur “[e]ven where Congress has not entirely displaced state regulation in a specific area” to the extent that the state regulation “actually conflicts” with federal law.¹⁹ Such conflict may arise when “compliance with both federal and state regulations is a physical impossibility”²⁰ or if compliance with state law “stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.”²¹ This type of preemption is typically referred to as “conflict preemption.”

II. THE FOOD DRUG AND COSMETIC ACT

In order to understand preemption as applied to drugs and medical devices, one must understand not only the general statutory scheme for the Food Drug and Cosmetic Act (FDCA), but also the regulations promulgated thereunder in some detail. We therefore begin with an overview of the regulatory scheme and the essential details needed to understand the preemption analysis that follows.

The Food and Drug Administration (FDA) is the oldest consumer protection agency in the U.S. federal government, originating in the

Cloverleaf Butter Co. v. Patterson, 315 U.S. 148, 154 (1942) (holding that the entire process of manufacture of renovated butter was subject to federal supervision, which superseded any Alabama state regulations that applied).

¹⁸ *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218, 230 (1947) (citing *Hines v. Davidowitz*, 312 U.S. 52 (1941)) (holding that immigration and naturalization laws are the exclusive province of Congress and preclude the enforcement of state alien registration acts).

¹⁹ *Pacific Gas & Elec. Co. v. State Energy Res. Conservation & Dev. Comm'n*, 461 U.S. 190, 203-05 (1983) (holding that a California code addressing storage capacity for a proposed nuclear powerplant’s spent fuel does not conflict with federal regulation of nuclear waste disposal).

²⁰ *Id.* at 204 (quoting *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 141, 142-43 (1963)); *see, e.g., Boggs v. Boggs*, 520 U.S. 833, 844 (1997) (holding that a Louisiana state law allowing a nonparticipant spouse to transfer by testamentary instrument an interest in undistributed pension plan benefits is in direct conflict with ERISA and that compliance with both is an impossibility and that therefore the state law is preempted); *Edgar v. MITE Corp.*, 457 U.S. 624 (1982) (finding federal preemption where filing a schedule with the SEC about a tender offer pursuant to the Williams Act would violate the Illinois Business Take-Over Act).

²¹ *Hines v. Davidowitz*, 312 U.S. 52, 67 (1941); *see, e.g., Crosby v. Nat’l Foreign Trade Council*, 530 U.S. 363, 388 (2000) (holding that a Massachusetts law, which barred state entities from buying goods or services from providers linked with Myanmar, frustrated a federal act that gave the President the flexibility to implement the sanctions policy and was thus preempted).

first decade of the Twentieth Century, albeit under a different name. In 1906, Upton Sinclair published “The Jungle,” a novel describing the appalling conditions in Chicago’s meat packing plants. An instant bestseller, Sinclair’s book reeked with the stink of the stockyards. He told how dead rats were shoveled into sausage-grinding machines, how bribed inspectors looked the other way when diseased cows were slaughtered for beef, and how filth and guts were swept off the floor and packaged as “potted ham.” The book has some horrifying excerpts:

. . . as for the other men, who worked in tank rooms full of steam, and in some of which there were open vats near the level of the floor, their peculiar trouble was that they fell into the vats; and when they were fished out, there was never enough of them left to be worth exhibiting—sometimes they would be overlooked for days, till all but the bones of them had gone out to the world as Durham’s Pure Leaf Lard!

Mr. Sinclair’s intent in writing the novel was to expose the “inferno of exploitation” of the typical American factory worker at the turn of the Twentieth Century, but the public instead fixated on food safety and meat sales fell by half. Mr. Sinclair wryly noted the limited effect of his book by stating, “I aimed at the public’s heart, and by accident I hit it in the stomach.”²²

The (un)popular press generated from “The Jungle” gave Congress the impetus to act. Thus, the original Food and Drug Act, also known as the “Wiley Act,” was passed in 1906. Although it was not known by its present name until 1930, the FDA’s modern regulatory functions began with the passage of the Wiley Act, which prohibited interstate commerce in “adulterated” or “misbranded” food and drugs.²³

Three decades later, more than a hundred people, many of them children, were killed by the “Elixir of Sulfanilamide”—an antibiotic dissolved in the sweet but poisonous solvent diethylene glycol.²⁴ In response, the Federal Food, Drug, and Cosmetic Act of 1938

²² Upton Sinclair, *What Life Means to Me*, COSMOPOLITAN MAG., May-Oct. 1906, at 591, 594.

²³ Wiley Act, ch. 3915, § 2, 34 Stat. 768, 768 (1906), repealed by 21 U.S.C. § 329(a) (1938).

²⁴ See *Deaths Following Elixir of Sulfanilamide-Massengill*, 109 JAMA 1367, 1367 (1937); see also Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, FDA CONSUMER, June 1981, at 18, 21.

(FDCA)²⁵ was passed, and for the first time required a drug to be proven “safe” before marketing.

The thalidomide tragedy sparked another expansion of FDA law. Launched in 1957, thalidomide was proclaimed a “wonder drug” for insomnia, coughs, colds and headaches. It was also found to inhibit morning sickness, and ten of thousands of pregnant women took the drug to relieve their nausea. Even though it had already been approved in over twenty European and African countries, Dr. Frances Oldham Kelsey withheld U.S. approval for the drug, requesting further studies to explain an English study that documented a side effect in the nervous system. Dr. Kelsey’s insistence that the drug should be fully tested prior to approval was dramatically vindicated²⁶ when some 10,000–20,000 children in forty-six countries were born with limb deformities as a direct result of the drug’s use. Even though not approved in the U.S., more than a thousand Americans had ingested unlabeled thalidomide tablets under the then unregulated clinical testing.²⁷ Partially in response to the thalidomide tragedy,²⁸ amendments to the FDCA were passed in 1962 requiring drugs to be proven “effective” and safe before marketing, as well as requiring informed consent for patients participating in clinical trials and the reporting of adverse drug reactions.

Thus, by 1962, the FDA’s core mandate was formulated: to ensure that drugs are (i) safe, (ii) effective, (iii) unadulterated, and (iv) not misbranded. Of course, there have been many amendments to the FDCA not elaborated herein, but the reader can nonetheless appreciate based on this abbreviated history that FDA powers and responsibilities have only increased since its inception.

²⁵ Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301 *et. seq.*).

²⁶ Dr. Kelsey was awarded the President’s Award for Distinguished Federal Civilian Service by President John F. Kennedy for her actions. S. Vincent Rajkumar, *Thalidomide: Tragic Past and Promising Future*, 79 MAYO CLINIC PROC. 899, 899 (2004).

²⁷ John Mulliken, *A Woman Doctor Who Would Not Be*, LIFE, Aug. 10, 1962, at 28 (“As part of the application procedure, [the manufacturer] had already sent the drug out to American doctors—the number eventually reached 1200—for testing. This was standard drug firm procedure, permitted by the law. . .”).

²⁸ Numbers vary, but only seventeen to forty American babies were born deformed due to inadequate regulations. Sarah Richardson, *Helping the Medicine Go Down*, NEWSDAY (NEW YORK), Apr. 6, 2003, at D35 (“Because of Kelsey’s caution, the estimated cases of affected American babies numbered about 40, while some 8,000 or more cases occurred in Europe.”); *The Return of Thalidomide*, WASH. TIMES, July 25, 1998, at C2 (“Since the FDA kept the drug from U.S. approval, not many American women had access to it, and there were only about two dozen American thalidomide babies.”).

Our preemption analysis will focus largely on the “misbranding” aspects of the Food, Drug, and Cosmetic Act—whereby the FDA ensures that the drug is correctly labeled and that all advertising relating to a drug is also correct.²⁹ A drug is misbranded if, among other things, the drug’s “labeling is false or misleading in any particular,” or if the labeling does not provide “adequate directions for use” or “adequate warnings.”³⁰ A drug that “is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof” does not comply with FDA regulations.³¹

Under the FDCA, a drug manufacturer may not market a new drug unless it has submitted a new drug application (NDA) to the FDA and received FDA approval.³² In addition to showing that the drug is safe and effective, as well as correctly manufactured (not adulterated), the drug application must contain “the labeling proposed to be used for such drug”³³—in other words, the drug must not be misbranded. Also required is “a discussion of why the benefits exceed the risks [of the drug] under the conditions stated in the labeling.”³⁴ Thus, unlike many other consumer products, the labeling of a medical product is the guidepost by which both safety and effectiveness are evaluated.³⁵ In other words, can the medical product be considered reasonably safe and effective under the conditions of use prescribed in the “label”?

The FDA will approve a new drug application if it finds, among other things, that (i) the drug is “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof”; (ii) there is “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof”; and (iii) the proposed labeling is not “false or misleading in any particular.”³⁶

Even after a drug has been approved and enters the market, the manufacturer must investigate and report to the FDA any adverse

²⁹ 21 U.S.C. § 331(a)-(b) (2006).

³⁰ 21 U.S.C. § 352(a), (f).

³¹ 21 U.S.C. § 352(a), (f), (j).

³² 21 U.S.C. § 355 (applying this provision to new drugs, but many drugs were grandfathered in since they were already on the market when these amendments were passed).

³³ 21 U.S.C. § 355(b)(1)(F); 21 C.F.R. § 314.50(c)(2)(i), (e)(2)(ii) (2010).

³⁴ 21 C.F.R. § 314.50(d)(5)(viii); 21 C.F.R. § 314.50(c)(2)(ix).

³⁵ Kim, *supra* note 3, at 405 (“The centerpiece of risk management for prescription drugs’ is its labeling”) (cite omitted).

³⁶ 21 U.S.C. § 355(d).

events associated with use of the drug in humans,³⁷ and must periodically submit any new information that may affect the FDA's previous conclusions about the safety, effectiveness, or labeling of the drug.³⁸ The FDA "shall" withdraw its approval of an application if it finds, among other things, that the drug is not safe or effective under the conditions of use specified in the drug's labeling.³⁹

Once approved, the manufacturer generally may **not** make changes to the drug, including "[c]hanges in labeling," without first submitting a supplemental application to the FDA and securing the agency's prior approval for the change.⁴⁰ A manufacturer must submit such a supplemental application "to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug,"⁴¹ although "[a]n applicant may ask FDA to expedite its review of a supplement for public health reasons."⁴²

Critical to an understanding of the Supreme Court's preemption analysis in the drug context is the FDA's so-called "changes being effected" or "CBE" regulation at 21 C.F.R. §314.70(c). On its face, this regulation seems to allow drug manufacturers to strengthen safety language **without** prior FDA approval, as long as the manufacturer simultaneously informs the FDA of the change. The regulation reads in relevant part:

. . . An applicant shall submit a supplement at the time the applicant makes any kind of change listed below in the conditions in an approved application . . . Changes labeling to accomplish any of the following: (i) To **add or strengthen a contraindication, warning, precaution, or adverse reaction** (emphasis added) . . .

Thus, on its face, 21 C.F.R. §314.70(c) **allows** the manufacture to add or strengthen a warning **without** prior approval by the FDA. Although quite permissive on its face, the FDA in practice does **not** allow label changes without prior approval except in cases of emergency and pharmaceutical companies rarely, if ever, invoke it. Instead, the FDA interprets the CBE regulation to permit changes without pri-

³⁷ 21 C.F.R. § 314.80.

³⁸ See 21 U.S.C. § 355(k) (describing post-approval reporting and record-keeping requirements); 21 C.F.R. § 314.81.

³⁹ 21 U.S.C. § 355(e).

⁴⁰ 21 C.F.R. § 314.70(b)(1)-(2).

⁴¹ 21 C.F.R. § 201.57(c)(6).

