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A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims

David A. Kessler and David C. Vladeck¹

I. Introduction

For most of its seventy-seven year history, the Food and Drug Administration (FDA) has regulated the drugs sold in the United States without any significant interaction with the world of state-law damages litigation.² Nothing in the statutes the FDA administers suggests that they eliminate state damages actions for pharmaceutical products. No appellate court, before or after the advent of the FDA, has held that a state-law failure-to-warn claim for a prescription drug is

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² The agency's modern history dates back to the enactment of the Food, Drug, and Cosmetic Act in 1938. John P. Swann, *History of the FDA*, <http://www.fda.gov/oc/history/historyoffda>. But the federal government's systematic regulation of pharmaceuticals began with the Federal Food and Drugs Act of 1906, when agency was known as the Bureau of Chemistry. The agency's name was changed to the Food, Drug, and Insecticide Administration in July 1927, and was shortened to its present form in July 1930. *Id.*

preempted by federal law.³ And Congress has not acted to preempt or limit state damage actions, even though it has long been aware of tort litigation over drug products.⁴

To be sure, there has been a steady stream of failure-to-warn cases brought against pharmaceutical manufacturers by consumers injured by FDA-regulated drugs. But historically the FDA has stayed on the sidelines in that litigation. Courts adjudicated those cases under the ordinary rules that govern state damages actions, and the question of preemption rarely, if ever, arose.⁵ The FDA made no effort to intercede in those cases. Indeed, the agency generally

³ This article focuses on the FDA's effort to persuade courts to find state-law failure-to-warn claims preempted. It does not address the broader question of whether federal law preempts other state-law claims that are advanced against drug companies, such as strict liability, design defect, negligent manufacture, and breach of warranty. As explained in more detail below, because the Federal Food, Drug, and Cosmetic Act does not contain an express preemption provision for drugs, drug companies have generally not asserted preemption defenses, and it is only recently, spurred on in part by the FDA, that companies have argued that state-law failure-to-warn claims are impliedly preempted by virtue of the FDA's approval of drug labeling.

⁴ See *Bonito Boats v. Thunder Craft Boats*, 489 U.S. 141, 167 (1989) (ascribing significance to Congress' failure to provide for preemption); see also Robert S. Adler & Richard A. Mann, *Preemption and Medical Devices: The Courts Run Amok*, 59 MO. L. REV. 895, 924 (1994) (pointing out that Congress rejected a proposal to include a right of action for damages in the 1938 Food, Drug and Cosmetic Act because "a common law right of action (already) exists.").

⁵ Compliance with regulatory standards is the common defense raised in pharmaceutical product liability litigation. See generally Robert L. Rabin, *Reassessing Regulatory Compliance*, 88 Geo. L.J. 2049 (2000); cf. Michael D. Green & William B. Schultz, *Tort Law Deference to FDA Regulation of Medical Devices*, 88 Geo L.J. 2119, 2122-23 (2000). Drug companies did not begin to raise preemption as a routine defense until after the Supreme Court's ruling in *Cipollone v. Liggett Group, Inc.*, 505 U.S. 504 (1992). There, the Court held that certain state damage claims for injuries alleged to have been caused by cigarette smoking were preempted by the Federal Cigarette Labeling and Advertising Act because common law duties could impose "requirements" akin to state positive law. *Id.* at 521. *Cipollone* also marked the first time that the Court invoked preemption to nullify a state damage action where the effect of doing so was to

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resisted efforts by parties to force it to take sides in private litigation.⁶

The agency's practice of non-participation in litigation was in keeping with the FDA's view that its regulatory efforts could coexist with state-law damages claims by consumers injured by drugs. As the agency saw it, state-law failure-to-warn litigation did not interfere with the agency's regulatory efforts. The agency is not the only institution that plays a role in monitoring the emergence of unforeseen adverse events. State damages litigation helps uncover and assess risks that are not apparent to the agency during a drug's approval process. Until recently, in the FDA's view, this "feedback loop" enabled the agency to better do its job. The agency also wanted to avoid the "harsh implications" of eliminating judicial recourse for consumers injured by dangerous drugs.⁷

The past few years have witnessed a seismic shift in FDA policy. The agency now maintains that state-law failure-to-warn cases threaten its ability to protect the public health. According to the agency, a determination in civil litigation that an FDA-approved label fails

leave injured parties without a remedy. *See generally* David C. Vladeck, *Preemption and Regulatory Failure*, 33 Pepp. L. Rev. 95, 105-06,112 (2006).

⁶ *See* 21 C.F.R. § 20.1; *cf. In re: David A. Kessler*, 100 F.3d 1015 (D.C. Cir. 1996).

⁷ *See* Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 9 (1997); *see also* FDA, Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) (codified at 21 C.F.R. pts. 201, 208, 314, 601, 610) (requiring Medication Guides for products that are deemed to pose significant public health concern) ("FDA does not believe that the evolution of state tort law will cause the development of standards that would be at odds with the agency's regulations."); FDA, Final Rule, Labeling and Prescription Drug Advertising; Content and Format for Labeling of Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,437 (Jun. 26, 1979) (codified at 21 C.F.R. pts. 201 & 202) ("It is not the intent of the FDA to influence the civil tort liability of the manufacturer...").

adequately to warn of risks may force manufacturers to add warnings that are not approved by the FDA, thus rendering the product “misbranded.” Even worse, the FDA says, adverse rulings could force manufacturers to add warnings that the FDA considered and rejected — thus placing manufacturers in the untenable position of having to violate federal law to avoid state damages judgments. For these reasons, the FDA now argues that the federal Food, Drug and Cosmetic Act (FDCA) impliedly preempts many failure-to-warn claims based on product labeling approved by the FDA. The FDA first announced this position in 2002, by filing amici briefs asking courts to dismiss failure-to-warn cases. More recently, the agency formalized this position in the preamble to a 2006 rule that revises requirements for drug labeling.⁸

This essay does not seek to review comprehensively the history of the FDA’s regulation of drug labeling, its new position favoring preemption of failure-to-warn claims for drugs, or the arguments that have been advanced in support of or in opposition to the FDA’s new policy.⁹

⁸ FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

⁹ We address the FDA’s main argument supporting preemption below. *See infra* at __-__. But we do not canvass many of the arguments that have been raised against the FDA’s position. Among them are (1) the contention that the FDA’s position new position is not entitled to deference (a) because Congress has not delegated to the FDA the authority to determine the preemptive effect of labeling decisions on state law, *see Gonzales v. Oregon*, 126 S. Ct. 904, 915 (2006), (b) because the FDA did not develop its new position through notice and comment rulemaking or other formal means, *see United States v. Mead Corp.*, 533 U.S. 218, 226-27 (2001), and (c) because the agency’s new position on preemption conflicts with its longstanding contrary position, *see Mead*, 533 U.S. at 228; (2) the claim that the FDA’s new preemption position can be applied, if at all, only prospectively, *see Bowen v. Georgetown University Hospital*, 488 U.S. 204-208-09 (1988); and (3) the more general claim that the agency’s position cannot be squared with basic principles of compensatory justice. *See generally* Thomas O. McGarity, *THE PREEMPTION WAR* (Yale Univ. Press) (forthcoming).

Others have plowed that field, and have done it well.¹⁰

Rather, this essay highlights what we believe are two of the most problematic aspects of the FDA's pro-preemption position — one legal, the other practical — that do not stand out in more comprehensive treatments of the issue. The first point we make is that the FDA's pro-preemption arguments are based on a reading of the FDCA that, in our view, undermine the incentives drug manufacturers have to change labeling unilaterally to respond to newly-discovered risks, or to seek labeling changes from the FDA. In fact, drug manufacturers have significant authority — and indeed a responsibility — to modify labeling when hazards emerge and may do so without securing the FDA's prior approval. The background possibility of failure-to-warn litigation provides important incentives for drug companies to ensure that drug labels reflect accurate and up-to-date safety information.

Our second concern is that the FDA's pro-preemption arguments are based on what we see as an unrealistic assessment of the agency's practical ability, once it has approved the

¹⁰ See generally Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 J. TORT L. VOL. 1 (2005), <http://bepress.com/jtl/vol1/iss1/art4>; Allison M. Zieve & Brian Wolfman, *The FDA's Argument for Eradicating State Tort Law: Why Its Wrong and Warrants no Deference*, 21 TOXICS L. REP. 516 (2006); Mary J. Davis, *The Final Battle for Preemption: The FDA and Prescription Drug Labeling Product Liability Actions* (Berkeley Elec. Press, Working Paper No. 1591, 2006) <http://www.bepress.com/expresso/eps/1591>; Thomas O. McGarity, *THE PREEMPTION WAR* (Yale Univ. Press) (forthcoming); but see Richard Epstein, *Why the FDA Must Preempt Tort Litigation: A Critique of Chevron Deference and a Response to Richard Nagareda*, 1 J. TORT L. VOL. 2 (2006) (making normative argument for a broad liability shield for drug companies). This essay leaves to one side the somewhat more complicated question of preemption of claims relating to medical devices — more complicated only because the 1976 Medical Device Amendments (MDA) to the Food, Drug, and Cosmetics Act contain a preemption provision. See David C. Vladeck, *Preemption and Regulatory Failure*, 33 PEPP. L. REV. 95 (2005) (arguing that the MDA preemption provision is addressed only to conflicting state positive law, not state tort or damages claims).

marketing of a drug, to detect unforeseen adverse effects of the drug and to take prompt and effective remedial action. After all, there are 11,000 FDA-regulated drugs on the market (including both prescription and over-the-counter drugs), with nearly one hundred more approved each year.¹¹ The reality is that the FDA does not have the resources to perform the Herculean task of monitoring comprehensively the performance of every drug on the market. Recent regulatory failures have demonstrated the FDA's shortcomings in this regard. Given the FDA's inability to police drug safety effectively on its own, we question the wisdom of the FDA's efforts to restrict or eliminate the complementary discipline placed on the market by failure-to-warn litigation.

Our differences with the FDA's current policy can be traced to a difference in perspective about the relevant agency decision that would be subject to review in a state-law failure-to-warn case. The FDA focuses on the approval process, suggesting that the FDA's approval of a drug's labeling reflects the agency's definitive judgment regarding risks that must be shielded from the possible second-guessing that might take place in a failure-to-warn case. Otherwise, the FDA claims, court rulings adverse to drug companies might force companies to add warnings not approved, or even rejected by, the FDA, thereby upsetting the balance of risks and benefits set by

¹¹ See Davis *supra* n. ___, at n.76 and accompanying text; Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER (Jan./Feb. 2006), http://www.fda.gov/fdac/features/2006/106_cder.html; CENTER FOR DRUG EVALUATION AND RESEARCH, REPORT TO THE NATION 2005: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 12 (Food and Drug Administration, 2005), *available at* <http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf> (stating that the FDA approved 78 new drugs and two new biologic products in 2005). Many of the new approvals are for new indications of drugs that have already been approved by the agency; only a handful of new drugs are approved each year that are new molecular entities.

the FDA when it approves a drug label. Of course, the moment the FDA approves a new drug is the one moment the agency is in the best position to be the exclusive arbiter of a drug's safety and effectiveness. On that day, the FDA has had access to and has devoted considerable resources to reviewing carefully all of the extant health and safety data relating to the drug.¹² On that day, and that day only, we agree that the FDA's determinations about labeling ought not be subject to re-examination by courts or juries in failure-to-warn cases.

