

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

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## INTRODUCTION

### A. EVOLUTION OF THE FDA'S NEW PREEMPTION POLICY

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.<sup>1</sup> Nothing in the statutes the FDA administers suggests that they oust 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 preempted by federal law.<sup>2</sup> 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, thus weakening the argument for preemption.<sup>3</sup> 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 such litigation. Courts adjudicated those cases under the ordinary rules that govern state damages actions, and the

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1. 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/fulltext.html> (last visited Aug. 22, 2007) (citing A HISTORICAL GUIDE TO THE U.S. GOVERNMENT 248–54 (George Thomas Kurian et al. eds., 1998)). But the federal government's systematic regulation of pharmaceuticals began with the Federal Food and Drugs Act of 1906, when the agency was known as the Bureau of Chemistry. *Id.* 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.*

2. This Essay 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. 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.

3. See 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" (alteration in original)); cf. *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 166–67 (1989) ("The case for federal pre-emption is particularly weak where Congress has indicated its awareness of the operation of state law in a field of federal interest, and has nonetheless decided to stand by both concepts and to tolerate whatever tension there is between them.").

question of preemption rarely, if ever, arose.<sup>4</sup> The FDA made no effort to intercede in those cases. Indeed, the agency generally resisted efforts by parties to force it to take sides in private litigation.<sup>5</sup>

The agency's practice of non-participation in litigation was in keeping with the FDA's view that its regulatory efforts could comfortably coexist with state-law damage 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.<sup>6</sup> 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 defective" drugs.<sup>7</sup>

The past few years have been marked by 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 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

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4. Compliance with regulatory standards is the common defense raised in pharmaceutical product liability litigation. See generally Robert L. Rabin, Keynote Paper: *Reassessing Regulatory Compliance*, 88 GEO. L.J. 2049 (2000) (discussing the origin of regulatory compliance defense and its impact on tort law); Michael D. Green & William B. Schultz, *Tort Law Deference to FDA Regulation of Medical Devices*, 88 GEO L.J. 2119, 2122–23 (2000) (agreeing with Professor Rabin's analysis of regulatory compliance defense). 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). See David C. Vladeck, *Preemption and Regulatory Failure*, 33 PEPP. L. REV. 95, 106 (2005) ("Prior to *Cipollone*, preemption defenses were a rarity; post-*Cipollone*, they were routine."). In *Cipollone*, 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. *Cipollone*, 505 U.S. 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 leave injured parties without any remedy." Vladeck, *supra* at 105–06, 112.

5. See 21 C.F.R. § 20.1 (2006); *In re Kessler*, 100 F.3d 1015, 1016 (D.C. Cir. 1996).

6. See Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) (to be 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 concerns and stating that the "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"); Labeling and Prescription Drug Advertising; Content and Format for Labeling for Human Prescription Drugs, 44 Fed. Reg. 37,434, 37,437 (June 26, 1979) (to be 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 . . .").

7. See Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 FOOD & DRUG L.J. 7, 9 (1997); see also sources cited *supra* note 6.

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 amicus 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.<sup>8</sup>

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.<sup>9</sup> Others have plowed that field, and have done it well.<sup>10</sup>

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, understates the ability of drug manufacturers 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

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8. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3933–36 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601).

9. We address the FDA's main argument supporting preemption below. See *infra* at note 10. 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 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*, 546 U.S. 243, 255 (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 Univ. Hosp.*, 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* (forthcoming 2008) (manuscript at ch. 3, on file with authors).

10. See MCGARITY, *supra* note 9. See generally Richard A. Nagareda, *FDA Preemption: When Tort Law Meets the Administrative State*, 1 J. TORT L. art. 4 (2006), available at <http://bepress.com/jtl/vol1/iss1/art4> (analyzing whether FDA regulations preempt state tort law actions); Allison M. Zieve & Brian Wolfman, *The FDA's Argument for Eradicating State Tort Law: Why It Is Wrong and Warrants No Deference*, 21 TOXICS L. REP. 516 (2006) (arguing that “[t]he FDA's preemption position is bad law and bad policy”); 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), available at <http://law.bepress.com/expresso/eps/1591> (describing battle over whether “federal prescription drug labeling regulations impliedly preempt state common law product liability actions”). 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. art. 5 (2006), available at <http://www.bepress.com/cgi/viewcontent.cgi?article=1043&content=jtl> (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 Vladeck, *supra* note 4 at 103–04, 118, 128–29 (arguing that the MDA preemption provision is addressed only to conflicting state positive law, not state tort or damages claims).

emerge and may do so without securing the FDA's prior approval.

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 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.<sup>11</sup> 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, such as the agency's ineffectual response to Vioxx, 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.<sup>12</sup>

Our differences with the FDA 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 the FDA when it approves a drug label.<sup>13</sup> 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.<sup>14</sup> 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

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11. CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. DEP'T. OF HEALTH & HUMAN SERVS. 2005 REPORT TO THE NATION: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 12, available at <http://www.fda.gov/cder/reports/rtn/2005/rtn2005.pdf> (stating that FDA approved seventy-eight new drugs and two new biologic products in 2005); Michelle Meadows, *Promoting Safe and Effective Drugs for 100 Years*, FDA CONSUMER MAG., Jan.–Feb. 2006, available at [http://www.fda.gov/fdac/features/2006/106\\_cder.html](http://www.fda.gov/fdac/features/2006/106_cder.html); Davis, *supra* note 10, at n.76 and accompanying text.