⁴² 21 C.F.R. § 314.70(b)(4).

or approval only to address “newly discovered risks.”⁴³ The FDA emphasized this point in the final rule approval, stating:

. . . CBE supplements were intended as a **narrow exception** to the general rule that labeling changes require FDA’s prior approval:

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling * * * are more likely than other changes to affect the agency’s previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately approved by FDA in advance, **unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.**⁴⁴

Initially, the Food Drug and Cosmetic Act did **not** apply to medical devices—but then came the Dalkon Shield. The Dalkon Shield, introduced in 1970, was a plastic intrauterine device that looked like a round bug with one large eye, five legs on each side, and a tail. The device was inserted into the uterus to prevent pregnancy, and the tail hung out of the cervix for easy removal of the device. According to one theory, the tail was composed of multiple fibers and thus “wick-ed” materials from the vaginal environment into the normal sterile environment of the uterus by capillary action, causing infection and resulting complications.⁴⁵

By the spring of 1974, the manufacturer had received hundreds of complaints and the device was voluntarily removed from the market. The Dalkon Shield was eventually linked to several deaths, thousands of infections, and allowed a higher rate of pregnancies than other

⁴³ 47 Fed. Reg. 46,622, 46,623, 46,635 (Oct. 19, 1982).

⁴⁴ 73 Fed. Reg. 2850 (Jan. 16, 2008) (quoting 50 Fed. Reg. 7470 (Feb. 22, 1985)) (emphasis added).

⁴⁵ Howard J. Tatum et al., *Morphological Studies of Dalkon Shield Tails Removed from Patients*, 11 *CONTRACEPTION* 465, 465-77 (1975) (“Examination of the tails of Dalkon Shields removed from patients showed that approximately 34% of the tails had breaks or holes in the nylon sheath immediately below the double knot at the base of the Shield. . . . Bacteria were found within the interfilamental spaces inside the sheath of 8 of the 10 tails. These observations suggest that bacteria which have ascended through the tail from the vagina could exit through these breaks in the sheath or from the terminal end of the tail directly into the endometrial cavity.”).

IUDs, many of which were complicated.⁴⁶ Over time, more than 300,000 complaints were filed against the company for its manufacture and sale of the Dalkon Shield.⁴⁷

Congress enacted the Medical Device Amendments (MDA) to the FDCA in 1976, largely in response to the Dalkon Shield debacle, and thereby extended the premarket approval process to medical devices.⁴⁸ Since the term “medical devices” covers a broad scope of devices—ranging from bandages to pacemakers—the MDA regulates medical devices according to the risks the device presents to its user. Thus, medical devices are categorized into three classes.

Class I devices, such as tongue depressors, are generally subject only to minimal controls by the FDA because of their generally accepted safety.⁴⁹ Class II devices, such as tampons, are subject to more specialized controls that may include performance standards or specific guidelines for each type of device.⁵⁰ Many (but not all) Class II devices are also subject to an abbreviated clearance process known as the premarket notification or 510(k) process. In the 510(K) application, all that needs to be shown is “substantial equivalence” to a predicate device already on the market. Thus, the 501(k) is somewhat analogous to the abbreviated new drug application for generic drugs. Class III devices—such as pacemakers—are the riskiest devices and must undergo a stringent premarket approval (PMA) process because of the central role they play in saving lives.⁵¹ The PMA process requires clinical testing to show safety and effectiveness, manufacturing details and proposed labeling, and is analogous to the new drug application, albeit differing in some details.⁵² Important to understanding medical device regulation is the fact that devices were grandfathered into the system if they were already on the market. Thus, many devices that might appear as though they should be subject to premarket approval are nonetheless cleared under the lenient 501(k) process, if that device or predicate devices were already on the market at the time the MDA was enacted. Thus, the classification system only roughly correlates

⁴⁶ Jacques-E. Rioux et al., *Long-term Study of the Safety of the Dalkon Shield and Gyne-T 200 Intrauterine Devices*, 134 CAN. MED. ASS'N J. 747, 747 (1986) (comparing two IUDs and noting that the rate of accidental pregnancy per 100 women were 3.8 for the Dalkon Shield users and 1 for another IUD, although rates of pelvic inflammatory disease, pregnancy outcomes, and infertility rates were similar).

⁴⁷ Georgene M. Vairo, *The Dalkon Shield Claimants Trust: Paradigm Lost (Or Found)?*, 61 FORDHAM L. REV. 617, 628 (1992).

⁴⁸ 21 U.S.C. §§ 360c-360e (2006).

⁴⁹ See 21 U.S.C. § 360c(a)(1)(A).

⁵⁰ See 21 U.S.C. § 360c(a)(1)(B).

⁵¹ See 21 U.S.C. § 360c(a)(1)(C).

⁵² 21 U.S.C. §360e; 21 C.F.R. § 814 (2010).

with the PMA process, and many Class III devices are only 510(k) cleared.

When the MDA was enacted in 1976 some states had already promulgated statutes designed to bridge the regulatory gap for medical devices.⁵³ Therefore, the MDA also provided an express preemption clause:

[N]o State or political subdivision of a State may establish or continue in effect with respect to a device intended for human use any requirement—

- (1) which is different from, or in addition to, any requirement applicable under this chapter to the device, and
- (2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under this chapter.⁵⁴

Thus, unlike the rest of the FDCA, preemption is expressly provided for medical device law and regulations only.

III. PREEMPTION AND MEDICAL DEVICES

The most recent Supreme Court case dealing with preemption and the FDA's regulation of medical devices was *Riegel v. Medtronic*,⁵⁵ in which the Court addressed the preemption provisions of the MDA. The device at issue in *Riegel* was a balloon catheter.⁵⁶ Balloon catheters are designed to be inserted into a blocked artery and inflated in order to clear the blockage.⁵⁷ The catheter was contraindicated for patients with diffuse or calcified stenoses, because those arteries may be insufficiently flexible for the procedure and might rupture on inflation of the balloon.⁵⁸ Further, the device's "label also warned that the catheter itself should not be inflated beyond its rated burst pressure of eight atmospheres."⁵⁹

In spite of the label, Riegel's doctor employed the balloon catheter in a coronary artery that was heavily calcified.⁶⁰ Additionally, the

⁵³ *E.g.*, 1970 Cal. Stats. ch. 1573, §§ 26670–26693.

⁵⁴ 21 U.S.C. § 360k(a) (2006).

⁵⁵ *Riegel v. Medtronic, Inc.*, 552 U.S. 312, 315 (2008).

⁵⁶ *Riegel*, 551 U.S. at 320.

⁵⁷ THE MERCK MANUAL OF HEALTH & AGING 672 (Mark H. Beers et al. eds., mass market ed. 2006).

⁵⁸ *Riegel*, 551 U.S. at 320.

⁵⁹ *Id.*

⁶⁰ *Id.*

doctor inflated the catheter to a pressure of 10 atmospheres.⁶¹ Not surprisingly, the catheter ruptured, Mr. Riegel developed a heart block and underwent emergency coronary bypass surgery.⁶²

The Riegels claimed the device was negligently designed, labeled, and manufactured in a manner that violated New York common law and that the defects led to severe and permanent injuries.⁶³ Thus, the Complaint contained a number of common law claims including strict liability, negligence, breach of implied warranty and loss of consortium.⁶⁴

The catheter was a Class III device and was subject to premarket approval before use.⁶⁵ Therefore, the federal district court held that the MDA preempted all of the Riegels' state claims, including the loss of consortium claim, because it was a derivative of the preempted state claim.⁶⁶ This decision was affirmed by the United States Court of Appeals for the Second Circuit on the basis that if the Riegels' claims were successful, they would impose state requirements that differed from the federal requirements imposed during the rigorous premarket approval process.⁶⁷

In reviewing the case, the Supreme Court stated that since the MDA expressly preempts state requirements that differ from federal requirements, it must answer two questions. First, it must first determine whether the government has established requirements for the catheter.⁶⁸ If so, then the second question is whether the common-law claims are based upon New York requirements that differ from or are in addition to the federal requirements.⁶⁹

With respect to the first question, the Court held that because Medtronic's catheter received premarket approval, the device could not be made with any deviation from the premarket approval application and thus the federal government had established specific requirements for the device.⁷⁰

⁶¹ *Id.*

⁶² *Id.*

⁶³ *Id.*

⁶⁴ *Id.* at 320-21.

⁶⁵ *Id.* at 320.

⁶⁶ *Id.* at 320-21.

⁶⁷ *Id.* at 321.

⁶⁸ *Id.*

⁶⁹ *Id.* 321-22.

⁷⁰ *Id.* at 323. "Premarket approval is a 'rigorous' process." The FDA grants premarket approval only if it finds there is a "reasonable assurance" of the device's "safety and effectiveness." *Id.* at 317-18 (quoting 21 U.S.C. § 360e(d) (2006)); *cf.* *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 471 (1996) (holding that preemption does not apply to devices only subject to a "substantial equivalence" analysis (e.g., 501(k) premarket notification) because such clearance did not include review of safety and

Turning to the second question, the Court held that references to State “requirements” clearly encompassed its common law duties and that the State requirements were in fact different from the device-specific federal requirements.⁷¹ As a result, the Court affirmed the Second Circuit’s ruling holding that Medtronic was subject only to the device-specific requirement of adhering to the standards contained in its individual, federally approved premarket approval application, and that any further state requirements that required the device to be safer—but possibly less effective—were preempted.⁷²

This decision was by an eight to one margin, with only Justice Ginsburg dissenting, making it highly unlikely that the Court will overrule its decision anytime in the near future. Thus, preemption of state failure-to-warn cases is the rule for those medical devices that—like drugs—are subject to premarket approval. Cases relating to devices that are only cleared under the 510(k) process are not preempted,⁷³ but we focus herein on the riskiest medical devices that are subject to same type of premarket approval process that drugs and biologics are subject to.

IV. PREEMPTION LAW AS IT APPLIES TO DRUGS

In contrast to medical devices, federal preemption is **not** the rule in pharmaceutical cases. The issue came to the Supreme Court cloaked in tragedy. Diana Levine—a bass, guitar and piano player and author of children’s music in Vermont—visited a clinic to receive treatment for severe headache-related nausea, but wound up losing her arm to gangrene and is now unable to play any musical instrument.

A physician’s assistant (PA) attending to Ms. Levine administered Phenergan using a delivery technique known as an “IV push,” inadvertently injecting the drug into one of Ms. Levine’s arteries in the process, severely damaging the tissue and causing gangrene. Not surprisingly, Ms. Levine sued the clinic and the PA for malpractice and received a \$700,000 settlement. But Ms. Levine also sued the manufacturer—Wyeth—alleging that the warning labels were insufficient.

effectiveness). The device at issue in the *Medtronic, Inc. v. Lohr* case—a pacemaker—was a significant risk class III device, but it was grandfathered in under the 501(k) exception because it was a substantial equivalent to a pacemaker already on the market when the MDA was enacted. Thus, the FDA never reviewed the safety and efficacy of that device.

⁷¹ *Riegel*, 552 U.S. at 323-24.

⁷² *Id.* at 325, 329-30.

⁷³ *Medtronic*, 518 U.S. at 471-72 (holding that the preemption clause in the medical device statute did not preempt common law causes of action for negligent design and labeling of a 501(k) medical device).