But in our view the FDA is wrong to focus on the moment of approval as determinative of the preemption question. The relevant time-frame is *post*-approval, and the question, in our view, is what the drug company knew about a drug's risks at the time the patient/plaintiff sustained injury and what the company told the FDA. After all, the FDA's knowledge-base of the risks posed by a new drug is far from static. At the time of approval, the FDA's knowledge-base may be close to perfect, but it is also highly limited because, at that point, the drug has been tested on relatively small populations of patients.¹³ Once the drug enters the marketplace, risks that are relatively rare, that manifest themselves only after an extended period of time, or that

¹² This assumes, of course, that the drug's sponsor has complied with the requirements governing new drug applications. That is not always the case. *See Buckman Co. v. Plaintiff's Legal Comm.*, 531 U.S. 341 (2001).

¹³ *See* INST. OF MED., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 36 (Alina Baciuc, Kathleen Stratton & Shelia P. Burke, eds., The National Academies Press 2006) available at <http://www.iom.edu/CMS/3793/26341/37329.aspx> (hereinafter IOM REPORT) (estimating that drugs are generally tested on between 600 and 3,000 patients).

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affect vulnerable subpopulations, begin to emerge.¹⁴ These are often not risks foreseen by the drug's manufacturer or the FDA and, for that reason, are not addressed on the label. After a drug is approved, the FDA cannot unilaterally compel labeling changes, but must instead negotiate changes with the drug's sponsor.¹⁵ The FDA's statutory and regulatory tools for gathering post-approval information are relatively crude and often ineffective, especially when contrasted with its tools for information gathering prior to approval. For that reason, the tort system has historically provided important information about these newly-emerging risks to physicians, patients and the FDA.¹⁶

The FDA's shift of position also comes at a particularly inopportune time for the agency. Although the FDA now argues for broad preemption of failure-to-warn claims, the agency's

¹⁴ See, e.g., *Hearings on Risk and Responsibility: The Roles of the FDA and Pharmaceutical Companies in Ensuring Safety of Approved Drugs, Like Vioxx Before the H. Comm. on Government Reform*, 109th Cong. 23, 55 (2005) (testimony of Steven Galston, Acting Director, Center for Drug Evaluation and Research, FDA).

¹⁵ See IOM Report *supra* n. ___, at 157; GOVERNMENT ACCOUNTABILITY OFFICE, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 10 (GAO-06-402) (March 2006), available at www.gao.gov/cgi-bin/getrpt?GAO-06-402 (hereinafter GAO DRUG SAFETY).

¹⁶ See Nagareda *supra* n. ___, at 5-6 & n.16 (referring to this as "a process of 'information updating' over time"); Wendy Wagner, *When All Else Fails: Regulating Risky Products through Tort Litigation*, 95 Geo. L. J. 693, 711 (2007); Robert L. Rabin, *Reassessing Regulatory Compliance*, 88 GEO. L.J. 2049, 2068-71 (2000) (ascribing to tort litigation an "educational role"); Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 Yale J. Health Pol'y L. & Ethics 587, 612 (2005) ("The tort system should remain free to redetermine product safety in the light of information developed during litigation, because the FDA may not always uncover relevant safety information and may not act quickly enough upon the information that it does receive"). There are feedback loops other than damages litigation, such as those governing adverse reporting, but, as discussed later on, they have not proved adequate. See *infra* at ___.

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assertion that it is able single-handedly to ensure drug safety has been undermined by a number of highly-publicized regulatory failures. Two recent independent studies of the FDA's oversight of drug safety — one by the Government Accountability Office and the other by the National Academy of Sciences' Institute of Medicine — have been critical of the agency's ability to keep unsafe drugs off the market and to respond effectively to unforeseen hazards with newly-approved drugs.¹⁷ Even the FDA has acknowledged its own limitations. In the aftermath of the agency's ineffective response to the reports of increased cardiac adverse events among Vioxx users, the FDA in 2005 established the Drug Safety Oversight Board (DSOB) to better monitor drugs on the market.¹⁸ But, by all accounts, the DSOB is too poorly funded and staffed to do its job effectively.¹⁹ In our view, these regulatory gaps in the FDA's system undermine the agency's case for preemption of state-law failure-to-warn claims.

II. *Background*

Since the passage of the landmark 1938 Federal Food, Drug, and Cosmetic Act, all drugs must be evaluated and approved by the FDA before they may be marketed in the United States.

¹⁷ See GAO DRUG SAFETY *supra* n. ___, at 18; IOM REPORT, *supra* n. ___, at 153-54.

¹⁸ See *FDA's Drug Approval Process: Up to the Challenge? Hearings Before the S. Comm. on Health, Education, Labor and Pensions*, 109th Cong., 10 (March 1, 2005) [hereinafter *Hearings: Up to the Challenge?*] (joint statement of Sandra L. Kweder, M.D., Deputy Director, Office of New Drugs, FDA and Janet Woodcock, M.D., Acting Deputy Commissioner for Operations, FDA); see also Davis, *supra* n. ___, at n.78 and accompanying text; FDA Improvements in Drug Safety Monitoring, FDA Fact Sheet, <http://www.fda.gov/oc/factsheets/drugsafety.html> (Feb. 15, 2005) (describing the creation of the DSOB).

¹⁹ See GAO DRUG SAFETY *supra* n. ___, at 1, 6.

Prior to 1962, the FDA's review focused on the drug's safety. Since then, the drug's sponsor must demonstrate that the drug is "safe and effective" for its approved uses and that its labeling is not "false or misleading."²⁰

To obtain the FDA's approval, a drug manufacturer must submit a "new drug application" (NDA) for the agency's review. An NDA must include all information bearing on a drug's safety and effectiveness, including the results of animal testing, pharmacological studies, and full reports of all of the clinical trials performed on human subjects.²¹ Drug companies are responsible for supervising and controlling these studies.²² Premarket human trials generally involve only a few thousand subjects and study design necessitates a careful control of the conditions of the study.²³ These conditions are a far cry from those that face a drug once it is approved and widely prescribed by thousands of doctors.²⁴ New drugs designed to "address unmet medical needs" for "serious or life-threatening conditions" may receive accelerated or

²⁰ In 1962, Congress passed the Kefauver-Harris amendments to the FDCA, Pub. L. No. 87-781, 76 Stat. 788-89 (1962) (codified at 21 U.S.C. §§ 321(p)(1)-(2) & 355(b)-(d) (2000)) (sponsor of the drug has to provide substantial evidence of effectiveness for the product's intended use as precondition to approval.)

²¹ 21 U.S.C. § 355(a)-(b) (2006); *see* Davis, *supra* n. ___, at n.77 and accompanying text; *see also* http://www.fda.gov/cder/cderorg/ond_reorg.htm (describing the Office of New Drugs); <http://www.fda.gov/cder/regulatory/applications/default.htm> (describing the drug approval process).

²² *See* McGarity *supra* n. ___, at 279; IOM REPORT, *supra* n. ___, at 34.

²³ Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 Food & Drug L.J. 295, 297 (2006).

²⁴ *Id.*

“fast track” consideration by the FDA. These drugs are subject to shorter review periods and may be approved based on less safety and effectiveness information than other drugs.²⁵

Because drug labeling provides doctors and other health care professionals information needed to make informed prescribing decisions, the FDA’s NDA review includes a detailed examination of the manufacturer’s proposal for the drug’s labeling. The labeling must accurately and fairly describe the drug’s intended uses. Because all drugs have adverse side effects, the labeling must also address the drug’s potential risks, contraindications, warnings, precautions and adverse reactions.²⁶ The manufacturer and the FDA ordinarily discuss the content of these warnings in some detail during the approval process.²⁷ When the FDA approves a drug, it also approves the precise final version of the drug’s label.²⁸

When the application is complete, the FDA then determines whether it meets a number of requirements set forth in the Act, including (1) whether the drug is “safe for use under the conditions prescribed, recommended or suggested in the proposed labeling,” (2) whether there is

²⁵ 21 U.S.C. § 356(a)(1) (2006); see McGarity, *supra* note 8, at 279-80; GAO DRUG SAFETY, *supra* n. ___, at 11; Struve, *supra* n. ___, at 595. See also 21 C.F.R. § 314.500-.520.

²⁶ 21 U.S.C. § 355(d) (2006). The FDA labeling regulations are extensive and include specific requirements on the format and content of drug labels. See 21 C.F.R. §§ 201.56, 201.57, 201.80. The FDA revised these regulations in 2006. See FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3922 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

²⁷ McGarity *supra* n. ___, at 281; see *Hearings: Up to the Challenge?*, *supra* n. ___, at 79 (response to questions by Sen. Hatch by Sandra L. Kweder, M.D., Deputy Director, Office of New Drugs, FDA).

²⁸ 21 C.F.R. § 201.57(c)(6)(i).

“substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use” reflected on the proposed labeling, and (3) whether, “based on a fair evaluation of all material facts, such labeling is false or misleading in any particular.”²⁹ If the statutory conditions are met, the FDA must approve the NDA.

The FDA’s approval of a drug does not spell the end of the agency’s oversight of the drug or its labeling. Prior to FDA approval, drugs are tested on relatively small populations of patients, for durations rarely exceeding a year or two. Thus, pre-approval testing generally is incapable of detecting adverse effects that occur infrequently, have long latency periods, or affect subpopulations not included or adequately represented in the studies (*e.g.*, the elderly, ethnic minorities and pregnant women).³⁰ As one expert put it, most clinical studies “can detect drug-related injuries that occur at a rate of between one in 500 and one in 1,000. Yet, if the drug is used by 200,000 people . . . a serious adverse event appearing in as few as one in 10,000 people is very significant, since it would occur 20 times. These rare reactions can be identified only

²⁹ See generally 21 U.S.C. § 355(d) (2006). The “substantial evidence” of safety and effectiveness required by the Act is “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.” *Id.*

³⁰ See IOM REPORT *supra* n. ___, at 38; see also Louis Lasagna, *Discovering Adverse Drug Reactions*, 249 J. Am. Med. Ass’n 2224, 2225 (1983) (pointing out that a study would have to have more than 600,000 subjects in order to have a ninety-five percent chance of detecting side effects that might injure 1 or 2 subjects out of 1,000 tested); Bruce M. Psaty & Curt D. Furberg, *COX-2 Inhibitors - Lessons in Drug Safety*, 352 New Eng. J. Med. 1133, 1134 (2005) (“In the initial evaluation of the COX-2 inhibitors [the class of drugs that includes Vioxx], the use of small, short-term trials, the exclusion of high-risk patients, and the methodologic inattention to cardiovascular events all minimized the possibility of uncovering evidence of cardiovascular harm.”).

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after a drug has been widely used.”³¹ For these reasons, the FDA’s approval of a drug is not a warrant that the drug will not cause serious adverse effects even if properly used for its approved purposes.³² The FDA does have a program in place for post-market surveillance of approved drugs, but that program has been chronically under-funded by Congress and, according to recent studies by the Institute of Medicine and the Government Accountability Office, has not performed well.³³ And although the FDA strengthened its system for the collection of adverse reaction data in the early 1990s to solicit reports from health care providers and consumers, only a small fraction of adverse reactions are reported to the FDA.³⁴

Because unanticipated adverse effects often emerge with approved drugs, there are

³¹ William B. Schultz, *How to Improve Drug Safety*, Washington Post (Dec. 2, 2004), A35 (Mr. Schultz served as the FDA’s Deputy Commissioner for Policy from 1994 to 1998). Many drugs are used by far more patients. Vioxx, for example, was used by an estimated 20 million patients. See *In re Vioxx Prods. Liab. Litig.*, 2007 U.S. Dist. LEXIS 43867 (E.D. La. July 3, 2007).