12. FDA SCIENCE BOARD REPORT OF THE SUBCOMMITTEE ON SCIENCE AND TECHNOLOGY, FDA SCIENCE AND MISSION AT RISK (2007) (extensive report of blue ribbon panel commissioned by the FDA that concludes that the FDA "is in a precarious position: The Agency suffers from scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities).

13. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3934–36.

14. Of course, this assumes that the drug's sponsor has complied with the requirements governing new drug applications. That is not always the case. See *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 345 (2001) (describing application requirements).

determinative of the preemption question. The relevant timeframe is *post*-approval, and the question, in our opinion, is what did the FDA and the drug company know about a drug's risks at the time the patient-plaintiff sustained the injury. 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 a relatively small population of patients.<sup>15</sup> Once the drug enters the marketplace, risks that are relatively rare, that manifest themselves only after an extended period of time, or that affect vulnerable subpopulations, begin to emerge.<sup>16</sup> These are often not risks foreseen by the drug's manufacturer or the FDA and, for that reason, are not addressed on the label. And at the time the FDA adopted its pro-preemption position, the agency did not have the authority to compel labeling changes, but instead had to negotiate changes with the drug's sponsor.<sup>17</sup> 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.<sup>18</sup>

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 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

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15. See INST. OF MED. OF THE NAT'L ACADS., *THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC* 36 (Alina Baciu, Kathleen Stratton & Shelia P. Burke eds., 2006) [hereinafter IOM REPORT] (estimating that drugs are generally tested on between 600 and 3,000 patients).

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

17. See IOM Report, *supra* note 14, at 157; U.S. GOV'T ACCOUNTABILITY OFFICE, *DRUG SAFETY: IMPROVEMENT NEEDED IN FDA'S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS* 10, available at [www.gao.gov/cgi-bin/getrpt?GAO-06-402](http://www.gao.gov/cgi-bin/getrpt?GAO-06-402) [hereinafter GAO DRUG SAFETY]. As discussed below, recent legislation has given the FDA authority to compel labeling changes, but the FDA may exercise that authority only after it has first sought to negotiate changes with the company.

18. See Nagareda, *supra* note 10, at 5–6 & n.16 (referring to this as “a process of ‘information updating’ over time”); Rabin, *supra* note 4, at 2049, 2068–71 (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.”); Wendy Wagner, *When All Else Fails: Regulating Risky Products Through Tort Litigation*, 95 GEO. L.J. 693, 711 (2007). 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* Section IV.B.

ability to keep unsafe drugs off the market and to respond effectively to unforeseen hazards with newly approved drugs.<sup>19</sup> Even the FDA has acknowledged its own limitations. In the aftermath of the agency's ineffective response to the reports of increased adverse cardiac events among Vioxx users, the FDA in 2005 established the Drug Safety Oversight Board (DSOB) to better monitor drugs on the market.<sup>20</sup> But the DSOB was not given the resources to do its job effectively.<sup>21</sup> 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.

#### B. THE IMPACT OF THE FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT OF 2007

Congress recently enacted legislation to respond to the shortcomings in the FDA's performance. On September 27, 2007, President George W. Bush signed into law the Food and Drug Administration Amendments Act (FDA Amendments Act),<sup>22</sup> a sweeping overhaul of the both the FDCA and the Public Health Service Act. We applaud the new legislation. Among other things, the Act provides the agency with new resources to monitor the safety of drugs on the market,<sup>23</sup> it authorizes the agency to compel manufacturers to make labeling changes if negotiations with the manufacturers are unsuccessful,<sup>24</sup> it provides

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19. See GAO DRUG SAFETY, *supra* note 16, at 18; IOM REPORT, *supra* note 14, at 153–54.

20. See *FDA's Drug Approval Process: Up to the Challenge?: Hearing Before the S. Comm. on Health, Educ., Labor and Pensions*, 109th Cong. 10 (2005) [hereinafter *Hearings: Up to the Challenge?*] (joint statement of Sandra Kweder, Deputy Dir., Office of New Drugs, FDA and Janet Woodcock, Acting Deputy Comm'r for Operations, FDA); see also Davis, *supra* note 10, at n.78 and accompanying text; Press Release, U.S. Food & Drug Admin., FDA Fact Sheet: FDA Improvements in Drug Safety Monitoring (Feb. 15, 2005), <http://www.fda.gov/oc/factsheets/drugsafety.html> (describing the creation of the DSOB).

21. See GAO DRUG SAFETY, *supra* note 16, at 1, 5–6.

22. Food & Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007) [hereinafter FDAAA]. The FDA Amendments Act is a sprawling piece of legislation, covering more than 150 pages of single-spaced text. It includes eleven titles, the first two of which reauthorize drug and medical device user fee programs and update the FDA's authority to track medical devices. Titles III–V address pediatric medical devices and pharmaceuticals and provide incentives for their development. Title VI mandates the establishment of a public-private partnership to enhance medical product development and product safety. Title VII addresses conflicts-of-interest issues among members of FDA advisory committees. Title VIII expands existing clinical trial and clinical trial results data banks. Title IX gives the FDA enhanced authority to mandate postmarket studies and clinical trials as well as postmarketing labeling changes. Title IX also gives the FDA expanded authority to require manufacturers to develop and follow risk evaluation and mitigation strategies postmarketing. Title X addresses food safety issues. And Title XI includes several miscellaneous provisions that are aimed at antibiotics, tropical diseases, and genetic testing.