The drug at issue—Phenergan®—is also known as promethazine and is an antihistamine used to treat allergy symptoms. Phenergan® also prevents motion sickness, and treats nausea and vomiting or pain after surgery, and can be used as a sedative or sleep aid. However, Phenergan®—like all drugs—has unwanted side effects, including the ability to cause gangrene when incorrectly injected into an artery. In fact, it has been known for decades that Phenergan® can cause gangrene when injected intra-arterially,⁷⁴ and the package insert specifically contraindicated intra-arterial injection:

CONTRAINDICATIONS

Under no circumstances should PHENERGAN Injection be given by intra-arterial injection due to the likelihood of severe arteriospasm and the possibility of resultant gangrene (see WARNINGS—Severe Tissue Injury, Including Gangrene).⁷⁵

The insert warned that **all** injection sites could cause severe reactions:

Injection Site Reactions

PHENERGAN Injection can cause severe chemical irritation and damage to tissues, regardless of the route of administration. Irritation and damage can also result from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration.⁷⁶

The insert went on to state that the symptoms of damage include pain and burning, and that gangrene and amputation could result:

⁷⁴ B.S. Goldman et al., *The Recognition And Management Of Peripheral Arterial Injuries*, 92 J. CAN. MED. ASS'N 1154, 1156 (1965) (“[A] 42-year-old man[] inadvertently received an injection of promethazine into the radial artery . . . [and] amputation of all or part of each digit was required because of gangrene.”).

⁷⁵ See Phenergan Package Insert (on file with author); see also NATIONAL PBM DRUG GUIDANCE, PROMETHAZINE HCL INJECTION, USP (PHENERGAN®) (2007), available at [http://www.pbm.va.gov/vamedsafe/IV%20Promethazine%20\(Phenergan\)%20and%20Tissue%20Injury%20%E2%80%93%20August%2010,%202006.pdf](http://www.pbm.va.gov/vamedsafe/IV%20Promethazine%20(Phenergan)%20and%20Tissue%20Injury%20%E2%80%93%20August%2010,%202006.pdf); *Information for Healthcare Professionals—Intravenous Promethazine and Severe Tissue Injury, Including Gangrene*, U.S. FOOD AND DRUG ADMIN. (Sept. 16, 2009), <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm182169.htm>; *Phenergan Injection Official FDA Information, Side Effects and Uses*, DRUGS.COM, <http://www.drugs.com/pro/phenergan-injection.html> (last visited Mar. 31, 2011).

⁷⁶ See *supra* note 75.

Signs, symptoms, and manifestations of severe tissue irritation include burning, pain, erythema, swelling, severe spasm of distal vessels, thrombophlebitis, venous thrombosis, phlebitis, abscesses, tissue necrosis, and gangrene. Administration of PHENERGAN Injection has resulted in nerve damage ranging from temporary sensory loss to palsies and paralysis. Injection into or near a nerve may result in permanent tissue damage. In some cases, surgical intervention (including fasciotomy, skin graft, and/or amputation) may be required (see ADVERSE REACTIONS).⁷⁷

The insert also warned specifically against inadvertent intra-arterial injections, which are known to happen on intravenous (IV) administration, and can result in gangrene and amputation:⁷⁸

Inadvertent Intra-Arterial Injection

Due to the close proximity of arteries and veins in the areas most commonly used for intravenous injection, extreme care should be exercised to avoid perivascular extravasation or unintentional intra-arterial injection. Reports compatible with unintentional intra-arterial injection of PHENERGAN Injection, usually in conjunction with other drugs intended for intravenous use, suggest that pain, severe chemical irritation, severe spasm of distal vessels, and resultant gangrene requiring amputation are likely under such circumstances. Intravenous injection was intended in all the cases reported but perivascular extravasation or arterial placement of the needle is now suspect. There is no proven successful management of unintentional intra-arterial injection or perivascular extravasation after it occurs. Sympathetic block and heparinization have been employed during the acute management of unintentional intra-arterial injection, because of the results of animal experiments with other known arteriolar irritants. Aspiration of dark blood does not preclude intra-arterial needle placement, because blood is discolored upon contact with PHENERGAN Injection. Use of syringes with rigid plungers

⁷⁷ *Id.*

⁷⁸ Douglas Goldsmith & Norman Trieger, *Accidental Intra-Arterial Injection: A Medical Emergency*, 22 ANESTHESIA PROGRESS 180, 180 (1975) (“One of the potentially serious complications of administering intravenous medication is the inadvertent injection into an artery.”).

or of small-bore needles might obscure typical arterial back-flow if this is relied upon alone.⁷⁹

Further, the insert specifically stated that the dosage rate should **not** exceed 25 mg per minute, and again stated that the preferred route was by intravenous infusion, also known as IV drip:

When used intravenously, PHENERGAN Injection should be given in a concentration no greater than 25 mg per mL and at a rate not to exceed 25 mg per minute. When administering any irritant drug intravenously, it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily.⁸⁰

It also warned that the injection should be stopped **immediately** if the patient reported pain during intravenous injection:

In the event that a patient complains of pain during intended intravenous injection of PHENERGAN Injection, the injection should be stopped immediately to provide for evaluation of possible arterial placement or perivascular extravasation.⁸¹

Phenergan was first approved by the FDA in 1951 and was later approved for intravenous use, during which time the FDA and Wyeth discussed IV push as one means of administering Phenergan.⁸² Intravenous therapy or “IV” therapy is the giving of liquid substances directly into a vein.⁸³ An intravenous drip is the continuous infusion of fluids, with or without additional medications, through an IV access device.⁸⁴ In IV push, a syringe is connected to the IV access device and the medication is injected directly into the vein over a few minutes.⁸⁵ In contrast, in IV drip the drug is usually diluted into other fluids and dripped slowly into the patient’s vein over a longer period of time.⁸⁶

⁷⁹ See *supra* note 75.

⁸⁰ *Id.*

⁸¹ *Id.*

⁸² Details for Phenergan (NDA # 008857) are no longer available at the Drugs@FDA website and the drug has been discontinued (see <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>). Thus, the information provided here was obtained from the dissenting opinion in *Wyeth v. Levine*, 129 S. Ct. 1187, 1222 (2009) (Alito, J., dissenting).

⁸³ See THE BANTAM MEDICAL DICTIONARY 375 (6th ed. 2009).

⁸⁴ See *id.* at 219.

⁸⁵ SHARON M. WEINSTEIN, PLUMER’S PRINCIPLES AND PRACTICE OF INTRAVENOUS THERAPY 479 (8th ed. 2007).

⁸⁶ NANCY BRUNING, COPING WITH CHEMOTHERAPY 109 (rev. ed. 2002).

In August of 1975, representatives from both Wyeth and the FDA met to discuss Phenergan's warning label.⁸⁷ At that meeting, the FDA specifically proposed that Phenergan Injection should not be used in Tubex®—a syringe system designed for IV push.⁸⁸ The agency's concerns arose from "5 cases involving amputation where the drug had been administered by Tubex together with several additional cases involving necrosis."⁸⁹ Rather than contraindicating Phenergan for IV push, however, the parties agreed "that there was a need for better instruction regarding the problems of intra-arterial injection."⁹⁰

A year later, a FDA advisory committee recommended an additional IV-push-specific warning for Phenergan's label, but did **not** recommend eliminating IV push from the drug label altogether.⁹¹ Thereon, the FDA instructed Wyeth to make several changes to strengthen Phenergan's label, including the addition of upper case warnings related to IV push.⁹²

In 1987, the FDA directed Wyeth to again amend its label to direct that the drug "should be given in a concentration no greater than 25 mg/ml and at a rate not to exceed 25 mg/minute," and that "[i]njection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement."⁹³

In its 1987 labeling order, the FDA provided voluminous materials to support its stronger warnings against IV push and preference for IV drip, including published case reports from the 1960s of gangrene caused by the intra-arterial injection of Phenergan and numerous cautionary articles—one of which urged the agency to consider contraindicating such drugs for IV use altogether.⁹⁴

Thus, the FDA was not ignorant of the risk of gangrene with IV push. In fact, **many** drugs are known to cause severe injury on accidental intra-arterial injection,⁹⁵ but IV push remains a valuable treatment option for certain patients.⁹⁶ Presumably in view of the potential advantages in quick response time, cost and time savings, decreased

⁸⁷ *Wyeth*, 129 S. Ct. at 1222 (Alito, J., dissenting).

⁸⁸ *Id.*

⁸⁹ *Id.*

⁹⁰ *Id.*

⁹¹ *Id.*

⁹² *Id.*

⁹³ *Id.* at 1123.

⁹⁴ *Id.* at 1123-24.

⁹⁵ See Goldsmith & Trieger, *supra* note 78, at 180 ("Any drug given intra-arterially should be considered toxic.").

⁹⁶ *Wyeth*, 129 S. Ct. at 1231 (Alito, J., dissenting). The appendix to the dissent lists several drugs for which IV push is allowed, even where such drugs are very toxic when accidentally injected into the artery.

fluid load, and increased nurse monitoring throughout the shorter IV push procedure,⁹⁷ the FDA declined to prohibit the method altogether.⁹⁸

The actual record regarding the FDA thought processes, however, is practically non-existent.⁹⁹ Instead, the FDA record merely provides that the 1997 label should be the same as to the prior label.¹⁰⁰ The label changes proposed by Wyeth did not address prohibiting IV push, but merely rewording the current warnings.¹⁰¹ Thus, the court found as a factual matter that the record was insufficient to establish that the FDA considered and rejected an IV push contraindication.¹⁰² The fact remains, however, that the risk of gangrene and amputation was known by the FDA at the time of approval and at each time thereafter that the labels were revised. However, the FDA repeatedly declined to contraindicate IV push use of the drug.

⁹⁷ Richard Rosenfeld, *Clinical and Economical Considerations for IV Push Drug Delivery: An Overview of the Historical Background for IV Push and a Model for Implementation of a Successful Program* 3-4, (2007), <http://www.baxa.com/resources/docs/technicalPapers/IVPushTechPaper.pdf> (discussing IV push versus IV piggyback and noting several advantages of IV push, including decreased time for administration where the nurse remains on hand to monitor patients' reactions to the drug, improved clinical outcomes since nurses can spend the one to two minutes of administration talking to patients, increased patient compliance due to the shorter time constraints, and decreased fluid load for fluid-restricted patients); James C. Garrelts et al., *Postinfusion Phlebitis After Intravenous Push Versus Intravenous Piggyback Administration of Antimicrobial Agents*, 7 *CLINICAL PHARMACY* 760, 760 (1988) ("The fact that the catheter sites lasted significantly longer in the i.v. push group, combined with elimination of the cost of syringe infusion pumps or i.v. tubing and minibags, suggests that use of the i.v. push method may result in substantial cost savings.").

⁹⁸ The FDA does not regulate the practice of medicine, and would only "contraindicate" a usage, not "prohibit" it. However, contraindicating a use has a strong deterrent effect on physician practice since prescribing a use in spite of a contraindication can result in liability in the event harm ensues.

⁹⁹ *Wyeth*, 129 S. Ct. at 1192.

¹⁰⁰ Brief for Petitioner at 16, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249) (instructing Wyeth to "[r]etain verbiage in current label' concerning inadvertent intra-arterial injection, thus rejecting the previously proposed changes").

¹⁰¹ *Wyeth v. Levine*, 944 A.2d 179, 189 (Vt. 2006) ("With respect to IV administration, the original label read, 'When administering any irritant drug intravenously it is usually preferable to inject it through the tubing of an intravenous infusion set that is known to be functioning satisfactorily,' while the proposed label stated, '[i]njection through a properly running intravenous infusion may enhance the possibility of detecting arterial placement. In addition, this results in delivery of a lower concentration of any arteriolar irritant.' Simply stated, the proposed warning was different, but not stronger. It was also no longer or more prominent than the original warning, so it could not have raised a concern that it might overshadow other warnings on the label or drive doctors away from prescribing the drug.").

¹⁰² *Id.*; see also *Wyeth*, 129 S. Ct. at 1199 n.5-6, 1200.