³² The FDA does not warrant the safety of the drugs it approves, and recognizes that even the most up-to-date and informative labels cannot avert adverse reactions. But the incidence of adverse reactions is cause for concern. Adverse drug reactions are believed to be a leading cause of death in the United States. See Joshua Lazarou, *et al.*, *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies*, 279 J. Am. Med. Ass’n 1200-1205 (1998) (estimating that adverse drug reactions are the fourth to sixth leading cause of death in the United States, with an estimated 106,000 deaths from adverse drug reactions in 1994).

³³ See GAO DRUG SAFETY, *supra* n. ___, at 18, 28; IOM REPORT, *supra* n. ___, at 51.

³⁴ *Reauthorization of the Prescription Drug User Fee Act: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 107th Cong. 49 (2002) (statement of Rep. Henry A. Waxman); see also IOM REPORT, *supra* n. ___, at 53 (reporting that although the FDA receives more than 400,000 reports each year, this is only a “small fraction of all adverse effects of drugs.”).

detailed procedures that regulate modifications to drug labeling. Generally labeling changes proposed by the manufacturers require prior FDA approval.³⁵ There are exceptions, however, and these exceptions are especially relevant to the preemption debate. Most importantly, “labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established.”³⁶ Statements that may be added without prior FDA approval are those (1) to “add or strengthen a contraindication, warning, precaution, or adverse reaction,” (2) to “add or strengthen a statement about drug abuse, dependence, psychological effect, or overdose,” (3) to “add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product,” or (4) to “delete false, misleading, or unsupported indications for use or claims of effectiveness.”³⁷ To be sure, the manufacturer must promptly inform the FDA of the change and submit a Supplemental New Drug Application that the FDA then reviews after-the-fact.³⁸ But this “safety valve” option gives manufacturers the ability to provide physicians, health care professionals, and patients with up-to-date information on an ongoing basis so long as a drug remains on the market, without the need to secure the

³⁵ 21 C.F.R. § 314.70(b) (2006) (FDA must approve any “major” labeling change in advance); *see also id.* (defining what changes are deemed “major”).

³⁶ 21 C.F.R. §§ 201.57(c)(6)(i); 201.80(e).

³⁷ 21 C.F.R. § 314.70(c)(6)(iii)(A)-(C) (2006).

³⁸ 21 C.F.R. § 314.70(c)(6)(iii) (2006).

FDA's advance approval.³⁹ And the FDA has long made it clear that its labeling rules are no obstacle to manufacturers providing warnings to doctors and patients through labeling, advertising, or "Dear Doctor" letters as soon as the manufacturer discovers risks that are not clearly stated on the label.⁴⁰

In 2006, the FDA issued revised labeling regulations to streamline labeling and make it easier for health care providers to access key information. The new rules add a number of features, including a "Highlights" section of the label that sets forth the major warnings that are described in more detail elsewhere on the label, a new format for labeling, and new requirements to make hazard and adverse reaction information generally more accessible.⁴¹ Consolidating important risk information on labeling will better ensure that physicians and patients are alerted to the drug's most serious potential side effects. But nothing in the new regulations alters the agency's longstanding requirements that manufacturers revise their labels to protect public health and may do so without first obtaining the agency's approval.

Nonetheless, the FDA contends in the preamble to the new regulations that state failure-to-warn actions have "directly threatened the agency's ability to regulate manufacturer

³⁹ *See generally* 21 C.F.R. §§ 201.57(c)(6), 201.80(e) (2006).

⁴⁰ Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,447 (Jun. 26, 1979) (codified at 21 C.F.R. pts. 201, 202).

⁴¹ 21 C.F.R. § 201.57(a); FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

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dissemination of risk information for prescription drugs” and are therefore preempted.⁴² In the past, when the FDA has claimed that its regulatory action has the effect of preempting state law, it has said so explicitly in regulations adopted through notice and comment proceedings that have the force of law.⁴³ But the FDA did not adopt a regulation that spells out the boundaries between federal and state law, as it has done for medical devices.⁴⁴

Rather, it is the preamble alone that addresses preemption, and there the FDA sketches out its case for preemption. Among other things, the agency asserts that its pro-preemption position reflects the agency’s “longstanding view,” even though the available evidence suggests otherwise.⁴⁵ The agency also reviews the pro-preemption position it has recently taken in a

⁴² FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3933 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

⁴³ *E.g.*, 21 C.F.R. § 808.1 (defining the scope of the preemption provision in the Medical Device Amendments of 1976, 21 U.S.C. § 360k).

⁴⁴ The FDA’s failure to address preemption directly in a regulation may be traced to the fact that, while there is an express preemption provision in the Medical Device Amendments of 1976, which specifically forbids states from imposing “requirements” in addition to or that are different from those imposed by the FDA, 21 U.S.C. § 360k(a), there is no counterpart provision in the FDCA for drugs.

⁴⁵ *See In re Bextra and Celebrex Marketing Sales Practices and Product Liability Litigation*, 2006 WL 2374742 at *8 (N.D. Cal. 2006) (observing that “the FDA’s current view of the preemptive effect of its labeling regulations is a 180-degree reversal of its prior position”); Davis, *supra* n. __, at n.140 and accompanying text; Brief for Public Citizen as Amicus Curiae Supporting Cross-Appellee Motus, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498), 2003 WL 22716063, at *12. Additionally, the proposal for the rule change stated that the new rules would not have a preemptive effect. *See* FDA, Proposed Rule, Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66378, 66384 (Dec. 1, 1998) (“the written patient medication information provided does not alter the duty, or set the standard of care for manufacturers....FDA does not believe that the evolution of

number of state failure-to-warn cases. And the agency argues that its labeling requirements are not minimum standards, as some courts had observed, but instead establish both a floor and a ceiling. Additional requirements imposed by state failure-to-warn rulings risk “erod[ing] and disrupt[ing] the careful and truthful representations of the benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.”⁴⁶ As the FDA sees it, many failure-to-warn claims are impliedly preempted, including those based on choices manufacturers make about what to put in the “Highlights” portion of labels, and labeling claims that were proposed to the FDA but not required by the agency at the time the claim arose.⁴⁷ The FDA does concede, however, that failure-to-warn claims based on state-law duties that parallel federal ones, or seek to enforce federal duties, are not preempted.⁴⁸

state tort law will cause the development of standards that would be at odds with the agency’s regulations.”). The FDA itself has acknowledged in amicus briefs that this pro-preemption stance is a change from past views held by the agency. *See* Brief for the United States as Amicus Curiae Supporting Appellee, *Horn v. Thoratec*, 376 F.3d 163 (3d Cir. 2004), 2004 WL 1143720 at *2 (“We acknowledge that...this [preemption] position represents a change for the United States.”).

⁴⁶ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3935.

⁴⁷ *Id.*

⁴⁸ *Id.* at 3936. This concession appears to be dictated by the Supreme Court’s decision in *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 495 (1996), which held that, a tort claim premised on state-law duties “equal to, or substantially identical to,” duties imposed by federal law are not preempted. *See also id.* at 513 (O’Connor, J., concurring in part, dissenting in part). The FDA has amplified its position on the scope of preemption in a September 21, 2006, amicus submission in *Perry v. Novartis Pharmaceuticals, Inc.*, Civ. No. 05-5350 (E.D. Pa.), although the agency is still less than clear about what claims might be permitted to proceed under its theory.

III. *FDA Labeling Determinations Are Subject To Constant Reevaluation and Revision and Failure-to-Warn Litigation Does Not Threaten to Displace the FDA's Role as Final Decision-Maker Regarding a Drug's Label.*

As noted above, one cornerstone of the FDA's preemption argument is its claim that agency decisions regarding a drug's labeling, made at the time of approval, are essentially set in stone and should therefore not be reviewed, in any way, by a court in a failure-to-warn case. The FDA also cites its expertise in balancing the benefits and risks of pharmaceuticals. According to the FDA, labeling decisions are often difficult and require the agency to engage in a complex balancing of interests. Warnings that overstate or exaggerate risks are no more help to physicians and patients than warnings that downplay risks or side effects. Striking the right balance takes expertise and judgment. For these reasons, the FDA claims, the final say over drug labeling must be left to the manufacturer and the FDA, and should not be subject to second-guessing by courts.

We agree that labeling decisions are often fraught with complexity and that the FDA should have the final word on drug labeling. We do not doubt that if a state enacted a drug labeling law that purported to compel drug manufacturers to add warnings unapproved by the

In *Perry*, the FDA acknowledged that the defendant's argument "that federal preemption bars any failure-to-warn claim premised on a drug manufacturer's failure to provide a warning not contained in the drug's approved labeling" is "incorrect." *Id.* at 11. The FDA further noted that it "has not attempted to 'occupy the field' of prescription drug labeling, and state tort liability for failure to warn does not necessarily prevent FDA from carrying out its regulatory goals. Federal regulations explicitly provide for labeling changes to be made to warn of new hazards or cautions relating to a drug without prior FDA approval. Under this regulatory scheme, preemptive conflict does not exist in every instance in which state tort law seeks to impose liability for the failure to provide a warning not affirmatively mandated by the FDA." *Id.* Under this approach, it appears that the FDA would not necessarily object to claims that a manufacturer has failed to provide a warning about a newly-discovered risk that the FDA has not considered, so long as the warning would not render the drug misbranded.

FDA, such an effort would properly be struck down on conflict preemption grounds.⁴⁹

Our claim does not challenge the FDA's supremacy over labeling. But we do not agree with the FDA's conclusion about preemption of failure-to-warn claims. In our view, the factors the FDA cites to support its position do not justify insulating labeling decisions from state failure-to-warn litigation, for two related reasons. First, failure-to-warn litigation does not challenge the FDA's decision to approve a label for a new drug; instead, it challenges the *company's* failure to revise its labeling to warn about risks that were unknown at the time the drug was approved, or risks that turn out to be more grave than the company and the FDA thought at the time of approval. Second, failure-to-warn litigation does not seek to force labeling changes or to substitute a jury or court's judgment for the FDA's; failure-to-warn litigation seeks compensation for injured patients.

A. Failure-to-Warn Claims Seek Compensation, Not Injunctions to Force Labeling Changes, and Preemption of Failure-to-Warn Claims Would Remove Incentives for Drug Manufacturers to Update Labels.

The first and most serious flaw in the FDA's interference argument is the assumption that failure-to-warn litigation seeks to supplant the FDA as final decision-maker as to the content and format of drug labeling. That is not the case. The FDCA gives that authority to the FDA and no one else. Failure-to-warn litigation does not undercut that authority. Failure-to-warn litigation challenges the *company's* failure to warn doctors and patients about a risk and seeks money damages for injuries caused by the lack of an adequate warning. Plaintiffs do not seek

⁴⁹ In fact, in just such a case, the California Supreme Court rejected, on conflict preemption grounds, the argument that California's Proposition 65 could require additional warning labels on certain drug products. *Dowhal v. SmithKline Beecham*, 88 P.3d 1 (Cal. 2004).

injunctions or other court decrees forcing a labeling change; they seek compensation for their injuries.