23. FDAAA, tit. I, sec. 103(b)(4), § 736(b), 121 Stat. 823, 828 (2007).

24. *Id.* tit. IX, sec. 901(a), § 505(o)(4), 121 Stat. at 924–26. The authority to compel labeling changes is, however, significantly circumscribed and cannot, as an ordinary matter, be used by the agency unilaterally or immediately. Section 505(o) requires the FDA to promptly notify the drug's manufacturer if the FDA becomes aware of new safety information the agency believes should be included in the drug's labeling. *Id.* § 505(o)(4)(A), 121 Stat. at 924. Following the notification, the manufacturer has thirty days to either (a) submit a supplement proposing changes in the labeling to reflect the new safety information, or (b) notify the FDA that the manufacturer does not believe that a labeling change is warranted. *Id.* § 505(o)(4)(B), 121 Stat. at 924–25. If the FDA disagrees with either

the agency greater power to require manufacturers to undertake safety studies after drugs have been approved,<sup>25</sup> and it promises to give the agency greater resources to monitor direct-to-consumer drug advertising.<sup>26</sup> These are all important steps.

But there are three important points about the FDA Amendments Act for the preemption debate that bear emphasis. First, at the time the FDA decided to reverse-field and advocate in favor of preemption, it had no inkling that Congress would boost its resources or bolster its statutory authority. Indeed, the infusion of resources that will come as a result of the enactment of the FDA Amendments Act suggests that Congress did not share the FDA's view that it is capable of adequately safeguarding the public health on its own.

Second, the FDA Amendments Act further undercuts the FDA's current position on preemption. Much to the pharmaceutical industry's disappointment, Congress did not add a preemption provision to the Act, which still has none.<sup>27</sup> Instead, Congress included a "Rule of Construction" in the Act that says the FDA's new authority over labeling "shall not be construed to effect the responsibility" of the manufacturer "to maintain its label in accordance with existing responsibilities, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations)."<sup>28</sup> The citations are to existing requirements that obligate drug manufacturers to provide up-to-date safety information to physicians and patients and authorize manufacturers to do so without first securing the FDA's approval. The codifica-

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the proposed labeling change, or the assertion that no change is needed, the FDA must then initiate discussions to reach agreement with the manufacturer. *Id.* § 505(o)(4)(C), 121 Stat. at 925. These discussions may not extend for more than thirty days, unless the FDA finds an extension justified. *Id.* § 505(o)(4)(D), 121 Stat. at 925. If the parties agree, the matter ends. But if an impasse is reached, then the FDA may, within fifteen days, issue an order requiring the manufacturer to make the changes the FDA deems appropriate. *Id.* § 505(o)(4)(E), 121 Stat. at 925. At that point, the manufacturer may, within five days, submit supplemental changes, or may appeal using dispute resolution procedures established by the agency. *Id.* § 505(o)(4)(F), 121 Stat. at 925. At the end of the appeals process, if the agency concludes that a supplement is required, one must be submitted within fifteen days. *Id.* § 505(o)(4)(G), 121 Stat. at 925. As this elaborate procedure makes clear, Congress wanted to ensure that the FDA has final say over drug labeling, but, at the same time, wanted to provide manufacturers with ample authority to make their case before the agency. The Act does give the FDA the power to "accelerate" this process, but not to by-pass it, based on a determination that "a labeling change is necessary to protect the public health." *Id.* § 505(o)(4)(H), 121 Stat. at 925.

25. *Id.* tit. IX, sec. 901(a), § 505(o)(3), 121 Stat. 823, 923–24 (2007).

26. *Id.* tit. I, sec. 104, § 736A, 121 Stat. 823, 832–40 (2007).

27. The pharmaceutical industry had sought such a provision and was disappointed that Congress did not add one. One law firm that represents pharmaceutical companies put it this way: "Contrary to the expectations of many, the FDA Amendments Act of 2007 (FDAAA), signed into law by the President in late September, does not contain any provision expressly preempting state law." DLA Piper, FDA Alert: Does the FDA Amendments Act of 2007 Preempt State Law? (Oct. 10, 2007), [http://www.dlapiper.com/state\\_preemption](http://www.dlapiper.com/state_preemption). Senator Allard made the same point on the Senate floor, expressing his disappointment in the Senate's acquiescence to the House language, contained in the Rule of Construction, which he claims will "open the floodgates" to litigation and is "a definite boon to trial lawyers." 153 CONG. REC. S11837 (daily ed. Sept. 20, 2007).

28. FDAAA, tit. IX, sec. 901(a), § 505(o)(4)(I), 121 Stat. 823, 925–26 (2007).

tion of this obligation undercuts the key pro-preemption argument the FDA and manufacturers make—namely, that the FDA alone decides the content of drug labels.

Third, although important, the FDA Amendments Act is not a panacea for what ails the FDA. While the Act is a needed tonic to get a severely under-resourced agency back on its feet, only time will tell whether increased resources will result in better performance by the agency. After all, the agency's mission has become ever more complex with the proliferation of new biological products and technological advances. Legislation cannot cure the fundamental problem the FDA faces in ensuring drug safety—namely, that pre-approval testing cannot reveal the safety problems that may emerge only after long-term, large-scale use. The FDA faces many challenges in implementing this dauntingly complex new law. The agency will have to attract and retain highly skilled professionals. The Act imposes myriad new affirmative obligations on the agency—including reports to Congress, rule-makings, the issuance of guidance documents—that will command (and perhaps consume) many of its new resources. And the agency will have to reorient its culture to take full advantage of the new enforcement tools given to it by Congress. For these reasons, nothing in the Act alters our position on preemption, to which we now turn.<sup>29</sup>