Unaware of the risks emphasized several times in Phenergan's package insert, the physician's assistant pushed a double dose of the drug into Ms. Levine's artery over the course of a few minutes, notwithstanding Ms. Levine's complaints of a burning sensation that she subsequently described as "one of the most extreme pains that I've ever felt."¹⁰³ Sometime thereafter, Ms. Levine's fingers turned black and her hand—and eventually the entire arm below the elbow—were amputated to treat the resulting gangrene.¹⁰⁴

Following a settlement with the health facility and the medical practitioner, Ms. Levine brought common-law negligence and strict liability claims against Wyeth, claiming that Phenergan's labeling was defective because it failed to instruct clinicians to use the IV drip method as opposed to the IV push method.¹⁰⁵ In response, Wyeth argued that Ms. Levine's state claims were impliedly preempted by federal law in two ways.¹⁰⁶ First, it would have been impossible for Wyeth to comply with state law without violating the federal labeling requirements, and secondly, state liability for use of an FDA-approved label would present an obstacle to the federal objectives of the Congress.¹⁰⁷

The court told the jury that they could consider the FDA's approval of the label in deciding whether Wyeth was negligent, but that the label's compliance with FDA rules did **not** establish the adequacy of the warnings therein.¹⁰⁸ At the conclusion of the trial in 2005, the jury found in favor of Ms. Levine and awarded her \$7.4 million in damages on both negligence and product liability claims.¹⁰⁹

Wyeth appealed and in October 2006 the Vermont Supreme Court affirmed and held that the jury's verdict did not conflict with the FDA's labeling requirements because Wyeth could have warned against the IV-push method **without** obtaining pre-approval from the FDA under the agency's changes being effected or "CBE" rule.¹¹⁰ Further, because the FDA rules create only **minimum** labeling re-

¹⁰³ *Wyeth*, 129 S. Ct. at 1226 (Alito, J., dissenting).

¹⁰⁴ *Id.* at 1191.

¹⁰⁵ *Id.* at 1191-92.

¹⁰⁶ *Id.* at 1193. There were additional arguments, including that the physician assistant's actions were an intervening cause, reliving Wyeth of liability, but we focus herein on preemption, not tort liability or other issues. *Id.* ("the jury found that Wyeth was negligent, that Phenergan was a defective product as a result of inadequate warnings and instructions, and that no intervening cause had broken the causal connection between the product defects and the plaintiff's injury.") (citations omitted).

¹⁰⁷ *Id.*

¹⁰⁸ *Wyeth v. Levine*, 944 A.2d 179, 182 (Vt. 2006).

¹⁰⁹ *Id.*

¹¹⁰ *Id.* at 187.

quirements, state tort liability for approved labels would not frustrate Congress's objectives when it enacted the FDCA.¹¹¹ The jury verdict established only that Phenergan's warning was insufficient.¹¹² It did **not** mandate a particular replacement warning, nor did it require contraindicating IV-push administration.¹¹³ Thus, concluded the Vermont Supreme Court, "[t]here may have been any number of ways for [Wyeth] to strengthen the Phenergan warning without completely eliminating IV-push administration."¹¹⁴

Wyeth then petitioned the Supreme Court for *certiorari*, which was granted. Wyeth first contended that the Vermont Supreme Court had misinterpreted the scope of an FDCA provision allowing manufacturers to modify product labels without FDA approval, suggesting that the provision only allowed changes when **new** risks had been discovered. Specifically, Wyeth contended that the CBE was not implicated because of a 2008 amendment that provided that a manufacturer may only change its label to reflect "newly acquired information."¹¹⁵ Because, as Wyeth argued, there existed no newly acquired information, it was impossible for it to provide a stronger label.¹¹⁶ Further, to unilaterally add a new warning, it would have violated a federal law governing misbranding.¹¹⁷

The Court, however, held that "newly acquired information" was not limited to new data, but also encompassed "new analyses of previously submitted data."¹¹⁸ Although the record of new evidence was limited, Ms. Levine produced some evidence indicating that there were at least twenty incidents prior to hers where Phenergan caused gangrene and amputations.¹¹⁹ Thus, the Court concluded that once these incidents were brought to Wyeth's attention, it could have worked with the FDA to change the warning label.¹²⁰ Further, strengthening the warning label would not have violated federal law. The FDCA does not state that a drug is misbranded simply because it has been altered.¹²¹ Rather the misbranded provision applies only to

¹¹¹ *Id.* at 190.

¹¹² *Wyeth*, 129 S. Ct. at 1193.

¹¹³ *Wyeth*, 944 A.2d at 189.

¹¹⁴ *Id.*

¹¹⁵ *Wyeth v. Levine*, 129 S. Ct. at 1196 (quoting 73 Fed. Reg. 49,609 (Aug. 22, 2008)).

¹¹⁶ *Wyeth*, 129 S. Ct. at 1196.

¹¹⁷ *Id.* at 1197.

¹¹⁸ *Wyeth v. Levine*, 129 S. Ct. at 1196 (2009) (quoting 73 Fed. Reg. 49,604 (Aug. 22, 2008)).

¹¹⁹ *Id.* at 1197.

¹²⁰ *Id.*

¹²¹ *Id.*

labels that do not provide “adequate warnings.”¹²² Thus, strengthening the warning label is permitted.

Wyeth also argued that Ms. Levine’s claims were “preempted because they interfere with “Congress’s purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives.”¹²³ Specifically, in determining whether a drug is safe, Wyeth argued that the FDA conducted a risk-benefit assessment in establishing a labeling standard that left no room for different state-law judgments.¹²⁴ As a result, when the agency approved Phenergan’s label, it knew that IV push administration carried risks that could result in gangrene, but it decided that the benefits of allowing its continued use via IV push outweighed those risks. Thus, according to Wyeth, this agency expert determination represented a “ceiling” level of safety whereby a state-law jury verdict could not further raise the standard.¹²⁵

The Court, however, held that had Congress believed that state-law suits posed an obstacle to the FDA’s mission, it would have enacted an express pre-emption provision at some point during the seventy-year existence of the FDCA.¹²⁶ Instead, the court held that the FDA standards represented a floor, not a ceiling, and that warnings could therefore be increased.¹²⁷ In addition, it appeared that Congress had always looked upon state law as complimentary to drug regulation, given the fact that the FDA has limited resources to monitor the thousands of drugs that are on the market at any given time.¹²⁸ Further state-law suits uncover previously unknown dangers and provide incentives for drug manufacturer to examine the risks and to disclose those risks quickly.¹²⁹

Ultimately, the Court ruled that since Congress repeatedly declined to preempt state law, and it was possible for Wyeth to comply with both state and federal obligations, there was no obstacle to the accomplishment of Congress’ purposes in the FDCA.¹³⁰ Further, public policy mandated that drug companies should be responsible for

¹²² *Id.* (quoting 21 U.S.C. § 352(f) (2006)).

¹²³ *Id.* at 1199 (quoting Brief for Petitioner at 46, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249)).

¹²⁴ Brief for Petitioner at 46, *Wyeth v. Levine*, 129 S. Ct. 1187 (2009) (No. 06-1249).

¹²⁵ *Wyeth*, 129 S. Ct. at 1199.

¹²⁶ *Id.* at 1200.

¹²⁷ *Id.* at 1200-02.

¹²⁸ *Id.* at 1202.

¹²⁹ *Id.*

¹³⁰ *Id.* at 1204.

keeping their warning labels current and complete, not the FDA.¹³¹ Thus, there is no preemption of failure-to-warn cases for pharmaceutical products.

V. RAMIFICATIONS OF FDA PREEMPTION

The ultimate effect of the Supreme Court's decision in *Wyeth v. Levine* is that state courts and juries now have a say (if not the final say) on the adequacy of the warnings in pharmaceutical package inserts. We wonder whether this is a good result and what the ramifications of this decision will be.

One real-world consequence is that in September 2009, the FDA finally moved the warnings about the serious risks of arterial injection to the so called "black box"—making the warnings more prominent.¹³² However, the FDA still declines to prohibit IV push as suggested by Ms. Levine.¹³³ The black box language has not been finalized as of the writing of this Article, but will appear at the top of the package insert inside a black box, in bold font and capital letters, alongside the existing black box warnings regarding use in pediatric patients.

Another real world consequence is that Phenergan has been withdrawn from the market, probably due in part due to the lawsuit, but also due to generic competition.¹³⁴ One group—PharmaForce, Inc.—requested that the FDA determine whether its withdrawal was due to safety and efficacy reasons, and the FDA concluded it was not.¹³⁵

The sole reason that courts have treated medical devices differently from drugs in the preemption arena is that Congress provided an express preemption clause in one regulatory regime and not the other.

¹³¹ *Id.* at 1202. These are not the only issues discussed in the case, but the Supreme Court's treatment of the FDA's change in posture, now arguing that failure to warn claims should be preempted after many years of having an anti-preemption positions, and judicial deference to an agency's position, are not addressed herein as ancillary to the points the authors wish to make.

¹³² See Press Announcement, U.S. Food and Drug Admin., FDA Requires Boxed Warning for Promethazine Hydrochloride Injection (Sept. 16, 2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm182498.htm>.

¹³³ See *id.*

¹³⁴ Baxter Healthcare Corp. acquired the injection version of Phenergan in 2002 when it acquired ESI Lederle, a division of Wyeth. The injectable, tablet and suppository forms of Phenergan have long been discontinued, although generic versions remain available. See Orange Book, searchable online at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

¹³⁵ Letter from Nikki Mueller, Office of Regulatory Policy, Center for Drug Evaluation and Research, to Marilyn Friedly, Pharmaforce, Inc. (Dec. 19, 2002), available at <http://www.fda.gov/ohrms/DOCKETS/dailys/02/Dec02/122002/80043a43.pdf>.

However, there is no reason to treat the two products differently. Both types of medical product are highly regulated—indeed, the regulatory regimes for drugs and Class III PMA devices are largely analogous. Each requires a detailed approval application including copious safety and efficacy data, as well as detailed manufacturing and packaging specifications, including the proposed text and layout of the package insert, which provides instructions for use of the drug or device.

For both types of medical products, highly technical medical issues are at issue in the decision to approve the product and under what conditions it should be used. Drugs and medical devices are not ordinary consumer products. They act by changing the function of the human body and can have dangerous side effects.¹³⁶ Yet, they can also reduce pain, improve function, and even save patients from an early death.¹³⁷ The FDA employs or consults¹³⁸ with statisticians, epidemiologists, toxicologists, medical generalists and specialists of all kinds in making these risk-benefit evaluations.¹³⁹ In each case the FDA must balance the patient safety risks versus the health benefits for each of the medical product's proposed uses.

The consumer interests are likewise the same in both instances—consumers want to safeguard their health and safety and be able to seek redress when accidents occur. Yet redress is curtailed only in medical device cases. Presumably, combination products, which contain both drugs and devices, would have to be decided on a case-by-

¹³⁶ See Anita Bernstein, *Enhancing Drug Effectiveness and Efficacy Through Personal Injury Litigation*, 15 J.L. & POL'Y 1051, 1075 (2007) (“The notion that drugs lacking in safety cause injury and drugs lacking in efficacy do nothing fails to reckon with the reason drugs are manufactured, prescribed, and ingested to alter the body, pursuant to a determination that such an alteration is necessary to ameliorate or prevent a pathological state.”).

¹³⁷ See *United States v. Rutherford*, 442 U.S. 544, 555 (1979) (“Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk. Thus, the Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use.”).

¹³⁸ In addition to FDA employees, the FDA makes extensive use of non-employee Advisory Committees in making its risk benefit evaluations. See, e.g., *Advisory Committees*, U.S. FOOD AND DRUG ADMIN., <http://www.fda.gov/AdvisoryCommittees/default.htm> (last updated 5/20/2011) (noting that the FDA makes use of forty nine Advisory Committees and providing information as to how the general public can join a committee).