In the typical failure-to-warn case, the plaintiff alleges that the drug's label failed adequately to warn of risks that were unknown, or poorly understood, at the time the drug was approved but were evident at the time the plaintiff was injured. In that kind of case, a judgment in favor of the plaintiff — or even serial plaintiffs' judgments — may cause one or both of two things to happen, neither of which impairs the FDA's decisional authority. First, the company might agree that the risk is worthy of a warning label and either ask the FDA to approve a labeling change or decide to add the warning and then seek the FDA's approval. Or second, as a result of the information that comes to light during the litigation, the FDA might recognize the risk as one requiring a warning and initiate discussions with the company to bring about such a change. Either way, the overriding public health interest is served, and the FDA exercises control over the labeling.

Even if the warning at issue was one considered and rejected by the FDA at the time of approval, that does not mean that a failure-to-warn case seeks to force the substitution of a court-required label for the label approved by the FDA. As noted above, because pre-approval testing is subject to serious limitations, post-approval use in large numbers of patients brings about a deeper understanding of the nature and magnitude of the risks posed by the drug. In a failure-to-warn case involving such a risk, a plaintiff's verdict might well prompt the company and the FDA to reconsider the appropriateness of a warning, even though they rejected it earlier on the

basis of less complete data.⁵⁰ As the Supreme Court has frequently observed, tort law often informs regulatory decisions,⁵¹ and the FDA has often acted in response to information that has come to light in state damages litigation.⁵²

But preemption would not be justified even if, in the midst of failure-to-warn litigation, the FDA reviews all of the new safety information and determines that a labeling change is not warranted. Of course, should such a case arise, the drug company would have a powerful defense. It would be able to argue to the jury that it complied with applicable FDA requirements and that the plaintiff is complaining about the absence of a warning the FDA had *rejected*. Moreover, as the FDA acknowledges, the FDCA does not *expressly* preempt state-law damages claims, or even occupy the field of drug regulation.⁵³ Accordingly, the only preemption argument available to the company and the FDA is that such claims are *impliedly* preempted because they either actually conflict with federal law or erect an impermissible obstacle to the achievement of

⁵⁰ The Supreme Court has noted that state damages actions “may aid the exposure of new dangers associated” with the product and prompt the agency to “decide that revised labels are required in light of new information that has been brought to its attention.” *Bates v. Dow Agrosciences, LLC*, 544 U.S. 431, 451 (2005) (quoting *Ferebee v. Chevron Chem. Co.*, 736 F.2d 1529, 1541-42 (D.C. Cir. 1984)).

⁵¹ *See, e.g., id.*

⁵² *See, e.g.,* Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J. Am. Med. Ass’n 2215, 2218 (2002); Aaron Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 287 J. Am. Med. Ass’n 308, 310 (2007) (citing examples).

⁵³ 71 Fed. Reg. 3922, 3935 n.8; *see also* n. ___, *supra*.

federal objectives.⁵⁴

Permitting failure-to-warn litigation to proceed does not pose a conflict with federal law or threaten the fulfillment of federal objectives. To begin with, there is no reason why a drug manufacturer cannot comply with both FDA-required labeling and pay a state damage judgment based on a determination that the labeling failed to adequately warn of a discrete risk.⁵⁵ The legal test is actual, irreconcilable conflict — not simply the burden of incurring the expense of an adverse judgment. As the Supreme Court recently explained in *Bates v. Dow Agrosciences LLC*, “a requirement is a rule of law that must be obeyed; an event, such as a jury verdict, that merely motivates an optional decision [whether to add a new warning to a drug label] is not a requirement” triggering preemption.⁵⁶ An adverse ruling in a failure-to-warn case would not *require* the manufacturer to do anything other than pay money damages. Of course, a

⁵⁴ See, e.g., *United States v. Locke*, 529 U.S. 89, 109 (2000); *Geier v. American Honda Motor Co.*, 529 U.S. 861, 873-74 (2000).

⁵⁵ Conflict preemption requires something more coercive than paying a judgment. As an example of conflict preemption, Justice Breyer’s concurrence in *Lohr* said “[i]magine that, in respect to a particular hearing aid component, a federal MDA regulation requires a 2-inch wire, but a state agency regulation requires a 1-inch wire. If the federal law, embodied in the ‘2-inch’ MDA regulation, pre-empts the state ‘1-inch’ agency regulation, why would it not similarly pre-empt a state-law tort action that premises liability upon the defendant manufacturer’s failure to use a 1-inch wire.” 518 U.S. at 504 (Breyer, J., concurring). Similarly, in *Geier v. American Honda Co.*, the Court found that a claim that a passenger vehicle that was not equipped with airbags was defectively designed preempted because permitting it go forward would conflict with NHTSA’s decision to provide for a gradual phase-in of air-bags. 529 U.S. 861, 867-71 & 875 (2000).

⁵⁶ 544 U.S. 431, 445 (2005); see also *Sprietsma v. Mercury Marine*, 537 U.S. 51, 64 (2002); *Goodyear Atomic Corp. v. Miller*, 486 U.S. 174, 185-86 (1988); Vladeck *supra* n. ___, at 115-16.

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manufacturer might decide to take measures to avoid future adverse rulings, including adding a warning to the drug's labeling. But a manufacturer could also rationally decide to do nothing, reasoning that the prospect of a recurrence is too remote to justify a labeling change, or that the cost of defending cases and paying judgments is less than the sales that would be lost as a result of making a labeling change.⁵⁷

Nor would an adverse ruling in a state failure-to-warn case stand as an obstacle to federal objectives. As articulated by the FDA, its overarching objective is to safeguard the public's health by ensuring that drug labeling is uniform, accurate, and fairly addresses the possible risks of a drug without overstating those risks.⁵⁸ But an adverse ruling in a state failure-to-warn case, even where the FDA has had access to all of the information before the court and believes that the plaintiff's claim is unsubstantiated, does not jeopardize that interest. If the FDA has considered the labeling change addressed in the litigation and found that it is unwarranted, the

⁵⁷ Consider one example. As explained in detail below, *see infra* n. ___, manufacturers of a certain class of widely-prescribed antidepressants, known as "selective serotonin reuptake inhibitors," or "SSRIs," were the target of failure-to-warn cases brought by families whose children committed suicide while taking the drug. The plaintiffs claimed, and some courts and juries agreed, that the drugs should have warned of the association between use of the drug and an increased risk of suicidal thoughts, ideations and acts. Despite having to pay judgments to prevailing plaintiffs, the companies resisted calls to change their warnings, and did so only after being directed to do so by the FDA.

⁵⁸ *Cf.* Brief for the United States as Amicus Curiae Supporting Appellee, *Horn v. Thoratec*, 376 F.3d 163 (3d Cir. 2004), 2004 WL 1143720 at *2-3 (in a case involving a medical device, the FDA stated that "the United States has a substantial stake in ensuring that state common law tort judgements do not interfere with implementation of this important federal scheme [of regulating safety and effectiveness]....A contrary rule would undermine overall public health protection."); *see also* FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601).

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court cannot compel a labeling change. The company may be forced to pay a price for the FDA's decision, but the court's ruling will not displace the FDA's authority over the label.⁵⁹

This result may appear harsh, but in reality there are few instances in which the company (which is trying to sell its drug) wants a *stronger* label than the FDA and the FDA (which is trying to safeguard public health) *resists* the change.⁶⁰ The FDA does not identify such a case. And if such a case arose, the company would have an out: the FDCA gives it the authority to change its label unilaterally to add the warning addressed in the litigation, so long as the amended label is not false and misleading, and then file a Supplemental New Drug Application seeking the FDA's after-the-fact approval. In such an instance, it is likely that the FDA and the company would strive to avoid an impasse over the labeling. To be sure, the FDA would have the authority to reject such a labeling change, but we are not aware of cases in which the FDA has refused any change to a label when pressed for a *stronger* warning by a manufacturer.⁶¹ And,

⁵⁹ Strict liability theory acknowledges that dangerous products will cause harm on occasion, but on balance, the product's benefits to society outweigh its risks. The product remains on the market, its manufacturer is responsible for warning users of the product's risks, but the manufacturer also compensates people injured using the product. *See generally* DAVID G. OWEN, JOHN E. MONTGOMERY & MARY J. DAVIS, PRODUCTS LIABILITY AND SAFETY: CASES AND MATERIALS 474 (Foundation Press 2007).

⁶⁰ *See Kesselheim & Avorn, supra n. __*, at 310 (reporting that discovery in civil litigation demonstrated the *manufacturer's* resistance to the FDA's effort to persuade the manufacturer to place a strong warning on the drug dexfenfluramine). Of course, if the "harshness" of the result factors into the preemption analysis, it bears mention that the abolition of a failure-to-warn remedy — as the FDA advocates — would be especially harsh to individual patients who are injured by drugs that do not carry adequate warnings of risk but would then be deprived of compensation for their injuries.

⁶¹ *See Feldman v. Lederle Laboratories*, 592 A.2d 1176, 1193 (N.J. 1991) ("for the FDA to have prevented a drug manufacturer from warning the public of a newly-discovered danger

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as best as we can tell, the FDA has never brought a misbranding claim against a company in those circumstances.⁶² Ironically, if it did, the agency would be back to where it started, because the ultimate decision-maker in a misbranding action would be the jury and not the FDA.⁶³

More serious is the problem the FDA barely mentions. Manufacturers often *resist* labeling changes the FDA believes are needed due to emerging safety concerns. For instance, the FDA acknowledges that it took over a year to persuade Merck, the manufacturer of Vioxx, to add a warning of the risks of heart attack and stroke to Vioxx's label.⁶⁴ During the lengthy

pending development of unequivocal factual evidence of adverse reaction in man 'would seem anomalous'').

⁶² This is not necessarily surprising. Bringing a misbranding action would consume substantial agency resources, the agency would bear the burden of proving that the drug was misbranded, and because the manufacturer has superior information about a drug's performance after the drug's approval, the agency might be at an informational disadvantage. The agency has brought successful misbranding actions for both injunctions and restitution against companies selling unapproved drugs or approved drugs for unapproved uses. *See, e.g., United States v. Lane Labs-USA, Inc.*, 427 F.3d 219 (3d Cir. 2005) (upholding restitution and injunction order against company selling shark cartilage as cancer treatment); FDA Consumer, *Drug Maker to Pay \$430 Million in Fines, Civil Damages* (July/Aug. 2004) (reporting that Warner-Lambert had agreed to plead guilty and to pay \$430 million to resolve criminal and civil charges stemming from its promotion of unapproved uses of Neurotin) available at http://www.fda.gov/fdac/features/2004/404_wl.html. But as best as we can tell, the FDA has rarely if ever brought a misbranding action against the manufacturer of an approved drug being promoted only for approved uses.

⁶³ 21 U.S.C. § 332(b) (providing jury trial right in injunction actions brought by FDA); *see also* 21 U.S.C. §§ 333, 334(b).