## I. BACKGROUND

Since the passage of the landmark 1938 Federal Food, Drug, and Cosmetic Act (FDCA), all drugs must be evaluated and approved by the FDA before they may be marketed in the United States. 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."<sup>30</sup>

To obtain the FDA's approval, a drug manufacturer must submit a "new drug

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29. The Act's principal Senate sponsor, Senator Ted Kennedy, made this point in introducing the legislation to his colleagues. After noting that the bill will increase the FDA's resources for post-marketing surveillance, he noted that the drug industry has annual revenues of over \$200 billion, one percent of which "exceeds the entire budget of the FDA." 153 CONG. REC. S11832 (daily ed. Sept. 20, 2007). Senator Kennedy went on to say:

Clearly, the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA, and no matter what we do, they will always have vastly greater resources to monitor the safety of their products than the FDA does. It is absurd to argue that the FDA, even with the enhanced resources and authorities provided by this legislation, commands the field when it comes to postmarket safety. The drug companies have the capacity to do a far more comprehensive job. If we are serious about quickly alerting the public to the health risks posed by drugs, the companies must be required to take the initiative in monitoring the safety of their products and immediately warning the public of newly discovered risks. Drug manufacturers cannot be allowed to ignore their responsibilities and wait for the FDA to act.

*Id.*

30. In 1962, Congress passed the Kefauver-Harris amendments to the FDCA. *See* Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, 781-82 (1962) (codified at 21 U.S.C. § 321(p)(1)-(2),

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 clinical trials performed on human subjects.<sup>31</sup> Drug companies are responsible for supervising and controlling (or contracting out) these studies.<sup>32</sup> Premarket human trials generally involve only a few thousand subjects, and study design necessitates a careful control of the conditions of the study.<sup>33</sup> These conditions are a far cry from those that face a drug once it is approved and widely prescribed by thousands of doctors.<sup>34</sup> New drugs designed to “address unmet medical needs” for “serious or life-threatening conditions” may receive accelerated or “fast track” consideration by the FDA.<sup>35</sup> These drugs are subject to shorter review periods and may be approved based on less safety and effectiveness information than other drugs.<sup>36</sup>

Because drug labeling provides doctors and other health care professionals with information needed to make informed prescription 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.<sup>37</sup>

## II. FDA DRUG APPROVAL

The manufacturer and the FDA ordinarily discuss the content of these

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§ 355(b)-(d) (2000)) (providing that the sponsor of the drug has to provide substantial evidence of effectiveness for the product’s intended use as precondition to approval).

31. 21 U.S.C. § 355 (2000 & Supp. IV 2004); see Davis, *supra* note 10, at n.77 and accompanying text; see also Food & Drug Admin. Office of New Drugs Reorganization, [http://www.fda.gov/cder/cderorg/ond\\_reorg.htm](http://www.fda.gov/cder/cderorg/ond_reorg.htm) (last visited Aug. 23, 2007) (describing the Office of New Drugs); Food & Drug Admin., Drug Approval Application Process, <http://www.fda.gov/cder/regulatory/applications/default.htm> (last visited Aug. 23, 2007) (describing the drug approval process).

32. See IOM REPORT, *supra* note 14, at 34; McGARITY, *supra* note 9 (manuscript at ch. 2, p.9) (“The prospective manufacturer of a drug or medical device, for example, must demonstrate to FDA that the product will perform its function safely and effectively. This ordinarily requires the applicant to supply appropriately conducted scientific studies demonstrating that the product meets the relevant statutory test, which often requires the agency to balance the product’s predicted benefits and risks.”).

33. 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).

34. *Id.*

35. 21 U.S.C. § 356(a)(1) (2000).

36. *Id.*; see GAO DRUG SAFETY, *supra* note 16, at 11; Struve, *supra* note 17, at 595; see also 21 C.F.R. § 314.500–520 (2006).

37. 21 U.S.C. § 355(d) (2005). 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 (2006). The FDA revised these regulations in 2006. See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3922 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601).

warnings in some detail during the approval process.<sup>38</sup> When the FDA approves a drug, it also approves the precise final version of the drug's label.<sup>39</sup>

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 "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."<sup>40</sup> 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 (for example, the elderly, ethnic minorities, and pregnant women).<sup>41</sup>

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 after a drug has been widely used.<sup>42</sup>

Moreover, the FDA's assessment of risks versus benefits is generally done population-wide, not sub-group by sub-group, because there are rarely enough clinical trial participants in a sub-group to permit that degree of refined analysis. 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

38. MCGARITY, *supra* note 9 (manuscript at ch. 2, p.9); *see Hearings: Up to the Challenge?*, *supra* note 19, at 79 (response to questions by Sen. Hatch by Sandra L. Kweder, Deputy Dir., Office of New Drugs, FDA).

39. 21 U.S.C. § 355(b)(1)(F) (2000).

40. 21 U.S.C. § 355(d) (2000).

41. *See* IOM REPORT, *supra* note 14, at 38; *see also* Louis Lasagna, *Discovering Adverse Drug Reactions*, 249 JAMA 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 one or two subjects out of ten thousand 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 [which are in 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.")