¹³⁹ See Peter H. Schuck, *FDA Preemption of State Tort Law in Drug Regulation: Finding the Sweet Spot*, 13 ROGER WILLIAMS U. L. REV. 73, 91 (2008) (“[T]he FDA exercises an authority that is probably more comprehensive and technocratically rigorous than that exercised by any other federal regulator.”); cf. *id.* at 96 (“[T]his political accountability of the FDA is in some tension with its expertise; politics may sometimes override or compromise the technical judgments of the agency’s professional staff, as in the case of the morning-after contraceptive pill.”).

case basis as to whether preemption should apply, but no rationale exists for determining which plaintiffs should be shut out of court in cases of medical injury involving combination drug-/medical devices. For example, if a drug eluting stent causes injury, a court would have no basis for deciding whether a failure to warn claim should be preempted under the medical device preemption or allowed under *Wyeth v. Levine*.

Additionally, one proclaimed benefit of litigation lies in its ability to uncover evidence that would otherwise remain safely hidden in the hands of the manufacturer. But this rationale applies equally to pharmaceutical companies as to medical device companies. Indeed, in many instances the same companies have both drug and device product lines.

These facts seem to suggest that both types of products should be treated the same—either preempted in both cases or not preempted in either. In fact, there is pending legislation to equalize the playing field by withdrawing preemption for federal medical device regulation. Bills that were first introduced in July 2008¹⁴⁰ to change the *Riegel* outcome died, but similar bills were proposed again in 2010.¹⁴¹

However, under a comparative institutional analysis, the complexity of the issues and the risk benefit balancing that is required suggests that an agency staffed by technical and medical experts is the better place for such issues to be decided. Agency control over package inserts would ensure that labels are consistent from state to state, plus an agency can adequately consider the benefits of a drug or device in deciding a warning label's content, and not just the associated risks as is typical in the litigation setting. Thus, we posit that preemption should be the rule in both instances, even if this limits plaintiff causes of action.

Two prior FDA commissioners—Drs. Kennedy and Kessler—submitted an *amicus* brief for the *Wyeth* case. The brief provided very good arguments **against** preemption, particularly given the qualifications of the authors.¹⁴² Drs. Kennedy and Kessler noted that a strong history of failure-to-warn cases in the pharmaceutical context, coupled

¹⁴⁰ See Medical Device Safety Act of 2008, S. 3398, 110th Cong. (2008); Medical Device Safety Act of 2008, H.R. 6381, 110th Cong. (2008).

¹⁴¹ See Medical Device Safety Act of 2009, S. 540, 110th Cong. (2009); Medical Device Safety Act of 2009, H.R. 1346, 111th Cong. (2009) (proposing to amend 21 U.S.C. § 360k to provide that “[n]othing in this section shall be construed to modify or otherwise affect any action for damages or the liability of any person under the law of any State.”).

¹⁴² Brief of Amici Curiae Former FDA Commissioners Dr. Donald Kennedy and Dr. David A. Kessler in Support of Respondent at 6, *Wyeth v. Levine*, 944 A.2d 179 (Vt. 2006) (No. 06-1249) [hereinafter Commissioners Brief].

with Congressional failure to provide for preemption, should warn the Court against finding implied preemption.¹⁴³ Further, petitioner's argument for preemption assumed that the FDA has timely access to safety information, and that its capacity and resources to monitor safety information are equal to that of the drug's manufacturer.¹⁴⁴ As noted in the brief:

Neither of these myths is true today; neither was true when Dr. Kennedy and Dr. Kessler headed FDA; and neither will be true tomorrow. The simple fact is that drug companies have far superior information-gathering tools about the safety profile of the drugs they sell, while FDA's tools to keep track of safety hazards post-approval are imperfect at best.¹⁴⁵

It only made sense, they argued, to allow state failure-to-warn cases, where petitioner's and FDA's claims of conflict were "not based on hard evidence of actual conflict but instead rest only on predictive judgments unanchored to history."¹⁴⁶

The ex-commissioners saw **no** conflict between FDA approval of drug labeling and state tort failure-to-warn claims. According to the brief, "failure-to-warn litigation does not challenge **FDA's** decisions about labels; rather, it challenges a **company's** failure to alert physicians and patients to risks that were unknown or poorly understood when FDA approved the drug's label, but were evident to the company at the time the plaintiff sustained injury. Litigation of that sort complements, not undercuts, FDA's job of protecting consumers from

¹⁴³ *Id.* at 6.

¹⁴⁴ *Id.* at 20.

¹⁴⁵ *Id.* at 5-6; see also Donald Kennedy, *Misbegotten Preemptions*, 320 SCIENCE 585, 585 (2008) (arguing that preemption could be dangerous to public health because the FDA is badly underfunded, and because the FDA cannot guarantee safety when approval trials include only a few hundred to a thousand patients, and concluding: "In view of these deficiencies, how can one seriously defend a no-liability clause to protect the manufacturer? In short, if you can't sue the maker of a product, you deserve some guarantee that it's safe. If the FDA can't provide that, why should you and I find the courtroom door closed?"); cf. Richard A. Epstein, *The Case for Preemption of State Laws in Drug Cases*, 103 NW. U. L. REV. COLLOQUY 54, 60 (2008) (arguing that Drs. Kessler and Vladeck are wrong in assuming that the undermanned FDA will simply roll over and allow new treatments onto the market without adequate safety testing and that instead FDA "insecurities translate into a systematic reluctance to let many drugs on the market, lest the agency has to pay a political price if something goes wrong. That cautious form of institutional protection translates into ever longer clinical trials and administrative delays. All in all, the real world risk is that too few drugs reach the market, not too many.").

¹⁴⁶ Commissioners Brief, *supra* note 142, at 6.

dangerous drugs.”¹⁴⁷ Further, a drug company can discharge its duty to warn through other means, including, for example, “Dear Doctor” letters, advertising and promotional materials, and other communications with doctors and patients.

It is hard to see, however, how a jury determination that IV push should have been prohibited can be reconciled with the FDA’s subsequent decision to allow the use. The FDA, indeed the entire pharmaceutical industry, is well aware of the Wyeth case and knows that the jury decided that the IV push warnings were inadequate. Yet, **again** the FDA declined to prohibit IV push, with full knowledge of the risks of gangrene on accidental interarterial injection. Therefore, the FDA at least implicitly disagrees with the jury’s determination in the *Wyeth* case.

If the record had contained sufficient evidence that the FDA considered and rejected an IV push contradiction, the failure to warn claim might have been preempted because the state-required label would “actually conflict” with the FDA-required label.¹⁴⁸ Indeed, some commentators predict that companies will now try to avoid the *Wyeth* outcome with additional papering of the record.¹⁴⁹ Thus, the drug approval process may become even more costly, as drug companies document each discussion with the FDA in exacting detail so that a sufficient record is available to prove actual conflict between the FDA labeling decision and the asserted failure to warn claim.

¹⁴⁷ *Id.* at 5; *cf.* Kim, *supra* note 3, at 403 (“Any requirement imposed by state tort law to warn of a danger that FDA has concluded is not scientifically substantiated **would create an impermissible conflict** for a manufacturer, since including the warning would render the product misbranded under the FDCA and subject the manufacturer to potential civil and criminal liability, while failure to include it could lead to tort liability. In other words, ‘manufacturers are put to the Hobson’s choice of incurring sanctions irrespective of the requirement they follow.’”) (citations omitted) (emphasis added).

¹⁴⁸ See *Geier v. American Honda Motor Co.*, 529 U.S. 861, 866 (2000) (holding “that this kind of ‘no airbag’ lawsuit conflicts with the objectives of FMVSS 208, a standard authorized by the Act, and is therefore pre-empted by the Act.”).

¹⁴⁹ See Val Jones, *Wyeth vs. Levine: FDA Labeling Overruled by Jury of Lay People*, BETTER HEALTH (Mar. 4, 2009), <http://getbetterhealth.com/wyeth-vs-levine-fda-labeling-overruled-by-jury-of-lay-people/2009.03.04> (Bert Rein, attorney for Wyeth, predicts that drug companies will react to the no preemption decision by attempting to obtain “clear records” from the FDA on every drug label controversy going forward and obtaining all FDA labeling decisions in writing, adding to the cost and delays); see also David C. Vladeck, *The FDA And Deference Lost: A Self-Inflicted Wound Or The Product Of A Wounded Agency? A Response To Professor O’Reilly*, 93 CORNELL L. REV. 981, 999 (2008) (critiquing the FDA as ill equipped, weakened from within, and neither transparent nor publicly accountable, but agreeing that “in the long run, probing judicial review will impede the Agency’s ability to do its work swiftly and efficiently.”).

Dr. Kessler elaborates his argument, in a law review article published in 2008, noting correctly that the agency only recently began to espouse a pro-preemption viewpoint, and that the agency was wrong to focus on the moment of approval as determinative.¹⁵⁰ Indeed, at the moment of approval, the agency **is** in the best position to balance the risks and benefits and decide on an appropriate label. But, argues Dr. Kessler, “[t]he relevant timeframe is post-approval.”¹⁵¹ Once a drug enters the market, even relatively rare risks begin to emerge, and FDA tools for gathering post-approval information are “relatively crude and often ineffective.”¹⁵²

Further, the author noted examples where litigation **has** uncovered adverse event data that was unknown by the agency, including the selective serotonin reuptake inhibitors or “SSRI” class of drug.¹⁵³ In one SSRI case, New York State Attorney General Eliot Spitzer brought suit against the sponsor of Paxil®, presenting evidence that the sponsor had **suppressed** the results of studies on children and adolescents that showed Paxil® to be ineffective **and** to increase the risk of suicidal thinking and behavior.¹⁵⁴ Further, an internal memo was discovered stating that the sponsor intended to “manage the dissemination of the[] data in order to minimize any potential negative commercial impact.”¹⁵⁵ In response to growing media attention and regulatory action by the European Agency for the Evaluation of Medicinal Products,¹⁵⁶ the FDA eventually decided to require a black box warning of increased suicide risk in children and adolescents.¹⁵⁷

¹⁵⁰ David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 464-65 (2008).

¹⁵¹ *Id.* at 466.

¹⁵² *Id.*; see also Gregory D. Curfman, et al., *Why Doctors Should Worry about Preemption*, 359 NEW ENG. J. MED 1, 2 (2008) (“Although frivolous lawsuits should not be condoned, product-liability litigation has unquestionably helped to remove unsafe products from the market and to prevent others from entering it. Through the process of legal discovery, litigation may also uncover information about drug toxicity that would otherwise not be known. Preemption will thus result in drugs and devices that are less safe and will thereby undermine a national effort to improve patient safety. Despite the diligent attention of the FDA, serious safety issues often come to light only after a drug has entered the market. The FDA, which—unlike most other federal agencies—has no subpoena power, knows only what manufacturers choose to reveal.”).

¹⁵³ Kessler & Vladeck, *supra* note 150, at 493.

¹⁵⁴ Bruce Levine, *Behind the Paxil Scandals*, Z MAG., Apr. 2005, at 11.

¹⁵⁵ Wayne Kondro & Barbara Sibbald, *Drug Company Experts Advised Staff to Withhold Data about SSRI Use in Children*, 170 CANADIAN MED. ASS'N. 783, 783 (2004).

¹⁵⁶ Jeremy Laurance, *Seroxat Controversy Deepens with Europe-wide Warning on Suicide*, THE INDEPENDENT (July 26, 2004), <http://www.independent.co.uk/life-style/health-and-families/health-news/seroxat-controversy-deepens-with-europe-wide->

However, such examples can be less compelling in hindsight. SSRI's, for example, appear to have a protective effect in adults, and the data in children and adolescents are difficult to interpret due to differences in coding between various trials, low numbers of young patients, and the fact that the adverse event—suicide—is one of the **same outcomes** as untreated depression. This makes it difficult to ascertain the cause in any given suicide.