⁶⁴ The FDA's inability to force a labeling change to Vioxx is only the most recent, and perhaps most widely publicized, example of this problem. Dr. Sandra Kweder, Deputy Director of the FDA's Office of New Drugs, said in testimony in a Senate Hearing that safety concerns over Vioxx prompted the FDA to convene an advisory committee meeting in 2001 to examine whether the drug raised the risk of heart attacks and strokes. But despite the panel's recommendation that Vioxx's label be changed to reflect this risk, it took more than a year of negotiations between the FDA and Merck before the company changed Vioxx's label. "They

negotiations, no change was made to Vioxx's label, and in the end, the FDA settled for a weaker warning than it had proposed. As noted, the FDA does not have statutory authority to compel manufacturers to make labeling changes, but must instead rely on its power of persuasion, backed up by the FDA's authority to seek withdrawal of the drug's NDA or to file a misbranding action. The FDA generally gets its way, but the negotiations with manufacturers are often quite lengthy and frequently result in compromise decisions, as was the case with Vioxx.⁶⁵ Removing the possibility of failure-to-warn litigation, as the FDA seeks to do, would further weaken the incentives a drug company has to comply with an FDA-requested labeling change.⁶⁶

rejected many of our proposals," Dr. Kweder told the Senate. "We don't have the authority to tell a company, 'This is how your label has to look.'" Instead, she said, "[w]e have to negotiate with the company the specific language of how things should be worded, the placement, those kinds of things, after talking to them." *Hearings: Up to the Challenge?*, *supra* n ___, at 23. And the Vioxx negotiations show that the FDA does not always get its way. The FDA had pushed Merck for a strong warning on Vioxx, but settled for a much weaker warning that simply said that patients with a history of heart disease should use Vioxx with caution. *See* Gardiner Harris, *FDA Official Admits "Lapses" on Vioxx*, N.Y. Times, A15 (March 2, 2005); Jim Drinkard, *Label Quibble Helped Cause Vioxx Lapse*, USA Today, (March 1, 2005). This problem is not a new one. *See, e.g., Salmon v. Parke-Davis & Co.*, 520 F.2d 1359, 1362-63 (4th Cir. 1975) ("the F.D.A. suggested, and Parke, Davis opposed, language that would tell physicians that they 'must' take certain precautions and 'must not' incur needless risks.").

⁶⁵ *See id.* *See also* IOM REPORT, *supra* n ___, at 157; *see also* Gardiner Harris, *F.D.A. Issues Strict Warnings on Diabetes Drugs*, N.Y. TIMES, Jun. 7, 2007, at A1 (announcing that prominent warnings about the risks of heart attacks would be placed on two diabetes drugs and reporting that the new warnings came several years after risks were known).

⁶⁶ As the Vioxx example shows, when confronted with an emerging threat from an approved drug, a company has to make a difficult economic choice — add a warning to the drug's label, almost certainly at the cost of lower sales, or resist a labeling change, recognizing that the company may be subject to future failure-to-warn litigation. It is hard to imagine that Merck did not make that calculus as evidence of Vioxx's heart attack and stroke risk mounted. If the threat of litigation is taken off the table, companies will have even less incentive to make needed labeling changes.

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B. The FDA's Justifications for Preemption are Legally Flawed.

In defending its preemption position, the FDA cites a handful of examples in the Federal Register preamble to support its claim that recent lawsuits have “threatened the agency’s ability to regulate ... risk information for prescription drugs.”⁶⁷ But these examples do not support the agency’s interference claim. The chief case the FDA relies on, *Dowhal v. SmithKline Beecham*,⁶⁸ was *not* a product liability case. Instead, it was an action for injunctive relief brought to compel a drug company to comply with labeling requirements imposed under California’s Proposition 65. Relying on conflict preemption principles, the California Supreme Court held that state-required warnings presented an actual conflict with FDA-imposed labeling requirements, and thus state law had to yield. Two other cases the FDA cites also involved state law actions to compel changes to drug labeling; neither succeeded.⁶⁹ Only a few of the FDA’s illustrative cases are failure-to-warn actions, and the FDA offers no explanation of how these cases threatened the FDA’s authority to control the content of drug labeling.⁷⁰ None sought to compel a labeling

⁶⁷ FDA, Final Rule, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601)

⁶⁸ 88 P. 3d 1 (Cal. 2004) cited in *id.*

⁶⁹ *In re Paxil Litigation*, 2002 WL 1940708 (C.D. Cal. 2002), was a class action brought against GlaxoSmithKline by users of Paxil who sought to enjoin the company from advertising that “Paxil is not habit forming.” Although the court initially agreed to enter injunctive relief, it reversed that ruling two months later. 2002 WL 31375497 (C.D. Cal. 2002). *Bernhardt v. Pfizer, Inc.*, 2000 U.S. Dist. LEXIS 16963 (S.D.N.Y. 2000), was an action seeking an order requiring that a “Dear Doctor” letter to be sent to physicians. The court found that the plaintiffs lacked standing and that the injunctive relief sought was preempted by the FDCA.

⁷⁰ The brevity of the FDA’s description is not altogether surprising because even the FDA’s “best cases” do not provide unalloyed support for its position. The case that apparently

change; no case resulted in a labeling change; and the only relief sought by the plaintiffs in these cases was money damages for injuries caused by the drugs.

Nor does the FDA address how its pro-preemption argument can be reconciled with the fact that the FDCA and the agency's own regulations give manufacturers significant leeway to revise labeling to reflect up-to-date risk information about a "clinically significant hazard"

disturbed the FDA the most — *Motus v. Pfizer* — could well be the bellwether case for those arguing against preemption. *Motus* was a damage action brought by the widow of a man who committed suicide after taking the anti-depressant Zoloft. Although there were a number of reports linking anti-depressants in Zoloft's class of drugs ("selective serotonin reuptake inhibitors," or "SSRIs") with suicide, the FDA rejected efforts by consumer and patient groups to add a warning for this class of drugs reflecting that possibility. 127 F. Supp. 2d 1085,1089-91 (C.D. Cal. 2000). Although the district court initially rejected Pfizer's preemption defense, *id.*, it later granted Pfizer summary judgment based on the plaintiff's inability to prove causation, 196 F. Supp. 2d 984 (C.D. Cal. 2001). The Ninth Circuit affirmed. 2004 U.S. App. LEXIS 1944 (9th Cir. Cal., Feb. 9, 2004). There were many failure-to-warn cases against the drug companies that sold SSRIs. A few district courts agreed with the FDA's pro-preemption argument. *See, e.g., Dusek v. Pfizer, Inc.*, 2004 WL 2191804 (S.D. Tex. 2004), *Needleman v. Pfizer, Inc.*, 2004 WL 1773697 (N.D. Tex. 2004). Many did not. *See, e.g., Zikis v. Pfizer, Inc.*, 2005 WL 3019409 (N.D. Ill. 2005); *NcNellis v. Pfizer, Inc.*, 2005 WL 3752269 (D. N.J. 2005); *Witczak v. Pfizer, Inc.*, 377 F. Supp. 2d 726 (D. Minn. 2005); *Cartwright v. Pfizer, Inc.*, 369 F. Supp. 2d 876 (E.D. Tex. 2005). What is important about *Motus* and similar cases is that, although Pfizer lost on preemption, the FDA did *not* change the labeling for SSRIs directly as a response to the litigation, and no one could plausibly argue that it had an obligation to do so. On the other hand, cases like *Motus* provided the FDA with substantial information about the correlation between SSRIs and suicidal behavior. Ultimately, after reexamining its position, the FDA ordered that labels of SSRIs include prominent warnings about the risk of suicide. *See* Food and Drug Administration, FDA Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications (Oct. 15, 2004); Food and Drug Administration, FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications (June 30, 2005). The FDA recently proposed to add warnings for young adult patients. Food and Drug Administration, FDA News: FDA Proposes New Warnings about Suicidal Thinking, Behavior in Young Adults Who Take Antidepressant Medication (May 2, 2007) <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01624.html>.

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without first obtaining the FDA's permission.⁷¹ To be sure, the FDA's approval must be sought after-the-fact. But the FDA's pro-preemption argument rests on the proposition that it, and it alone, determines drug labeling. That just is not so. The process is a dynamic one in which the manufacturer also plays a critical role. The ability of manufacturers to make labeling changes first and then seek the FDA's approval undercuts the FDA's claim.

That the FDA had to struggle to find a handful of isolated (and ambiguous) cases to make out its interference claim also raises a red flag. There is a seventy-seven year history of federal regulation of drug safety, and yet all the evidence the FDA can muster in support is, at most, a few cases that it claims raise a specter of interference, even though there are hundreds of failure-to-warn cases brought each year. The FDA does not cite jury verdicts that actually disrupted the agency's functioning, let alone explain how the agency has been able to carry out its responsibilities in the face of this steady procession of failure-to-warn cases.⁷²

Nor does the FDA's account come to grips with the other side of the ledger, that is, the benefits that flow to the FDA from failure-to-warn cases. Failure-to-warn litigation has often preceded and clearly influenced FDA decisions to modify labeling, and, at times, to withdraw drugs from the market. Preemption of failure-to-warn cases would thus come at a high price — information provided by this litigation would be lost to the FDA. That is a serious trade-off

⁷¹ See *supra* at ____.

⁷² See Richard A. Merrill, *Compensation for Prescription Drug Injuries*, 59 VA. L. REV. 1, 87, 107-08 (1973) (arguing that consumers should not bear the risk of unsafe medications, that some form of no-fault system should be developed to compensate injured consumers, and never suggesting that companies might have a preemption defense based on FDA-approved labels or that such a liability regime would impair the FDA's ability to protect the public).

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which at least merits the FDA's consideration.⁷³ The FDA has benefitted considerably from the interplay between state damages litigation and federal regulatory efforts. We see no reason to disturb this system.⁷⁴

IV. *The FDA's Post-Approval Monitoring System Cannot, By Itself, Assure Drug Safety and Failure-to-Warn Litigation Provides an Important Backstop.*

In addition to our concerns about the FDA's legal position, we also have reservations about the FDA's preemption position because it depends on the proposition that the FDA is capable of policing the marketplace effectively on its own. Again, the FDA views the preemption question through the prism of the initial approval process, and spends little time addressing its ability to monitor drug safety *post*-approval. In its public statements, the FDA paints a confident self-portrait, describing itself as capable of single-handedly monitoring drug safety, of reacting swiftly and effectively to warning signs that a drug may pose unanticipated risk, and possessing the personnel, resources and statutory authority it needs to safeguard the public health.⁷⁵

⁷³ It is a trade-off that other commentators argue would short-change the FDA. *See generally* Nagardea, *supra* n. __, at 6 (expressing concern that preemption may do "too little in return" to benefit the FDA); *cf.* Wendy Wagner, *When All Else Fails: Regulating Risky Products Through Tort Litigation*, 96 Geo. L. J. 693, 711-13 (2007) (explaining the informational advantages of litigation).

⁷⁴ *See, e.g.*, Karen Lasser, *et al.*, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 J. Am. Med. Ass'n 2215, 2218 (2002); Kesselheim & Avorn *supra* n. __, at 310 (citing examples).

⁷⁵ *See Ensuring Drug Safety: Where Do We Go From Here? Hearings before the S. Comm. on Health, Education, Labor and Pensions*, 109th Cong., 4-6 (March 3, 2005) (testimony of Janet Woodcock, M.D., Acting Deputy Commissioner for Operations, FDA); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed.