42. William B. Schultz, *How To Improve Drug Safety*, WASH. POST, Dec. 2, 2004, at 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.*, 501 F. Supp. 2d 776, 779 (E.D. La. 2007).

purposes.<sup>43</sup> 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.<sup>44</sup> 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.<sup>45</sup> The FDA Amendments Act seeks to improve the FDA's post-market risk identification process by giving the FDA more funds to manage its programs and to expand the sources of data the agency reviews.<sup>46</sup> But improvements are a long way off. The Act requires the agency to mine existing electronic databases relating to patient health to detect adverse events. But the Act recognizes that it will take considerable time for the FDA to design and make such a program operational, and given the recognized under-reporting of adverse events, it remains to be seen whether database surveillance will help the agency recognize emerging safety problems more quickly.<sup>47</sup>

Because unanticipated adverse effects often emerge with approved drugs, there are detailed procedures that regulate modifications to drug labeling. Generally, labeling changes proposed by the manufacturers require prior FDA approval.<sup>48</sup> There are exceptions, however, and these exceptions are especially

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43. The FDA does not warrant the safety of the drugs it approves, and it 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 Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies*, 279 JAMA 1200, 1202 (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).

44. See GAO DRUG SAFETY, *supra* note 16, at 18, 28; IOM REPORT, *supra* note 14, at 51.

45. *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) (“[T]he FDA estimates that it hears of less than 1 percent of serious adverse reactions.”); see also IOM REPORT, *supra* note 14, 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”).

46. See FDAAA, tit. I, sec. 102(5)(F), § 735, 121 Stat. 823, 826 (2007) (authorizing use of user fees to collect and review safety information on approved drugs and to develop improved adverse-event data-collection systems). Section 905 of the FDAAA, which amends FDCA section 505(k) by adding a new section 3, requires the FDA to establish an “active post-market risk identification and analysis” program. FDAAA, tit. IX, sec. 905(a), § 505(k)(3), 121 Stat. 823, 944–49 (2007). But the FDA has two years to develop a process by which it will obtain access to a variety of data sources, including data from the Medicare program and private insurers, so that by 2012 the agency will have access to data on 100 million patients. Ultimately, the Act requires the agency to have procedures in place for risk identification based on electronic health data. *Id.*

47. FDAAA, tit. IX, sec. 905(a), § 505(k), 121 Stat. 823, 944–49 (2007). Even more fundamental, the government databases that the FDA is supposed to use for drug safety information—especially the Medicare database—are by law not to be used for this purpose. Thus, until new legislation is enacted amending the Medicaid statute, the FDA will not have access to these databases. See 153 CONG. REC. S11839 (daily ed. Sept. 20, 2007) (colloquy between Senators Baucus and Kennedy).

48. 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”).

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."<sup>49</sup> 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 . . . .<sup>50</sup>

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.<sup>51</sup> 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 FDA's advance approval.<sup>52</sup> 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.<sup>53</sup> Nothing in the FDA Amendments Act alters these requirements; indeed, the Act explicitly ratifies them.<sup>54</sup>

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.<sup>55</sup> 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

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49. 21 C.F.R. § 201.57(c)(6)(i) (2006); *see also* § 201.80(e) (stating same in slightly different language).

50. 21 C.F.R. § 314.70(c)(6)(iii)(A)–(D) (2006).

51. 21 C.F.R. § 314.70(c) (2006).

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

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

54. FDAAA, tit. IX, sec. 901(a), § 505(o)(4)(I), 121 Stat. 823, 925–26 (2007).

55. 21 C.F.R. § 201.57(a); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601).

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 dissemination of risk information for prescription drugs" and are therefore preempted.<sup>56</sup> 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.<sup>57</sup> 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.<sup>58</sup>

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.<sup>59</sup> The agency also reviews the pro-preemption position it has recently taken in a 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.<sup>60</sup> 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."<sup>61</sup> As the FDA now sees it, many failure-to-warn claims are impliedly preempted, including those based on choices manufacturers make

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56. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3934.

57. *E.g.*, 21 C.F.R. § 808.1 (2006) (defining the scope of the preemption provision in the Medical Device Amendments of 1976).

58. 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, *see* 21 U.S.C. § 360k(a) (2000), there is no counterpart provision in the FDCA for drugs.

59. *See In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, No. M: 05-1699 CRB, 2006 WL 2374742, at \*8 (N.D. Cal. Aug. 16, 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"); Brief for Public Citizen as Amicus Curiae Supporting Cross-Appellee at \*12, *Motus v. Pfizer, Inc.*, 358 F.3d 659 (9th Cir. 2004) (Nos. 02-55372, 02-55498), 2003 WL 22716063; Davis, *supra* note 10, at 25 n.140 and accompanying text. Additionally, the proposal for the rule change stated that the new rules would not have a preemptive effect. *See* Prescription Drug Product Labeling; Medication Guide Requirements, 63 Fed. Reg. 66,378, 66,384 (Dec. 1, 1998) (to be codified at 21 C.F.R. pts. 201, 208, 314, 601, & 610) ("[T]he 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 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 at \*3, *Horn v. Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2004) (No. 02-4597), 2004 WL 1143720 ("We acknowledge that . . . this [preemption] position represents a change for the United States.").

60. *See supra* note 12 and accompanying text.

61. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3935 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601).

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.<sup>62</sup> 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.<sup>63</sup>

### 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.<sup>64</sup> 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.<sup>65</sup>

We agree that labeling decisions are often fraught with complexity and that

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62. *Id.* at 3935–36.

63. *Id.* at 3936. This concession appears to be dictated by the Supreme Court's decision in *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 496–97 (1996), which held that a tort claim premised on state-law duties “equal to, or substantially identical to,” duties imposed by federal law is 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.*, although the agency is still less than clear about what claims might be permitted to proceed under its theory. *See* Brief for Food & Drug Admin. as Amicus Curiae, *Perry v. Novartis Pharm., Inc.*, 456 F. Supp. 2d 678 (E.D. Pa. 2006) (No. 05-5350) (on file with author). In the *Perry* brief, 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.

64. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3934.

65. *Id.* at 3934–36.

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 FDA, such an effort would properly be struck down on conflict preemption grounds.<sup>66</sup>

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, failure-to-warn litigation 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. 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. The FDCA gives that authority to the FDA and no one else, a conclusion fortified by the FDA Amendments Act.<sup>67</sup> 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 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 to adequately 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. 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

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66. In fact, in just such a case, the Supreme Court of California 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 Consumer Healthcare*, 88 P.3d 1, 14–15 (Cal. 2004).

67. *See supra* note 23.

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 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.<sup>68</sup> As the Supreme Court has frequently observed, tort law often informs regulatory decisions,<sup>69</sup> and the FDA has often acted in response to information that has come to light in state damages litigation after a drug has been approved.<sup>70</sup>

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 damage claims, or even occupy the field of drug regulation.<sup>71</sup> 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 federal objectives.<sup>72</sup>

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

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68. The Supreme Court has noted that state damages actions "may aid in 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) (discussing benefit of state damages actions).

69. *See, e.g., id.*

70. *See, e.g.,* Aaron Kesselheim & Jerry Avorn, *The Role of Litigation in Defining Drug Risks*, 297 *JAMA* 308, 310 (2007) (citing examples); Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 *JAMA* 2215, 2215-18 & tbl.1 (2002).

71. Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934-35 n.8 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601) (arguing that "under existing preemption principles" the FDCA implies preemption).

72. *See, e.g.,* *United States v. Locke*, 529 U.S. 89, 109 (2000) ("It is fundamental in our federal structure that States have vast residual powers. Those powers, unless constrained or displaced by the existence of federal authority or by proper federal enactments, are often exercised in concurrence with those of the National Government."); *Geier v. Am. Honda Motor Co.*, 529 U.S. 861, 873-74 (2000) (discussing implied preemption).

labeling and pay a state damage judgment based on a determination that the labeling failed to adequately warn of a discrete risk.<sup>73</sup> 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.<sup>74</sup> 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 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.<sup>75</sup>

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 and accurate, and fairly addresses the possible risks of a drug without overstating those risks.<sup>76</sup> But an adverse ruling in a state failure-to-warn case,

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73. Conflict preemption requires something more coercive than paying a judgment. As an example of conflict preemption, Justice Breyer’s concurrence in *Lohr* said:

Imagine 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.

*Medtronic, Inc. v. Lohr*, 518 U.S. 470, 504 (1996) (Breyer, J., concurring). Similarly, in *Geier v. American Honda Motor Co.*, the Court found that a claim that a passenger vehicle that was not equipped with airbags was defectively designed was preempted because permitting it to go forward would conflict with NHTSA’s decision to provide for a gradual phase-in of air-bags. 529 U.S. at 867–71, 875.

74. 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.4, at 115–16.

75. Consider one example. As explained in detail below, see *infra* note 90, 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.

76. See Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3928 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601). Cf. Brief for the United States as Amicus Curiae Supporting Appellee at \*2–3, *Horn v. Thoratec*, 376 F.3d 163 (3d Cir. 2004) (No. 02-4597), 2004 WL 1143720 (in a case involving a medical device, the FDA stated that “[t]he 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.”).

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 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.<sup>77</sup>

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.<sup>78</sup> 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. Nothing in the FDA Amendments Act withdraws that authority. 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.<sup>79</sup> And, as best as we can tell, the FDA has never brought a misbranding claim against a company in those circumstances.<sup>80</sup> Ironically, if it did, the agency would be

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77. 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 (5th ed. 2007).

78. See Kesselheim & Avorn, *supra* note 69, 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 are then deprived of compensation for their injuries.

79. See *Feldman v. Lederle Labs.*, 592 A.2d 1176, 1193 (N.J. 1991) ("[F]or the FDA to have prevented a drug manufacturer from warning the public of a newly-discovered danger pending development of unequivocal factual evidence of adverse reaction in man 'would seem anomalous.'" (quoting *Feldman v. Lederle Labs.*, 479 A.2d 374, 390 (N.J. 1984))).

80. 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); U.S. Food & Drug Admin., *Drug Maker To Pay \$430 Million in Fines, Civil Damages*, FDA CONSUMER MAG., July–Aug. 2004, available at [http://www.fda.gov/fdac/features/2004/404\\_wl.html](http://www.fda.gov/fdac/features/2004/404_wl.html) (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). 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.

back to where it started, because the ultimate decision-maker in a misbranding action would be the jury and not the FDA.<sup>81</sup>

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 force Merck, the manufacturer of Vioxx, to add a warning of the risks of heart attack and stroke to Vioxx's label.<sup>82</sup> During the lengthy 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, at the time of the Vioxx controversy, the FDA did not have statutory authority to compel manufacturers to make labeling changes, but instead had to 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 got its way, but negotiations with manufacturers are often quite lengthy and frequently result in compromise decisions, as was the case with Vioxx.<sup>83</sup> 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.<sup>84</sup> This problem is not obviated by the FDA Amendments Act. Although the Act makes explicit that the FDA may compel a labeling change, it requires the agency to first negotiate with the

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81. 21 U.S.C. § 332(b) (2000) (providing jury trial right in injunction actions brought by FDA); *see also* 21 U.S.C. § 334(b) (2000).