In fact, in 2008, the World Health Organization (WHO) **recommended** SSRI use in children to treat depression and anxiety disorders with close monitoring,¹⁵⁸ and has concluded that SSRIs **reduce** the overall risk of suicide.¹⁵⁹ Further, evidence suggests that treatment of childhood depression with these drugs has decreased since the

warning-on-suicide-554456.html (“A new warning that the controversial antidepressant Seroxat [aka Paxil, an SSRI] may increase the risk of suicide in young adults up to the age of 30 is to be issued throughout Europe.”).

¹⁵⁷ Press Announcement, U.S. Food and Drug Admin., FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated with Antidepressant Medications (Oct. 15, 2004), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108363.htm>.

¹⁵⁸ WHO, Second Meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines: WHO Essential Drugs For Common Psychiatric Disorders In Children (Sept. 29 - Oct. 3, 2008), http://www.who.int/entity/selection_medicines/committees/subcommittee/2/Psychotherapeutic_review.pdf (“SSRIs are the medications of choice in treating childhood anxiety disorders. They are well tolerated with mild transient side effects. Controlled trials have established the safety and efficacy of SSRI's for childhood anxiety disorders. Fluoxetine, Fluvoxamine and Sertraline have been shown to be more effective than Placebo in RCT's. As anxiety disorders often coexist with depression, children prescribed SSRI's for both conditions should be monitored closely for increased suicidal thoughts and behaviour. . . SSRIs: Fluoxetine is the only medication which has proven efficacy in clinical trials for treating depressive illness in children and adolescents. Other SSRI's have shown small differences between the drug and placebo. Caution: SSRI's are associated with an increased risk of suicidal thoughts and behaviour in the early phases of treatment. There have been no reports of completed suicides attributed to treatment with SSRI's. Children need careful monitoring with regular reviews during the early phases of treatment. *Overall the use of SSRI's has decreased suicide rates in children and adolescents.*”) (emphasis added).

¹⁵⁹ Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-analysis of Randomized Controlled Trials*, 297 JAMA 1683, 1683 (2007) (“Relative to placebo, antidepressants are efficacious for pediatric MDD, OCD, and non-OCD anxiety disorders, although the effects are strongest in non-OCD anxiety disorders, intermediate in OCD, and more modest in MDD. *Benefits of antidepressants appear to be much greater than risks* from suicidal ideation/suicide attempt across indications, although comparison of benefit to risk varies as a function of indication, age, chronicity, and study conditions.”) (emphasis added).

black box warnings,¹⁶⁰ and that suicides have increased at the same time.¹⁶¹

This example illustrates the consequences of over-warning and the failure to treat serious medical problems.¹⁶² The preemption decisions are premised on the false assumption that, while the FDA applies a **floor** to warning labels, tort law should be permitted to raise the ceiling on labels because increasing the strength of a warning cannot hurt individuals. But the SSRI example indicates that over-warning **is** a real phenomenon and it affects more than Big Pharma's bottom line. As noted by Dr. Thomas Laughren, Director of the Division of Psychiatry Products at the FDA's Center for Drug Evaluation and Research:

We put a black box on antidepressants for adolescents, but it did have an impact on prescribing and there's been a lot of negative feedback from the clinical community. It's important to recognize that something as dramatic as a black box can have a dramatic effect on prescribing.¹⁶³

Not only is over-warning a real threat, but litigation is naturally biased towards false positives or an unbalanced result. In other words, when the plaintiff prevails there is a significant possibility that the drug manufacturer will thereby either increase warnings or remove the drug from the market. In contrast, litigation has no effect on a drug or

¹⁶⁰ Charles B. Nemeroff et al., *Impact of Publicity Concerning Pediatric Suicidality Data on Physician Practice Patterns in the United States*, 64 ARCHIVES GEN. PSYCHIATRY 466, 466 (2007) ("The analyses suggest that the number of children and teenagers who were prescribed antidepressants has decreased significantly (P = .02) in the wake of widespread publicity surrounding the FDA public health advisories.").

¹⁶¹ Brady E. Hamilton et al., *Annual Summary of Vital Statistics: 2005*, 119 PEDIATRICS 345, 345 (2007) ("The death rates **increased** for intentional self-harm (suicide), whereas rates for other causes did not change significantly for children.") (emphasis added).

¹⁶² See, e.g., Brief for the United States as Amicus Curiae Supporting Petitioner at 17, *Wyeth v. Levine*, 552 U.S. 1161 (2008) (No. 06-1249) ("Exaggeration of risk could discourage appropriate use of a beneficial drug, and thereby harm the public health. In addition, excessive warnings can cause more meaningful risk information to 'lose its significance.'" (quoting 71 Fed. Reg. 3935 (Jan. 24, 2006))).

¹⁶³ *ADHD Drugs: Controversy over the "Black Box" Warning*, DRUGS.COM, <http://www.drugs.com/news/adhd-controversy-over-black-box-warning-1734.html> (last visited Sept. 22, 2010); *Black Box Warnings Have Hampered Eczema Therapy*, HEMONC TODAY, <http://www.hemonctoday.com/article.aspx?rid=35581> (last visited Sept. 22, 2010) (statement of Dr. Ilene L. Rothman) ("[T]he black box warning has brought about a marked unwillingness among both physicians and patients to use this valuable addition [Protopic ointment and Elidel cream] to treatment options for atopic dermatitis, a difficult disorder. . . .").

its labeling where the defendant prevails. Further, litigation can never correct overzealous regulatory action that prevents drugs from ever reaching the market in the first place.¹⁶⁴

One example of overcorrection is the drug Bendectin. Bendectin is a mixture of pyridoxine (Vitamin B6) and doxylamine¹⁶⁵—an anti-histamine that also has sedative effects and is the sedative ingredient in NyQuil.¹⁶⁶ It was prescribed to treat nausea and vomiting associated with morning sickness, but was voluntarily removed from the market in 1983 following numerous lawsuits alleging that it caused birth defects. Most of the evidence suggested that the drug was safe and that the incidence of birth defects for women taking the drug was no higher than for women who did not take the drug. However, some accused the manufacturer of funding research to create favorable evidence.¹⁶⁷ Although the manufacturer won many cases, litigation costs convinced it to remove the drug from the U.S. market.¹⁶⁸ Nonetheless, the drug remains available in Canada and Europe, and most evidence over the following two decades confirms that Bendectin's withdrawal from the U.S. market has **not** reduced the incidence of birth defects in America, although the number of hospitalizations for women having severe nausea and fluid loss has **doubled**.¹⁶⁹ Thus, Bendectin seems to provide another example of overcorrection, resulting in an increase in overall harm.

¹⁶⁴ Epstein, *supra* note 145, at 60 (“Where the FDA incorrectly blocks a drug from entering the market, litigation can do nothing to correct that error.”).

¹⁶⁵ Raafat Bishai et al., *Critical Appraisal of Drug Therapy for Nausea and Vomiting of Pregnancy: II. Efficacy and Safety of Diclectin (Doxylamine-B6)*, 7 CAN. J. CLINICAL PHARMACOLOGY, 138, 139 (2000).

¹⁶⁶ See NyQuil label (on file with author).

¹⁶⁷ Christina Marie Martin, *Hugs And Drugs: Research Ethics, Conflict of Interest, And Why the FDA's Attempt to Preempt Pharma Failure-To-Warn Claims is a Dangerous Prescription*, 6 AVE MARIA L. REV. 587, 618-19 (2008) (arguing that Bendectin's manufacturer “was able to create and influence a scientific subdiscipline devoted to result-driven studies that [it] could then cite to defeat lawsuits brought by those who alleged that their birth defects were caused by Merrell Dow's Bendectin. In light of such a powerful declaration, the Bendectin litigation should no longer serve as evidence that trial courts cannot justly rule in pharma products liability suits.”) (citation omitted).

¹⁶⁸ Alex Kozinski, *Brave New World*, 30 U.C. DAVIS L. REV. 997, 1006 (1997) (“Due to the litigation, Bendectin was taken off the U.S. market because the manufacturer decided it just was not worth it.”).

¹⁶⁹ Jeffrey S. Kutcher et al., *Bendectin and Birth Defects. II: Ecological Analyses*, 67 BIRTH DEFECTS RES. 88, 88 (2003) (“The temporal trends in prevalence rates for specific birth defects examined from 1970 through 1992 did not show changes that reflected the cessation of Bendectin use over the 1980-84 period. Further, the [nausea and vomiting of pregnancy] hospitalization rate doubled when Bendectin use ceased.”).

Further, although some argue that litigation is corrective, in fact much litigation merely follows on agency corrections and contributes nothing to safety.¹⁷⁰ Anita Bernstein argues that “not since the litigation-hastened demise of the very dangerous Dalkon Shield intrauterine device in 1974 has any pharmaceutical product demonstrated that personal-injury liability can be a source of social utility.”¹⁷¹ Perhaps we should not concede that pharmaceutical tort litigation improves the public health until better evidence is available.¹⁷²

Commissioners Kennedy and Kessler do make a very good point that FDA information gathering tools are limited and that litigation can supplement safety information about drugs. However, recent amendments to the FDCA take significant steps to provide both the public and the FDA with additional safety information and reduce the power of their argument. Section 801 of the Food and Drug Administration Amendments Act of 2007 (the FDAAA) increases the information that must be published by sponsors at ClinicalTrials.gov—a database established and maintained by the National Institutes of Health (NIH) for the reporting of clinical trials.¹⁷³ The FDAAA expanded clinical trial registration to **all** Phase II-IV clinical trials and

¹⁷⁰ See Bernstein, *supra* note 136, at 1055 (“Take Vioxx as exemplar of what personal-injury liability has not achieved. Plaintiffs’ lawyers did not discover its dangers; the drug had already left the market before a jury verdict came in against it; increases in talk about improving drug safety policy also had predated liability for this drug; and personal-injury litigation did not generate information to benefit the consuming public.”); Epstein, *supra* note 145, at 60-61 (“The drugs that usually generate the most litigation—such as Rezulin and Vioxx—usually are withdrawn before litigation commences. Indeed the plaintiffs’ bar rightly free rides on FDA determinations, reducing the social gain from litigation.”); Paul Howard & Marie Gryphon, *Manhattan Moment: The Right Prescription for Drug Safety*, WASH. EXAMINER, Dec. 4, 2008, available at http://www.washingtonexaminer.com/opinion/Manhattan_Moment_The_right_prescription_for_drug_safety_120408.html (“The FDA is famously imperfect. But it does not follow that interference from tort lawyers will do more good than harm when it comes to drug safety and labeling practices. Plaintiffs’ lawyers receive contingency fees of 33% or more. This is a powerful incentive to press any colorable claim, even those involving drugs that unquestionably do more good than harm.”).

¹⁷¹ Bernstein, *supra* note 136, at 1055.

¹⁷² James M. Beck & Mark Herrmann, *Does Tort Litigation Improve Drug Safety?*, DRUG AND DEVICE LAW (Oct. 27, 2008, 7:59 AM) <http://druganddevicelaw.blogspot.com/2008/10/does-tort-litigation-improve-drug.html> (“Until the empirical data exist, defendants should not concede that pharmaceutical tort litigation improves the public health. What little we’ve found on the subject suggests that it does not.”). The authors are aware that the evidence on either side of the question is less than rigorous.

¹⁷³ See, e.g., *About ClinicalTrials.gov*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/ct2/info/about> (last updated Apr. 2, 2008).

expanded the information that must be reported to include final results.¹⁷⁴

Trials must be registered at Clinical.Trials.gov within twenty-one days of enrolling the first patient,¹⁷⁵ and results must be posted within one year of the **earlier** of the estimated completion date or the actual completion date, **unless** the manufacturer is in the process of submitting a new drug application (NDA) or new use application.¹⁷⁶ The “completion date” is defined as the date that the “final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome” and thus, does not include analysis time or patient care relating to secondary outcomes.¹⁷⁷ Further, since the completion date relates to last patient care date, rather than completion of the analysis, the FDAAA applies even to drug trials that are **discontinued**.