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We question whether the FDA's resources and performance match its rhetoric. The case for preemption must be examined in light of a clear-eyed appraisal of the FDA's ability to assure the safety of the drugs being marketed in the United States. As we see it, the reality departs from the one described by the FDA. In our view, the FDA is hamstrung by resource limitations and gaps in the agency's statutory authority. The FDA benefits from failure-to-warn litigation that forces the disclosure of information that otherwise would be unavailable to the agency.

A. *The FDA Faces Resource Limitations.*

An agency can go only so far as far its resources can take it, and the FDA, like other federal regulatory agencies, faces serious resource constraints. The FDA now regulates products that amount to one-quarter of consumer spending in the United States.⁷⁶ But it has only 9,000 employees nationwide.⁷⁷ Not surprisingly, there are resource limitations that impair the agency's ability to detect adverse reactions and to take prompt and effective measures once previously unidentified risks surface. The Institute of Medicine reported in 2006 that the FDA "lacks the

Reg. 3922, 3934 (Jan. 24, 2006) (codified at 21 C.F.R. pts. 201, 314, 601); Brief for the United States as Amicus Curiae Supporting Appellee, *Horn v. Thoratec*, 376 F.3d 163 (3d Cir. 2004), 2004 WL 1143720 at *1-2.

⁷⁶ FDA News, *The Food and Drug Administration Celebrates 100 Years of Service to the Nation* (Jan. 4, 2006) available at: <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01292.html>.

⁷⁷ Food and Drug Administration, *An Overview of the FDA* (available at www.fda.gov/oc/opacom/fda101/sld015.html (last visited July 11, 2007)). In addition to drug safety, these employees also review applications to market new medical devices, monitor the safety of the medical devices on the market, inspect drug and device manufacturing facilities, inspect virtually all of the non-meat food products sold in this country (including a rising flood of imported foods), inspect food processing and storage facilities, regulate dietary supplements, oversee the safety of the blood supply and tissues for transplantation, regulate radiologic and biologic products, and veterinary medicines and cosmetics. *Id.*

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resources needed to accomplish its large and complex mission today, let alone to position itself for an increasingly challenging future.”⁷⁸ FDA doctors and scientists share this view; 70 percent believe that the FDA lacks sufficient resources to protect the public health, and two-thirds worry that the FDA is not adequately monitoring the safety of drugs once they are on the market.⁷⁹ Even the pharmaceutical industry has urged Congress to increase FDA appropriations to shore up its flagging drug safety resources.⁸⁰

Resource constraints are especially acute with the agency’s post-marketing surveillance efforts. According to the most recent statistics available, the FDA’s Office of New Drugs (OND), which reviews NDAs, employs over 1,000 physicians and scientists to review the approximately 100 new NDAs each year and to supervise post-marketing studies. In contrast, FDA’s Office of Drug Safety, the unit charged with monitoring adverse events associated with the 3,000 prescription drugs (and 11,000 drugs altogether) the agency has approved over the

⁷⁸ IOM REPORT, *supra* n. ___, at 193.

⁷⁹ UNION OF CONCERNED SCIENTISTS, VOICES OF SCIENTISTS AT FDA: PROTECTING PUBLIC HEALTH DEPENDS ON INDEPENDENT SCIENCE 2 (Union of Concerned Scientists, 2006); *see also* DEP’T OF HEALTH & HUMAN SERVS. OFFICE OF THE INSPECTOR GENERAL, FDA’S REVIEW PROCESS FOR NEW DRUG APPLICATIONS, 12, 19 (March 2003) *available at* <http://oig.hhs.gov/oei/reports/oei-01-01-00590.pdf> (finding that significant numbers of FDA’s own physicians and scientists reported pressure to recommend that drugs be approved even when they had reservations about safety or efficacy, and that two-thirds of the agency’s drug reviewers lacked confidence that the agency “adequately monitors the safety of prescription drugs once they are on the market.”).

⁸⁰ *See, e.g.*, Diedra Henderson, *Drug Makers Lobby U.S. to Hike FDA Funds*, BOSTON GLOBE, July 13, 2006, at E1.

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years, has around 100 professional employees.⁸¹ Part of the disparity is historic, but part of it stems from the fact that when Congress initially authorized “user fees” — fees companies pay for NDA reviews — it directed the FDA to use the fees to support the review of new drug applications, and nothing else.⁸² When Congress reauthorized the user fee statute in 2002, it eased the restrictions on the FDA’s use of the funds, but the resource disparity remains.⁸³

B. *Statutory Gaps Hamper FDA’s Post-Approval Data Gathering.*

But it is not just resource limitations that impair the agency’s ability to engage effectively in post-approval surveillance. The agency is also hamstrung by statutory gaps that limit the data demands it may make on drug companies after a new drug is approved. As noted above, pre-approval clinical testing cannot identify all of the possible adverse effects associated with new

⁸¹ *Hearings: Up to the Challenge?*, *supra* n. ___, at __ (Joint Statement of Sandra L. Kweder, M.D., Deputy Director, Office of New Drugs, and Janet Woodcock, M.D., Acting Deputy Commissioner for Operations, Food and Drug Administration, to the Committee on Health, Education, Labor and Pensions, U.S. Senate) (March 1 & 3, 2005) (reporting that for fiscal year 2005 the Office of Drug Safety had about 90 full time employees, but projecting for fiscal year 2006 an increase to about 110 full time employees) available at: <http://www.fda.gov/ola/2005/drugsafety0301.html> (table).

⁸² As originally enacted, the user fee legislation restricted the use of fees to the costs of “the process for the review of new drug applications.” 21 U.S.C. § 379h(g)(1)-(2) (2000). More recent user fee legislation has relaxed that requirement somewhat. 21 U.S.C. § 379g(6)(F) (Supp. 2004) (providing for the use of PDUFA funds “In the case of drugs approved after October 1, 2002, under human drug applications or supplements: collecting, developing, and reviewing safety information on the drugs including adverse event reports, during a period of time after approval of such applications or supplements, not to exceed three years.”) One result of user-fee funding is that the new drug approval process has remained fully funded. On the other hand, funding for other FDA programs has not kept pace. *See generally* Prescription Drug User Fee Act (PDUFA); Public Meeting, 65 Fed. Reg. 47,993, 47,994 (Aug. 4, 2000).

⁸³ *See* n. ___, *supra*.

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drugs.⁸⁴ Professor Richard Merrill once quipped that “[a]ll consumers of prescription drugs serve as guinea pigs for the pharmaceutical industry.”⁸⁵ So the question that the FDA has long faced is how to acquire information about risks systematically once a drug has been approved. Until recently, for most new drugs the FDA “could count on cautious practicing physicians to assure a gradual, measured roll-out” that would permit the agency time to assess actual marketing experience.⁸⁶

But those days are gone, mainly for two reasons. First, as a result of the 1992 user fee legislation, the FDA devotes enormous resources to expediting the new drug review process. With the infusion of \$400 million or more annually in user-fees, the FDA is now generally the first regulatory agency in the world to approve new drugs, and thus the agency cannot look to experiences elsewhere in evaluating an NDA.⁸⁷

⁸⁴ Congress has understood these limitations for decades. Shortly after the 1962 Kefauver-Harris Amendments went into effect, then FDA Commissioner George P. Larrick explained to a House panel that “even the most extensive” clinical trials will reveal only a fraction of the information that emerges once the drug is generally marketed. *See Drug Safety (Part One) Hearings before a Subcomm. of the H. Comm. On Gov’t Operations, 88th Cong., 152 (1964)*. This history is discussed in Steenburg, *supra* n. ___, at 297.

⁸⁵ Merrill, *supra* n. ___, at 20; *see generally* Steenburg, *supra* n. ___, 298 & nn.23-24.

⁸⁶ Steenburg, *supra* n. ___, at 299.

⁸⁷ *See* Steenberg, *supra* n. ___, at 324 (“In 1988, FDA was the first agency in the world to approve a given drug only four percent of the time. That figure rose to sixty-six percent in 1998.”). Faster drug reviews, however, may spawn safety problems as well. In 2002, the General Accounting Office, now the Government Accountability Office, (GAO) found that “a higher percentage of drugs has been withdrawn from the market for safety reasons since [user fee legislation] was enacted.” GENERAL ACCOUNTING OFFICE, FOOD AND DRUG ADMINISTRATION: EFFECT OF USER FEES ON DRUG APPROVAL TIMES, WITHDRAWALS, AND OTHER AGENCY ACTIVITIES 4 (GAO-02-958) (Sept. 2002) *available at* <http://www.gao.gov/new.items/d02958.pdf>. *See also Hearings: Where Do We Go?*, *supra* n. ___,

Second, and perhaps more daunting, drug companies often launch mass marketing campaigns for their drugs directed at consumers, not just doctors, as soon as they obtain FDA approval.⁸⁸ Drug companies spend over \$27 billion annually to promote their products, including \$11.4 billion on advertising. Nearly forty percent of the advertising expenditures — over \$4.2 billion annually — pay for direct-to-consumer (DTC) ads that are designed to encourage patients to ask their doctors to prescribe the advertised drug.⁸⁹ DTC advertising has proven to be highly successful in stimulating demand for drugs.⁹⁰ As a result of these developments, for many drugs

at 45 (statement of Bruce Psaty) (stating that “drug recalls following approval increased from 1.56 percent in 1993-1996 up to 5.35 percent for 1997-2001.”)

⁸⁸ Merck, for example, trumpeted the FDA’s approval of Vioxx with what it proclaimed to be its “biggest, fastest, and best launch ever.” *See, e.g.,* Robert Langreth, *FDA Approval of Vioxx Allows Merck to Compete with New Arthritis Drugs*, Wall S. J., May 24, 1999, at B3.

⁸⁹ A 2005 study found that \$4.2 billion was spent on DTC advertising annually, or 37% of total pharmaceutical advertising. Kaiser Family Foundation, *Prescription Drug Trends*, May 2007, http://www.kff.org/rxdrugs/upload/3057_06.pdf. To put these expenditures in context, the pharmaceutical industry spends as much money on advertising as the tobacco industry spends on all of its product promotion (including price reductions and samples). *Compare id., with* FEDERAL TRADE COMMISSION CIGARETTE REPORT FOR 2003, at 2 (2005), *available at* <http://www.ftc.gov/reports/cigarette05/050809cigrpt.pdf> (reporting that the tobacco industry spent a total of \$15.15 billion in 2003 to promote its products). To give one example, in 2000, Vioxx was the number one DTC-advertised drug – at \$160 million, larger than the campaigns that year for Pepsi and Budweiser – and retail sales of Vioxx quadrupled. NATIONAL INSTITUTE FOR HEALTH CARE MANAGEMENT, *PRESCRIPTION DRUGS AND MASS MEDIA ADVERTISING*, 2000, at 5 (2001) *available at* <http://www.nihcm.org/DTCbrief2001.pdf>.