82. 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. "[T]hey rejected many of our proposals," Dr. Kweder told the Senate. "[W]e 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* note 19, at 23. 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* Jim Drinkard, *Label Quibble Helped Cause Vioxx Lapse*, USA TODAY, Mar. 2, 2005; Gardiner Harris, *FDA Official Admits "Lapses" on Vioxx*, N.Y. TIMES, Mar. 2, 2005, at A15. This problem is not a new one. *See, e.g.*, *Salmon v. Parke, Davis & Co.*, 520 F.2d 1359, 1362-63 (4th Cir. 1975) ("[T]he 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.").

83. *See* Harris, *supra* note 81; *see also* IOM REPORT, *supra* note 14, at 157; Gardiner Harris, *F.D.A. Issues Strict Warnings on Diabetes Drugs*, N.Y. TIMES, June 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).

84. 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.

company over its proposed changes, and the process will likely take months.<sup>85</sup> While the FDA's new authority is designed to prevent recurrence of the agency's year-long fight with Merck over Vioxx's label, it will not result in immediate, or even swift, labeling changes.

#### 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."<sup>86</sup> But these examples do not support the agency's interference claim. The chief case the FDA relies on, *Dowhal v. SmithKline Beecham*,<sup>87</sup> 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.<sup>88</sup> 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.<sup>89</sup> Two other cases the FDA cites also involved state law actions to compel changes to drug labeling; neither succeeded.<sup>90</sup> 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.<sup>91</sup> None sought to compel a labeling change; no case resulted in a

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85. See *supra* note 23.

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

87. 88 P.3d 1 (Cal. 2004); see Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. at 3934 n.7 (citing *Dowhal*).

88. See *Dowhal*, 88 P.3d at 3.

89. See *id.* at 934–35.

90. *In re Paxil Litigation*, No. CV 01-07937 MRP, 2002 WL 1940708 (C.D. Cal. Aug. 16, 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. *In re Paxil Litig.*, No. CV01-07937 MRP, 2002 WL 31375497 (C.D. Cal. Oct. 18, 2002). *Bernhardt v. Pfizer, Inc.*, Nos. 00 civ. 4042 Lmm, 00 Civ. 4379 Lmm, 2000 WL 1738645 (S.D.N.Y. Nov. 22, 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.

91. 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 disturbed the FDA the most—*Motus v. Pfizer, Inc.*, 127 F.Supp. 2d 1085 (C.D. Cal 2000)—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. See *id.* at 1086–87. 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. See *id.* at 1089–91. Although the district court initially rejected Pfizer's preemption defense, *id.* at 1092–1101, it later granted Pfizer summary judgment based on the plaintiff's inability to prove causation, 196 F. Supp. 2d 984, 999 (C.D. Cal. 2001). The Ninth Circuit affirmed. 358 F.3d 659, 661 (9th Cir. 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., *Needleman v. Pfizer, Inc.*, No. Civ. A. 3:03-CV-3074-N, 2004 WL

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" without first obtaining the FDA's permission.<sup>92</sup> 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. This argument is not true. 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.<sup>93</sup>

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.<sup>94</sup>

Nor does the FDA's account come to grips with the other side of the ledger,

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1773697, at \*6 (N.D. Tex. Aug. 6, 2004); *Dusek v. Pfizer, Inc.*, No. Civ. A. H-02-3559, 2004 WL 2191804, at \*10 (S.D. Tex. Feb. 20, 2004). Many did not agree with the FDA's argument. *See, e.g.*, *McNellis v. Pfizer, Inc.*, No. civ. 05-1286 JBS, 2005 WL 3752269, at \*11 (D. N.J. Dec. 20, 2005); *Zikis v. Pfizer, Inc.*, No. 04 C 8104, 2005 WL 3019409, at \*4 (N.D. Ill. Nov. 8, 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* Press Release, U.S. Food and Drug Admin., FDA Public Health Advisory: Suicidality in Adults Being Treated with Antidepressant Medications (June 30, 2005), <http://www.fda.gov/cder/drug/advisory/SSRI200507.htm>; Press Release, U.S. Food and Drug Admin., FDA Public Health Advisory: Suicidality in Children and Adolescents Being Treated with Antidepressant Medications (Oct. 15, 2004), <http://www.fda.gov/CDER/drug/antidepressants/SSRIPHA200410.htm>. The FDA recently proposed to add warnings for young adult patients. Food and Drug Admin., 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>.

92. *See supra* note 48.

93. As noted above, the FDA Amendments Act reinforces the duty of drug manufacturers to ensure that labeling reflects up-to-date safety information and the ability of manufacturers to add warnings to the labels without the FDA's prior approval. *See supra* note 23.

94. *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).

that is, the benefits that flow to the FDA from failure-to-warn cases. Time and again, failure-to-warn litigation has 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 which at least merits the FDA's consideration.<sup>95</sup> The FDA has benefitted considerably from the interplay between state damages litigation and federal regulatory efforts. We see no reason to disturb this system.<sup>96</sup>

#### 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.<sup>97</sup>

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 has long been hamstrung by resource limitations and gaps in the agency's statutory authority. The most fundamental problem is that drugs are approved on the basis of clinical testing that cannot, and is not designed to, uncover risks that are relatively rare or have long latency periods. Legislation cannot solve this problem. To be sure, the FDA Amendments Act adds resources and provides the agency with greater authority to oversee drug

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95. It is a trade-off that other commentators argue would short-change the FDA. See Nagareda, *supra* note 10, at 6 (expressing concern that preemption may do "too little in return" to benefit the FDA); cf. Wagner, *supra* note 17, at 711–13 (explaining the informational advantages of litigation).