Most harmful data is probably collected in discontinued trials, and indeed is a significant factor in the decision to discontinue a trial. Further, there is a natural scientific tendency to be less interested in publishing negative results. In the drug safety context, however, such data is essential to evaluate accurately the risks and benefits of a drug.¹⁷⁸

If the sponsor intends to file an NDA or new use application **and** files a certification to that effect, posting can be delayed, but results must still be posted within thirty days of approval or rejection, within 120 days of withdrawal without resubmission, or within two years of

¹⁷⁴ The FDAAA also gave expanded FDA authority for the postmarket safety of drugs, including the power to require postmarketing studies, to order changes in a drug’s label and to restrict distribution of a drug. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 922-26 (2007).

¹⁷⁵ See § 801(a)(j)(2)(C), 121 Stat. at 907.

¹⁷⁶ § 801(a)(j)(3)(E), 121 Stat. at 912-13. The Secretary may increase this to eighteen months. § 801(a)(j)(3)(D)(iv)(I), 121 Stat. at 911.

¹⁷⁷ § 801(a)(j)(1)(A)(v), Stat. at 905.

¹⁷⁸ Howard A. Denmark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side Effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market*, 40 CASE W. RES. L. REV. 413, 437 (1990) (“It is quite common in epidemiology for the first published studies of an association to suggest a positive association, with subsequent reports being negative; . . . The reason for this is fairly obvious. Investigators are more likely to write up positive findings, reviewers to consider them of interest, editors to publish them, and the press to publicize them. It is only after the initial observation is published that investigators who have negative data feel obliged to report them.”) (quoting Michael B. Bracken, *Spermicidal Contraceptives and Poor Reproductive Outcomes: The Epidemiologic Evidence Against an Association*, 151 AM. J. OBSTETRICS & GYNECOLOGY 552, 555 (1985)).

the certification date if none of these actions have occurred.¹⁷⁹ Thus, all safety data should eventually become available.

The type of information to be reported includes descriptive information regarding study design, recruitment, contact and administrative information.¹⁸⁰ Further, the Act directs the NIH to expand the database to include the “results” of applicable clinical trials.¹⁸¹ Basic results are to include demographic and baseline data, as well primary and secondary outcome measures.¹⁸² An expanded results registry is to be available not later than three years after the Act [i.e., September 2010] and is to include both technical and non-technical summaries of the clinical trial, the full protocol and such other categories as deemed appropriate.¹⁸³ More importantly, updates are required not less than once every twelve months, and recruitment status updates and completion updates are required with thirty days of such status change.¹⁸⁴ Sponsors are also to submit tables of adverse events, including frequent (>5%) adverse events.¹⁸⁵

Once the expanded results database is available, preemption of state regulations is provided.¹⁸⁶ Although the database updates and implementing regulations are not yet completed, the FDA has indicated that it expects adverse events reporting to begin on September 27, 2009. Thus, both the public and the FDA will have increased access to safety data an ongoing basis.

In addition to the publication requirements, the FDAAA also gave the FDA the power to **require** Phase IV studies and to **order** label changes.¹⁸⁷ The FDAAA also requires a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number. This analysis must be submitted within eighteen months after the approval of an NDA or after 10,000 individuals use the drug, whichever is later.¹⁸⁸ These changes close a significant gap in FDA authority and give the FDA additional

¹⁷⁹ § 801(a)(j)(3)(E)(iii-v), 121 Stat. at 913-14.

¹⁸⁰ § 801(a)(j)(2)(A)(ii), 121 Stat. at 905.

¹⁸¹ § 801(a)(j)(2)(A)(i), 121 Stat. at 906.

¹⁸² § 801(a)(j)(2)(C), 121 Stat. at 909-10.

¹⁸³ § 801(a)(j)(2)(D), 121 Stat. at 910-11.

¹⁸⁴ § 801(a)(j)(4)(C)(i), 121 Stat. at 916-17.

¹⁸⁵ § 801(a)(j)(3)(H)(I)(iii), 121 Stat. at 915.

¹⁸⁶ § 801(d)(1), 121 Stat. at 922 (“Upon the expansion of the registry and results data bank . . . no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.”).

¹⁸⁷ § 901(a)(o)(3-4), 121 Stat. at 923-24.

¹⁸⁸ § 915, 121 Stat. at 957-58.

enforcement tools. Thus, much of the force of Drs. Kennedy and Kessler's lack of FDA information gathering ability argument is diminished by the new publication requirements and the additional powers granted to the FDA.

Although FDA resources will always be constrained, the FDA is not the only watchdog monitoring the pharmaceutical and medical device industries. Several watchdog groups supplement the agency's enforcement activities.¹⁸⁹ Such groups provide public education on drug safety,¹⁹⁰ and file both lawsuits and citizens' petitions at the FDA to improve drug safety and change drug labels.¹⁹¹ Thus, the FDA's meager enforcement resources are supplemented by a variety of drug safety watchdog groups.

Even with insufficient resources and in the face of significant criticism, the available evidence suggests that FDA enforcement activity has increased recently.¹⁹² According to studies, the FDA issued device

¹⁸⁹ See, e.g., CENTER FOR SCIENCE IN THE PUBLIC INTEREST, <http://www.cspinet.org/> (last visited Sept. 22, 2010); HEALTHY SKEPTICISM, <http://www.healthyskepticism.org/global/> (last visited Sept. 22, 2010); MARKETING OVERDOSE, <http://www.marketingoverdose.org/> (last visited Sept. 22, 2010); PHARMEDOUT, <http://www.pharmedout.org> (last visited Sept. 22, 2010); PRESCRIPTION ACCESS LITIGATION, <http://www.prescriptionaccess.org/> (last visited Sept. 22, 2010); *Pushing Prescriptions*, THE CENTER FOR PUBLIC INTEGRITY: PUSHING PRESCRIPTIONS, <http://www.publicintegrity.org/projects/entry/289/try> (last visited Sept. 22, 2010); KAISER FAMILY FOUNDATION, <http://www.kaiserhealthnews.org/> (last visited Sept. 22, 2010); THE PRESCRIPTION PROJECT, <http://www.prescriptionproject.org/> (last visited Sept. 22, 2010); THE US DRUG WATCHDOG, <http://usdrugwatchdog.com/> (last visited Sept. 22, 2010); PUBLIC CITIZEN, <http://www.citizen.org/> (last visited Sept. 22, 2010).

¹⁹⁰ See, e.g., PUBLIC CITIZEN, <http://www.worstpills.org> (last visited Nov. 9, 2010). Worstpills.org is a searchable, online drug database that provides comprehensive information about prescription drugs and warns of drugs that are unsafe or ineffective.

¹⁹¹ See, e.g., Petition from Sidney M. Wolfe et al., Dir., Public Citizen Health Research Group, to Andrew von Eschenback, Comm'r, U.S. Food and Drug Admin., (Jan. 23, 2008), available at <http://www.citizen.org/hrg1834> (petitioning for regulatory action concerning the spread of botulinum toxin to other parts of the body); see also *Bayer Sued Over Unsupported Prostate Cancer Claims on One A Day*, CENTER FOR SCIENCE IN THE PUBLIC INTEREST, <http://www.cspinet.org/new/200910011.html> (last visited Sept. 22, 2010) (suing Bayer for falsely claiming that the selenium in its multivitamins might reduce the risk of prostate cancer).

¹⁹² John B. Reiss et al., *Your Business in Court 2008-2009*, 64 FOOD & DRUG L.J. 755, 755, 757 (2009) ("Throughout 2008 and 2009, FDA increased both the number and the severity of its enforcement actions. FDA issued device recalls and warning/untitled letters in record numbers. According to Becker Consulting, 845 medical device recalls were announced in 2008, representing a 43 percent increase over the previous year's medical device recalls. Similarly within the first quarter of 2009, FDA's Division of Drug Marketing, Advertising, and Communication

recalls, warning letters and untitled letters in record numbers in 2008–2009, including a 43 percent increase over the previous year’s medical device recalls. Indeed, as many warning or untitled letters were issued in first quarter of 2009 as in nearly all of the past three years combined. These results suggest that the FDA is addressing some of the criticisms previously leveled against it.¹⁹³

Another argument against preemption arises from the issue of redress. If preemption is to be the rule, plaintiffs arguably lack any recourse for serious injuries. As noted by former FDA Commissioner Donald Kennedy “if you can’t sue the maker of a product, you deserve some guarantee that it’s safe. If the FDA can’t provide that, why should you and I find the courtroom door closed?”¹⁹⁴

Yet, that view point is overly simplistic, and the courtroom doors would not necessarily be barred. For example, cigarette labels have long been prescribed by the federal government, which also provided a preemption clause against additional state labeling requirements. Yet, in *Cipollone v. Liggett Group, Inc.* plaintiffs litigating the preemption issue for tobacco labeling were not denied breach of express warranty, fraud, or conspiracy to conceal material facts claims.¹⁹⁵ Such claims would be appropriate for the pharmaceutical company with misleading direct-to-consumer advertising or who failed to timely bring important safety data to the FDA’s attention.¹⁹⁶

Many cases have held that there is no private right of action to enforce the FDCA under 21 U.S.C. § 337.¹⁹⁷ While this is a generally

(DDMAC) published as many warning/untitled letters as in nearly all of the past three years.” (citations omitted).

¹⁹³ *E.g.*, DEPT. OF HEALTH & HUMAN SERVICES, CHANGING THE FUTURE OF DRUG SAFETY: FDA INITIATIVES TO STRENGTHEN AND TRANSFORM THE DRUG SAFETY SYSTEM (2009) (outlining the status of FDA efforts to address criticisms), available at <http://www.fda.gov/downloads/Safety/SafetyofSpecificProducts/UCM184046.pdf>.

¹⁹⁴ Donald Kennedy, *Misbegotten Preemptions*, 320 SCIENCE 585, 585 (2008).

¹⁹⁵ 505 U.S. 504 (1992).

¹⁹⁶ *Id.* at 515, 530-31 (holding that a tobacco preemption clause that read “[n]o requirement or prohibition based on smoking and health shall be imposed under State law with respect to the advertising or promotion of any cigarettes the packages of which are labeled in conformity with the provisions of this Act” preempted state failure-to-warn claims, but **not** breach of express warranty, fraudulent misrepresentation, or conspiracy to conceal material fact). (emphasis added) (citation omitted); *cf.* *Buckman v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 348 (2001) (barring stand-alone fraud-on-the-FDA claims involving a regulated medical device as impliedly preempted).

¹⁹⁷ *See, e.g.*, *Loreto v. Procter & Gamble Co.*, 737 F.Supp. 2d 909 (S.D. Ohio 2010) (holding no private right of action under the FDCA); *see also* 21 U.S.C. § 337 (2006) (“[A]ll such proceedings for the enforcement, or to restrain violations, of this [Act] shall be by and in the name of the United States.”).

true statement, the Supreme Court has only noted that there is no *federal* cause of action for violation of the FDCA.¹⁹⁸ However, that does not mean there are no state law causes of action that may relate to FDCA violations. Indeed, the Supreme Court in *Medtronic v. Lohr* expressly stated that parallel claims would **not** be preempted in the medical device context:

Nothing in §360k [related to 510(k) clearance for medical devices] denies Florida the right to provide a traditional damages remedy for violations of common law duties when those duties parallel federal requirements. Even if it may be necessary as a matter of Florida law to prove that those violations were the result of negligent conduct, or that they created an unreasonable hazard for users of the product, such additional elements of the state law cause of action would make the state requirements narrower, not broader, than the federal requirement. While such a narrower requirement might be “different from” the federal rules in a literal sense, such a difference would surely provide a strange reason for finding pre-emption of a state rule insofar as it duplicates the federal rule. The presence of a damages remedy does not amount to the additional or different “requirement” that is necessary under the statute; rather, it merely provides another reason for manufacturers to comply with identical existing “requirements” under federal law.¹⁹⁹

Thus, under *Cipollone* and *Medtronic v. Lohr*, a variety of claims could remain available for the injured plaintiff.²⁰⁰ Further, in both the

¹⁹⁸ *Merrell Dow Pharmaceuticals, Inc. v. Thompson*, 478 U.S. 804, 810 (1986) (“[B]oth parties agree with the Court of Appeals’ conclusion that there is no federal cause of action for FDCA violations. For purposes of our decision, we assume that this is a correct interpretation of the FDCA.”).