⁹⁰ Several studies have shown that DTC advertising does have an impact on patients and doctors. An assessment by the National Institute for Health Care Management found that between 1999 and 2000 the number of prescriptions written for the 50 most advertised drugs rose 24.6%, as compared to a 4.3% increase in prescriptions for all other drugs, although this study did not take into account the fact that these drugs are also heavily promoted to doctors. *See n. __, supra; see also* GAO Prescription Drugs: FDA Oversight of Direct-to-Consumer Advertising has Limitations 16 (GAO-03-177) (Oct. 2002) (“surveys...consistently show that DTC advertisements have an impact on whether consumers request and receive a specific brand-name

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there is no longer a transitional period between pre- and post-approval. Drugs that have been tested in controlled clinical trials involving at most a few thousand patients are, within a few weeks after approval, being prescribed by thousands of doctors to perhaps hundreds of thousands of patients.⁹¹

Despite these new pressures on the agency, its ability to systematically gather and evaluate post-marketing information has not kept pace and is far from optimal. According to the IOM, “[t]he existing regulatory framework is structured around the premarketing testing process; few tools are available for addressing postmarketing safety issues, short of the blunt instruments available to respond to clear-cut adulteration and misbranding.”⁹²

The “blunt instruments” available to the FDA are two far-from-perfect tools. First, the FDA often requires companies to perform post-marketing studies (so-called Phase IV studies) to see how the drug performs when given to large numbers of patients over a period of a year or

prescription”). The FDA also has problems regulating the content of these ads, some of which the FDA has found misleading. *See id.* at 22-23 (“reviews of draft regulatory letters from FDA have taken so long that misleading advertisements may have completed their broadcast life cycle before FDA issued the letters.”); *see also* Barry Meier, *et al.*, *Medicine Fueled by Marketing Intensified Trouble for Pain Pills*, N.Y. TIMES, Dec. 19, 2004, at 1 (finding that COX-2 drugs are “perhaps the clearest instance yet of how the confluence of medicine and marketing can turn hope into hype” and stating that Vioxx and Celebrex are examples of “how difficult it is for the Food and Drug Administration to monitor the safety of drugs after they have been approved for the market.”).

⁹¹ More than 19 million prescriptions for Celebrex were written its first year on the market, largely due to a massive DTC ad campaign. *See* Diedra Henderson, *How Safe Is Celebrex?*, Boston Globe, D1 (Feb. 25, 2007). During the five years Vioxx was on the market, over 100 million prescriptions were written for drug for an estimated 20 million patients. *See In re Vioxx Prods. Liab. Litig.*, 2007 U.S. Dist. LEXIS 48367 (E.D. La. July 3, 2007).

⁹² IOM REPORT, *supra* n. ___, at 153.

more.⁹³ Indeed, recent studies show that the FDA requires Phase IV testing in nearly three-quarters of all new drug approvals.⁹⁴ But the FDA has been lax in its oversight of Phase IV studies. Fewer than one-quarter of the Phase IV studies required by the FDA have ever been completed and many have never been started.⁹⁵

In addition to requiring Phase IV studies, the FDA monitors post-approval performance by gathering reports of adverse reactions through its Adverse Event Reporting System (AERS)

⁹³ The FDA's authority to mandate Phase IV studies is clearly set forth in statute only where the drug received accelerated approval (typically drugs for life-threatening diseases), where preapproval human subject studies of drugs for protection against chemical, radiological or nuclear materials are barred by ethical issues, or where the use of an approved drug for children requires study. 21 U.S.C. § 356(b)(2) (2000) (for "fast-track" drugs); 21 U.S.C. § 355c (Supp. 2004) (for pediatric studies); 21 C.F.R. §§ 314.610(b)(1), 601.91(b)(1) (for drugs that protect against chemical, radiological and nuclear materials); *see generally* Steenburg, *supra* n. ___, at 343-44. In those cases in which the FDA wants a company to engage in a Phase IV study of a drug that does not fall into one of these categories, the agency generally imposes the Phase IV study as a condition of approval. The FDA claims that FDCA § 505(k), 21 U.S.C. § 355(k) (2000), which requires drug companies to "establish and maintain" records of "data relating to clinical experience and other data," and to report this information to the agency, empowers the agency to require Phase IV studies whenever it sees fit. That interpretation of section 505(k) has been questioned by drug company lawyers. *See* Steenburg, *supra* n. ___, at 343.

⁹⁴ Tufts Center for the Study of Drug Development, *FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals*, IMPACT REPORT, July/August 2004, at 2, available at <http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/SampleIssue2005.pdf>.

⁹⁵ GAO REPORT, *supra* n. ___, at 28 (citing *id.*). At least in some cases, there may be sound reasons for the FDA's failure to demand that companies initiate and complete Phase IV studies. For one thing, the FDA may be uncertain of its legal authority under section 505(k), and thus may be reluctant to force the issue. *See supra* note 80. For another, once a drug is approved and is accepted by physicians, it becomes more difficult for a manufacturer to find participants meeting necessary criteria who are willing to enroll in the study (thereby risking getting a placebo) and more difficult to secure institutional review board approval for a double-blind study with a placebo group. *See* Steenburg, *supra* n. ___, at 372-73. Drug companies may also be reluctant to conduct comparative efficacy studies for fear that their products will not measure up to other drugs on the market. IOM REPORT, *supra* n. ___, 115-16.

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and its “MedWatch” program. Under the AERS, companies have a duty to report adverse reactions to the FDA, and to report serious or life-threatening adverse reactions quickly.⁹⁶

MedWatch extends the reporting program, on a voluntary basis, to health professionals and consumers.⁹⁷ Even with these programs in place, most adverse reactions go unreported to the FDA.⁹⁸ As a result, many serious adverse reactions escape the FDA’s attention.⁹⁹ Moreover, adverse reactions reports are of limited utility from an epidemiological standpoint because the FDA does not know how many people are using the drug or have information about their conditions and therefore may have difficulty determining the incidence of an adverse reaction.¹⁰⁰

Finally, even when the FDA identifies an unanticipated risk, the agency’s statutory authority gives it only limited options to remedy or ameliorate the problem. As noted above, the

⁹⁶ 21 C.F.R. § 310.305 (2006).

⁹⁷ The MedWatch program was inaugurated by the FDA in 1993 to enable the FDA to obtain adverse reaction reports directly from physicians and other health care providers, thereby skipping the intermediate step of having such reports go first to the drug companies. See David A. Kessler, *Introducing MedWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 J. Am. Med. Ass’n 2765 (1993). The MedWatch program is described in depth on the FDA’s website. Food and Drug Administration MedWatch, <http://www.fda.gov/medwatch/index.html> (last visited June 15, 2007).

⁹⁸ *Reauthorization of the Prescription Drug User Fee Act: Hearing Before the Sucomm. on Health of the H. Comm. on Energy and Commerce*, 107th Cong. 49 (2002) (statement of Rep. Henry A. Waxman).

⁹⁹ See Steenburg, *supra* n. ___, at 298. Steenburg also points out that such systems require reporting but do not require manufacturers to “develop their own data-gathering efforts or otherwise track clinical experiences in an organized manner.” *Id.*

¹⁰⁰ This is the so-called “denominator” problem, which is addressed in FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 11 (2005). See also GAO DRUG SAFETY, *supra* n. ___, at 24; IOM REPORT, *supra* n. ___, at 53-54.

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agency has no statutory right to direct a company to add warnings to the label of an approved drug. The statutory options available to the FDA — initiate a proceeding to withdraw the drug’s NDA or file a misbranding action against the drug company¹⁰¹ — are so Draconian that they are rarely employed by the FDA.¹⁰² The FDA’s threat to take action does give the agency bargaining leverage to persuade companies to add warnings the companies would otherwise omit or would not voluntarily place in a prominent, “black box” warning.¹⁰³ But, as both the Institute of Medicine and the Government Accountability Office point out, because the agency cannot simply require labeling changes, negotiations between the FDA and drug companies over labeling issues are often drawn out, often result in compromises, and, as a result, often have adverse effects on safety.¹⁰⁴

C. Litigation Uncovers Information Within the Control of Drug Companies That Is Otherwise Unavailable to the FDA.

Failure-to-warn litigation exposes the shortcomings in the FDA’s statutory authority to

¹⁰¹ 21 U.S.C. §§ 331(a), 355(e). A drug is “misbranded” if its labeling is false or misleading, does not provide adequate directions for use, or warnings against any use dangerous to health. *Id.* at §§ 331(a), (b) & (k); and *id.* at §§ 352(a), (f), and (g).

¹⁰² Indeed, all of the ten drugs withdrawn from the market between 2000 and 2006 were withdrawn voluntarily by the drug’s sponsor. GAO DRUG SAFETY, *supra* n. ___, at 10.

¹⁰³ “Black box” warnings signal a high degree of risk and are taken seriously by physicians and patients. 21 C.F.R. § 201.57(e); *see generally* Judith E. Beach, *et al.*, *Black Box Warnings in Prescription Drug Labeling: Results of a Survey of 206 Drugs*, 53 Food & Drug L.J. 403 (1998). As discussed above, Merck and the FDA did battle for more than a year over whether the heart attacks and stroke risks warranted a black box warning for Vioxx. The FDA finally relented, and agreed to a warning that simply said that patients with a history of heart disease should use Vioxx with caution. *See* Gardiner Harris, *FDA Official Admits “Lapses” on Vioxx*, N.Y. Times, A1 (Mar. 2, 2005).

¹⁰⁴ *See id.* at 10; IOM REPORT, *supra* n. ___, at 157.

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gather information.¹⁰⁵ Prior to a drug's approval, drug companies are required under the new drug application provisions of the FDCA to provide the FDA with all data — positive and negative — relating to the drug's safety and effectiveness, chemical formulation, proposed manufacturing, and patent protection.¹⁰⁶ But companies are not under an obligation to provide the agency with records of internal discussions or evaluations by company physicians and scientists. Post-approval, the FDA's information-gathering power is more limited. Companies have an ongoing obligation to provide to the FDA records "relating to clinical experience"¹⁰⁷ and adverse reactions,¹⁰⁸ and have a duty to permit the FDA to review business records during the course of a factory inspection.¹⁰⁹ But companies have no obligation to provide the FDA with the company's evaluations of the drug's performance in the market, let alone the company's assessment (memos, E-mails, and so forth) of the drug's safety profile. So while the FDA has substantial information-gathering power, its authority is by no means comprehensive.

The information-gathering tools lawyers have in litigation are, by any measure, more extensive than the FDA's. Indeed, the FDCA does not give the FDA the most important tool

¹⁰⁵ See generally Kesselheim & Avorn *supra* n. ___, and authorities cited therein.

¹⁰⁶ Section 505(b)(1)(A)-(F) of the Act, 21 U.S.C. § 355(b)(1)(A)-(F). An NDA must contain, among other things, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use."

¹⁰⁷ See FDCA § 505(k), 21 U.S.C. § 355(k).

¹⁰⁸ See *supra* at ____.

¹⁰⁹ See FDCA § 704, 21 U.S.C. § 374.