¹⁹⁹ *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996) (“Nothing in § 360k [relating to 510(k) medical devices] denies Florida the right to provide a traditional damages remedy for violations of common-law duties when those duties parallel federal requirements.”).

²⁰⁰ *See e.g., In re Orthopedic Bone Screw Prod. Liab. Litig.*, 159 F.3d 817, 823 (3d Cir. 1998) (allowing a common law fraudulent misrepresentation claim based on *Lohr* because the “state common law relied upon does not impose any obligation . . . inconsistent with federal law.”); *Femrite v. Abbott Nw. Hosp.*, 568 N.W.2d 535, 539 n.4 (Minn. Ct. App. 1997) (“21 U.S.C. § 337(a) only bars actions to ‘enforce’ the FDCA . . . [A]ppellants’ action alleging that Abbott was negligent because it failed to comply with FDA regulations is not an action to enforce the FDCA. The FDCA regulates the marketing of medical devices, not the practice of medicine.”); *Hofts v. Howmedica Osteonics Corp.*, 597 F.Supp.2d 830, 832-33 (S.D. Ind. 2009) (holding that plaintiff “may pursue civil claims against Howmedica based on theories that

Wyeth and the *Riegel* cases, as in many such cases, both plaintiffs also had claims against the medical practitioners, each of whom used the medical product improperly and in a way specifically warned against on the respective instructions for use.²⁰¹

Additionally, Congress could craft a preemption clause that is narrowly tailored to prevent litigants from disputing the content of package inserts without foreclosing other causes of action. For example, direct-to-consumer advertising is far less controlled by the FDA than package inserts, and deceptive or misleading advertising should still be litigable because the same balancing of risks and benefits issues are less apparent on direct-to-consumer advertising which never contain the full range of package insert warnings. Likewise, the preemption clause can provide an express exception clause, allowing litigation to proceed where there was actual concealment or delay in reporting damaging data or provision of misleading or fraudulent data to the FDA, in a manner similar to the approach used in Texas and Michigan.²⁰²

Howmedica failed to comply with federal requirements for manufacturing the replacement hip joint implanted in him.”).

²⁰¹ It is true that tort reform has in some cases placed limits on damages and in certain states already provides for FDA preemptive effect. However, that is an issue democratically decided on a state by state basis and although tort reform may limit plaintiffs in some respects, it usually does not prevent all redress. *See, e.g.*, TEX. CIV. PRAC. & REM. CODE ANN. § 82.007 (West 2010) (“[T]here is a rebuttable presumption that the defendant or defendants . . . are not liable with respect to the allegations involving failure to provide adequate warnings or information if: (1) the warnings or information that accompanied the product in its distribution were those approved by the [FDA]”). The Texas statute also provides that the presumption can be rebutted if the defendant withholds or misrepresents material information to the FDA, if an off-label use was promoted, or if the defendant violated the statute, among other things.

²⁰² *See* TEX. CIV. PRAC. & REM. CODE ANN. § 82.007 (West 2010) (“[T]here is a rebuttable presumption that the defendant or defendants . . . are not liable with respect to the allegations involving failure to provide adequate warnings or information if: (1) the warnings or information that accompanied the product in its distribution were those approved by the [FDA][.] (b) The claimant may rebut the presumption . . . by establishing that: (1) the defendant . . . withheld from or misrepresented . . . required information . . . that was material and relevant to the performance of the product and was causally related to the claimant’s injury[.]”); *see also* MICH. COMP. LAWS ANN. § 600.2946(5) (West 2010) (“[A] drug is not defective or unreasonably dangerous, and the manufacturer or seller is not liable, if the drug was approved for safety and efficacy . . . and the drug and its labeling were in compliance with the [FDA’s] approval . . . This subsection does not apply if the defendant . . . [i]ntentionally withholds from or misrepresents . . . information concerning the drug . . . and the drug would not have been approved . . . if the information were accurately submitted.”).

Some might argue that such an exception would merely shift early litigation efforts toward the discovery of evidence that the manufacturer withheld, delayed, or misrepresented the significance of negative data, and thus the industry would be no better off.²⁰³ However, our aim herein is not to protect the industry from litigation, but to retain the FDA's careful balancing of risks and benefits in approving the package inserts and prevent the over-warning or state-by-state variability that may result when juries decide failure-to-warn cases.²⁰⁴ Thus, a carefully crafted preemption clause, with express exceptions for fraud, misrepresentation and delay, would retain the information uncovering and issue redress benefits of litigation, without allowing a jury to interfere with the careful risk benefit evaluations undergone by the FDA in deciding what the package insert should say.

CONCLUSION

In concluding, we emphasize that we do **not** consider *Wyeth v. Levine* to be incorrectly decided on a legal basis, although we might have disagreed with lower courts findings of fact.²⁰⁵ There was no

²⁰³ See, e.g., Schuck, *supra* note 139, at 105-06 (arguing for a higher standard to access the preemption exceptions and stating: "A danger exists, however, with respect to all of these exceptions. Under the modern system of notice pleading, it is all too easy to allege fraud, non-fraudulent misrepresentation, or non-disclosure of material facts—and indeed all of them simultaneously. Unless the rules for pleading these torts are more demanding than usual, a plaintiff can defeat one of the principal purposes of preemption—avoiding costly litigation under state law in situations in which uniform federal law should apply—simply by alleging fraudulent or non-fraudulent misrepresentation or non-disclosure.").

²⁰⁴ See *id.* at 110 ("[S]tate variation and experimentation, often a virtue in other areas, is decidedly unwelcome in the particular context of comprehensive FDA drug regulation.").

²⁰⁵ E.g., there was no evidence that there was anything "new" with regards to the risks of IV push. Thus, the CBE provision arguably did not apply and Wyeth could not have changed the label unilaterally. Cf. Timothy Ardizzone, *The FDA: Advocate Or Regulator Of The Pharmaceutical Industry? The Attempted Preemption By The FDA Of State Tort Claims For Failure To Warn On Pharmaceutical Labeling*, 75 U. CIN. L. REV. 763, 787 (2006) (noting that the Restatement (Third) of Torts states that a drug manufacturer is liable for injuries caused by a drug marketed without reasonable warnings regarding "'foreseeable risks of harm posed by [that] drug . . .'", but being willing to impose liability before the risk is validated, and stating "the FDA appears to argue that a risk is not foreseeable for the purposes of tort liability until the risk is scientifically validated. . . . Contrary to the FDA's argument for preemption, the fact that some people are injured by a drug implies that there is a risk to a fraction of the population of having an adverse event, which should prompt the common law duty to warn." (footnote omitted)). Further, considering that the FDA was well aware of the risks of IV push, yet didn't prohibit it, there was arguably an actual conflict. Indeed, when the FDA revisited the warning label again after the decision, they still did not prohibit IV push. According to the lower courts analysis, if

express preemption provision in the statute,²⁰⁶ and there was a long history of state regulation of public health and welfare, coupled with a long history of state failure-to-warn claims against the pharmaceutical industry.²⁰⁷ Thus, a presumption against preemption was correctly applied. The Court found no actual conflict because the record was insufficient to establish that the FDA considered and rejected an IV push contraindication. There was no field preemption because the FDA had long accepted state tort claims to be a valid means of complementing FDA enforcement, and because the FDA only established a floor, beyond which the warnings may not be reduced. Further, the CBE regulation expressly allowed a drug sponsor to increase unilaterally the warnings and obtain FDA approval after the fact. Thus, state failure-to-warn claims were not preempted.

However, we do suggest that there is insufficient justification for treating medical devices and pharmaceuticals differently. Both should be treated similarly. Further, although there is legislation to remove device preemption, we suggest that the better approach might be to provide a limited preemption for both types of medical products.

It is true that FDA resources are constrained and that litigation has helped to uncover instances of withheld negative data and has resulted in an increased use of warnings. However, litigation is a crude tool for balancing the risks and benefits of a medical product. Indeed, in any failure to warn case, no one represents the patient whose life is significantly improved by a particular medical product and thus there can only be a bias towards over-warning. Further, the dangers of over-warning are not merely theoretical. Over-warning discourages drug

the FDA again failed to document their decision making process, the next case could come out the same way. *Cf.* Leslie C. Kendrick, *FDA's Regulation of Prescription Drug Labeling: A Role for Implied Preemption*, 62 *FOOD & DRUG L.J.* 227, 246 (2007) (noting that it is difficult to decide what the FDA's position is when they are silent and stating "[i]t might be unclear from this silence whether FDA thought that the need for a warning was unsubstantiated, or that a warning would be an overdeterrent, or that a warning would actually make a drug misbranded," and that "[i]f the agency wants broad preemptive force for its determinations, it is within its power to articulate those determinations explicitly. Thus implied preemption should not cover instances of agency silence.").

²⁰⁶ Marilyn P. Westerfield, Comment, *Federal Preemption And The FDA: What Does Congress Want?*, 58 *U. CIN. L. REV.* 263, 272 (1989) ("It is clear that the courts are not willing to infer preemption of state law without something more from Congress.").

²⁰⁷ Gregory J. Wartman, *Life After Riegel: A Fresh Look at Medical Device Preemption One Year After Riegel v. Medtronic, Inc.*, 64 *FOOD & DRUG L.J.* 291, 293 (2009) (noting that although health and safety have traditionally been areas of state concern, that "[o]ver the last several decades, however, the federal government has become 'increasingly' involved in the regulation of matters of health and safety.").

use, and can leave patients without a viable treatment alternative, resulting in an overall increase in public harm.

Furthermore, requiring all Phase II–IV trials to be published along with summaries of adverse events will provide the FDA, the medical community, and the public at large with much better information regarding the true safety and potential side effects of drugs, thus negating one of the proposed reasons for retaining the litigation safety valve. The databases are not yet fully operational, and it will take some time to collect and analyze enough data to realize the full potential of the new publication system. However, in a few years time we should have access to safety data for discontinued trials within a short time of their discontinuance, and it will be much more difficult to hide or delay unfavorable data. At least at that time—if not today—we believe that society should consider making the FDA the final arbitrator of drug labels, and specifically call for preemption of failure-to-warn claims relating to package inserts. Plaintiffs need not lose all recourse and bad behavior can still be litigable under express exceptions to the preemption clause, such as fraud or misrepresentation of data, or misleading direct-to-consumer advertising.

As Justice Breyer asked during the oral argument in *Warner-Lambert Co. v. Kent* case, “[W]ho would you rather have make the decision as to whether this drug is, on balance, going to save people or, on balance, going to hurt people? An expert agency, on one hand, or 12 people pulled randomly for a jury role who see before them only the people whom the drug hurt and don’t see the people who need the drug to cure them?”²⁰⁸ That is the question we must wrestle with, and we would be wiser to consider both the benefits—as well as the risks—in deciding our answer.

²⁰⁸ Transcript of Oral Argument at 30, *Warner-Lambert Co. v. Kent*, 552 U.S. 440 (2008) (No. 06-1498).