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trial lawyers have — the right to subpoena relevant information from any source.¹¹⁰ A few examples drawn from the litigation over Vioxx and Celebrex make this point. For instance, litigation uncovered the fact that Pfizer, the maker of Celebrex, conducted an unpublished clinical study in 1999 to see if Celebrex could be used to treat Alzheimer's disease. That study showed a statistically significant increase in heart attacks. But Pfizer waited to submit the study to the FDA until 2001 — *after* the FDA convened an advisory committee meeting to consider whether drugs of Celebrex's class should carry warnings for heart attack and stroke. The advisory committee recommended a warning be added to the labeling for Vioxx, Celebrex's main competitor. But without the Pfizer study linking Celebrex to increased heart attacks and strokes, the committee did not make a similar recommendation for Celebrex.¹¹¹

¹¹⁰ Compare Fed. R. Civ. P. 26-27, 45, with 21 U.S.C. §§ 355(k), 374. Under the Federal Rules, any party to civil litigation in federal court may compel any person to provide testimony under oath or furnish records relevant, or reasonably calculated to lead to the discovery of any information relevant, to any issue. State discovery rules are generally equally permissive. As noted above, the FDA's information-gathering power is much more limited. The FDA's authority does not reach evaluations and other analyses performed by companies about the performance of their drugs, let alone to company E-mails and internal deliberations over possible safety hazards. It is an odd system that gives plaintiff's lawyers far more leeway to probe company records than the FDA, but that is the system that exists today. See David C. Vladeck, *Defending Courts: A Brief Rejoinder to Professors Fried and Rosenberg*, 31 Seton Hall L. Rev. 631 (2001) (explaining comparative advantage plaintiff's lawyers engaged in civil litigation have in information-gathering over agency officials). We do not suggest that the FDA, as a matter of routine, should be provided internal company documents. We do suggest that the agency ought to have the authority, when necessary, to examine any company record relating to scientific information that may be relevant to the FDA's regulatory responsibilities, even where that information does not appear in reports required to be filed with the agency.

¹¹¹ See Alex Berenson & Gardiner Harris, *Pfizer Says 1999 Trials Revealed Risks With Celebrex*, N.Y. TIMES, Feb. 1, 2005, at C1. An equally telling example is reported regarding the antipsychotic medication olanzapine. Lawsuits filed after the drug's approval alleged that the

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Litigation also brought to light the fact that Merck was acutely concerned about the heart attack risk associated with Vioxx before the FDA understood the risk, and before Merck alerted the FDA to the risk. During the Vioxx cases, the plaintiffs' lawyers uncovered internal company memos and E-mails that were not provided to the FDA. One memo warned that a study of Vioxx, conducted to show that it decreased the risk of gastrointestinal bleeding, should be limited to patients also taking aspirin; otherwise there would be a "substantial chance that significantly higher rates" of cardiovascular disease would show up in the Vioxx group. An internal E-mail similarly warned that if Vioxx patients did not receive aspirin, "you will get more thrombotic events and kill [the] drug." In response, a senior company doctor agreed that "the possibility of increased CV [cardiovascular] events is of great concern," and she recommended that potential subjects with high risk of cardiovascular problems be kept out of the study so cardiovascular problems "would not be evident."¹¹² Evidence uncovered in litigation also revealed the fact that Merck scientists in 2000 were considering combining Vioxx with other

manufacturer, Eli Lilly, recognized that the drug was linked to weight gain and diabetes, but did not warn patients about the risks. In September 2003, after the litigation was filed, the FDA required Lilly to change the drug's label to warn about the diabetes-related adverse effects. During litigation, documents were uncovered that Lilly had long downplayed the research showing the links to weight gain and high blood sugar, informing sales-staff "Don't introduce the issue!!!" See Kesselheim & Avorn *supra* n. ___, at 309. For a detailed treatment of the Celebrex incident, see McGarity, *supra* n. ___, at 13.

¹¹² Anna W. Mathews & Barbara Martinez, *Warning Signs: E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage*, WALL ST. J., Nov. 1, 2004, at A1; see also McGarity, *supra*, n. ___, at 17.

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agents to reduce the risk of heart attacks and strokes.¹¹³

These recent examples echo prior FDA experience. Litigation brought to light the risks associated with the sleeping medication Halcion, the arthritis medication Zomax, ultra-absorbent tampons, and the weight loss pill ephedra, leading the FDA to take Halcion, Zomax, and ephedra off the market, and to more rigorously regulate tampons.¹¹⁴ Litigation also revealed evidence that manufacturers of a certain class of anti-depression medication — selective serotonin reuptake inhibitors (SSRIs) — withheld adverse event data regarding children. The issue was pushed into the spotlight in June 2004 when New York State Attorney General Eliot Spitzer brought a civil action against GlaxoSmithKline, alleging that the company had fraudulently withheld clinical studies showing that its SSRI drug, Paxil, increased the risk of suicide in children and young adults but did not effectively treat their depression. The complaint further alleged that the company's internal memos urged company officials to “manage the dissemination of data in order to minimize any potential negative commercial impact” while, at the same time, the company told its sales representatives to tell doctors that “Paxil demonstrates remarkable efficacy and safety in the treatment of adolescent depression.”¹¹⁵ Three months later, GlaxoSmithKline

¹¹³ *File Shows Merck Sought to Change Vioxx*, L.A. Times, June 23, 2005, at C3. See also Heather Won Tesoriero, *Attorneys Question Disclosure by Merck of Vioxx-Study Deaths*, Wall St. J., Sept. 28, 2005, at D4 (reporting that litigation uncovered Merck-sponsored studies finding a high death rate among Alzheimer's patients taking Vioxx as compared to placebo group).

¹¹⁴ Wagner, *supra* n. ___, at 707 n.73, and 711 & nn.79-82 (and authorities cited therein).

¹¹⁵ See, e.g., Gardiner Harris, *Spitzer Sues a Drug Maker, Saying It Hid Negative Data*, N.Y. Times (June 3, 2004), A1; see also Press Release, Office of the New York State Attorney General, *Settlement Sets New Standard for Release of Drug Information* (Aug. 26, 2004)

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settled the case by, among other things, agreeing to make its data public. Shortly thereafter, the FDA required warnings on SSRIs to highlight the association between use of SSRIs and an increased suicide risk in children and adolescents.¹¹⁶

Litigation helped force silicone gel breast implant makers to conduct long-overdue safety studies of their products. In 1976, Congress enacted the Medical Device Amendments to the FDCA.¹¹⁷ Part of that law required manufacturers of medical devices on the market in 1976 to submit health and safety data to the FDA showing that the device was safe for its intended use.¹¹⁸ In May 1990, the FDA called for the makers of silicone gel breast implants to provide safety information for their products. It was not produced. After giving the implant manufacturers several extensions, the FDA ultimately withdrew the implants from the market. The agency took this drastic step, not because there was evidence proving the implants to be unsafe (although there was evidence raising safety concerns),¹¹⁹ but because the industry failed to submit evidence

available at http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html (last visited July 13, 2007).

¹¹⁶ See *supra* n. ___. See also Shankar Vedantam, *Depression Drugs to Carry A Warning; FDA Orders Notice of Risks to Youths*, Wash. Post, Oct. 16, 2004, at A1.

¹¹⁷ 21 U.S.C. §§ 351-360m.

¹¹⁸ 21 U.S.C. § 301.

¹¹⁹ By the early 1990s, there had already been a number of lawsuits against silicone gel breast implant manufacturers, some of which ended in sealed settlements, but some of which ended in judgments against the manufacturers. See Heidi Li Feldman, *Science and Uncertainty in Mass Exposure Litigation*, 74 Tex. L. Rev. 1, 19-21 (1995). Some scientists reported that silicone breast implants could cause a serious autoimmune disorder. See, e.g., *Researcher Says Breast Implants May Be Linked To Autoimmune Disease*, Cancer Weekly, Dec. 21, 1992, at 16. Others reported a high incidence of rupture, running as high as thirty percent at five years, fifty percent at ten years, and seventy percent at seventeen years. J.S. Marotta et al., *Silicone Gel*

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showing that the implants did not pose an unreasonable risk when used as intended.¹²⁰ Whatever one might think about the breast implant product liability litigation,¹²¹ there is no doubt that the litigation “was uniquely successful in divulging important, asymmetric information about the risks of implants held by implant manufacturers,” including information that one major implant manufacturer not only knew that its implants were leaking, but suppressed internal research on the few animal studies that had been conducted to assess the risks associated with the leakage.¹²²

We could go on. But we do not believe that there is any serious dispute on this point. Statutory gaps in the FDA’s authority to gather information, especially post-approval, hamstringing its ability to ensure the safety of the drugs on the market. Failure-to-warn litigation brings to light information that would not otherwise be available to the FDA, to doctors, to other health care providers, and to consumers. At some point, Congress may close the gaps in the FDCA and give the agency comprehensive authority to obtain whatever records it deems necessary to do its

Breast Implant Failure and Frequency of Additional Surgeries: Analysis of 33 Studies Reporting Examination of More Than 8,000 Explants, J. Biomed. Materials Res. 48(3):354-64 (1999). In 1999, a study by the Institute of Medicine did not find a greater risk of chronic illness in women with silicone implants. IOM, *Safety of Silicone Breast Implants* (1999) available at: <http://www.nap.edu/books/0309065321/html>.

¹²⁰ David A. Kessler, *The Basis of the FDA’s Decision on Breast Implants*, 326 New Eng. J. Med. 1713, 1715 (1992). Even Marcia Angell, a critic of the breast implant litigation, acknowledges that these legal interventions led to long delayed scientific research on implants. Marcia Angell, *Shattuck Lecture — Evaluating the Health Risks of Breast Implants: The Interplay of Medical Science, the Law, and Public Opinion*, 334 New Eng. J. Med. 1513, 1515 (1996).

¹²¹ See, e.g., Rochelle Cooper Dreyfuss, *Galileo’s Tribute: Using Medical Evidence in Court*, 95 Mich. L. Rev. 2055, 2070 (1997) (discussing competing views); Feldman, *supra* n. ___, at 19-21.

¹²² Wagner, *supra* n. ___, at 715 & nn.95-97 (and authorities cited therein).

work. But that day has not come. And closing that gap would not guarantee that emerging safety information is made available to physicians and patients, who need it just as much as the FDA.¹²³

V. *Conclusion*

The point of this essay is not to denigrate the job the FDA does in protecting consumers. The talented and dedicated men and women who work at the FDA do an admirable job with the tools they have been given. But those tools are imperfect, and the FDA cannot, at least at this point, effectively safeguard our nation's drug supply on its own. In an ideal world, the FDA would have immediate access to data enabling it to pinpoint problems as they emerge, the personnel and other resources needed to deal effectively and swiftly with emerging hazards, and the insulation from political and other forces that often seek to apply pressure to influence agency decision-making. In the meantime, however, we believe it would be a mistake to broadly preempt state-law failure-to-warn cases, which impose a complementary discipline on the marketplace, prompt disclosure of safety information that is not otherwise available to the FDA

¹²³ As of this writing, Congress is considering drug safety legislation that would strengthen the FDA's ability to force drug companies to accept labeling changes the FDA deems necessary, increase the agency's information-gathering authority, and clarify the obligation of drug companies to report data to the FDA. *See Food and Drug Administration Revitalization Act*, S.1082, 110th Cong. (2007) (as passed by the Senate on May 9, 2007); *Enhancing Drug Safety and Innovation Act of 2007*, H.R. 2900, 110th Cong. (2007); *see also* Congressional Research Service Report for Congress, *FDA Legislation in the 110th Congress: A Guide to S. 1082 and H.R. 2900* (July 18, 2007).. These are important measures, but our views about preemption would not change even if they are adopted. Enhancing the FDA's statutory authority does not solve the agency's resource problems. Nor would it ensure that physicians and patients have timely access to up-to-date safety information for approved drugs. And this essay has steered clear of the corrective justice rationale underlying state-law damage claims — a rationale we believe independently justifies the preservation of state-law claims by injured consumers, but has been addressed in-depth by other commentators. *See n. __ supra.*

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and the public, and provide redress for consumers injured through no fault of their own.