96. See, e.g., Kesselheim & Avorn, *supra* note 69, at 310 (citing examples); Lasser, *supra* note 69, at 2218.

97. See *Ensuring Drug Safety: Where Do We Go From Here?: Hearings Before the S. Comm. on Health, Educ., Labor and Pensions*, 109th Cong. 4–6 (2005) (testimony of Janet Woodcock, Acting Deputy Commissioner for Operations, FDA); Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, 601); see also Brief for the United States as Amicus Curiae Supporting Appellee at \*1–2, \*26 n.5, *Horn v. Thoratec*, 376 F.3d 163 (3d Cir. 2004) (No. 02-4597), 2004 WL 1143720 (arguing that the FDCA preempts state tort claims and that the FDA is fully capable of protecting consumer health).

safety post-approval. But there is no guarantee that these new tools and resources will actually lead to more effective oversight of the market, let alone an expectation that an enhanced FDA post-market surveillance program will detect all emerging safety problems with drugs. Top-down surveillance is no substitute for failure-to-warn litigation, which provides the FDA, doctors, and patients with information about new risks that is otherwise unavailable to the agency.<sup>98</sup>

#### A. THE FDA FACES RESOURCE LIMITATIONS

An agency can go only so far as 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 the consumer spending in the United States.<sup>99</sup> But it has only 9,000 employees nationwide.<sup>100</sup> The addition of greater resources as a result of the FDA Amendments Act—an estimated \$50 million for drug safety efforts<sup>101</sup>—will help the agency add needed staff to regulate a pharmaceutical industry that has annual revenues in excess of \$200 billion.<sup>102</sup>

Whether this addition of resources will turn the tide for the agency remains to be seen. There is much work to be done to shore up the agency's ability to detect adverse reactions and to take prompt and effective measures once previously unidentified risks surface. The Institute of Medicine (IOM) reported in 2006 that the FDA “lacks the resources needed to accomplish its large and

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98. See *supra* note 28.

99. Press Release, U.S. Food & Drug Admin., FDA News: The Food and Drug Administration Celebrates 100 Years of Service to the Nation (Jan. 4, 2006), <http://www.fda.gov/bbs/topics/NEWS/2006/NEW01292.html>.

100. U.S. Food & Drug Admin., An Overview of the FDA, [www.fda.gov/oc/opacom/fda101/sld001.html](http://www.fda.gov/oc/opacom/fda101/sld001.html) (last visited Sept. 15, 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 regulate veterinary medicines and cosmetics. *Id.*

101. 153 CONG. REC. S11831 (daily ed. Sept. 20, 2007) (statement of Sen. Kennedy). The basis for Senator Kennedy's estimate is not clear, and the new funds earmarked for drug safety may be less than he has estimated. Title I of the FDA Amendments Act addresses user fees, and section 103(b)(4)(B) provides that for fiscal year 2008 an additional \$25 million in user fees should be allocated for drug safety, and increasing amounts for the following years. Presumably Senator Kennedy's estimate is based on the notion that an additional \$25 million in appropriations will also be allocated for drug safety purposes. Whether additional appropriations will materialize, however, is far from clear. One of the main House sponsors of the legislation, Rep. Henry Waxman, expressed concern over funding. He noted that the “FDA will need a significant influx of resources to do what we are asking them to do,” and that, although the legislation “gives FDA the enhanced ability to dedicate user fee dollars to these activities, it will be critical for Congress to come forward with additional appropriated dollars. We simply have got to get the FDA the funds it needs to do their job well.” 153 CONG. REC. H7602 (daily ed. July 11, 2007). See also *id.* at H7606 (statement of Rep. Van Hollen) (“Congress must also significantly increase federal appropriations to FDA so that the agency is able to fulfill its most basic responsibilities.”).

102. 153 CONG. REC. S11833 (statement of Sen. Kennedy) (daily ed. Sept. 20, 2007).

complex mission today, let alone position itself for an increasingly challenging future.”<sup>103</sup> FDA doctors and scientists share this view; 70% 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.<sup>104</sup> Even the pharmaceutical industry supported the FDA Amendments Act as a way of fortifying the agency’s flagging drug safety resources.<sup>105</sup>

Resource constraints have been especially acute with the agency’s post-marketing surveillance efforts. According to a 2005 Senate Hearing, in the FDA’s Office of New Drugs (OND), which reviews NDAs, “more than 1,000 employees work to review a few dozen new drugs each year.”<sup>106</sup> In contrast, the 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 years, currently has around 100 professional employees.<sup>107</sup> 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.<sup>108</sup> 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.<sup>109</sup>

As noted, the FDA Amendments Act direct additional funds for drug safety, although the bulk of user fees remain directed towards the drug approval process, not post-approval surveillance. And the new resources come with a

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103. IOM REPORT, *supra* note 14, at 193.

104. UNION OF CONCERNED SCIENTISTS, DANGEROUS INTERFERENCE IN SCIENCE AT THE FDA (2006); *see also* OFFICE OF THE INSPECTOR GENERAL, DEP’T OF HEALTH & HUMAN SERVS, FDA’S REVIEW PROCESS FOR NEW DRUG APPLICATIONS: A MANAGEMENT REVIEW 12, 19 (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”).

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

106. *Ensuring Drug Safety*, *supra* note 96, at 42 (statement of Dr. Bruce S. Psaty).

107. *Hearings: Up to the Challenge?*, *supra* note 19, at 11 tbl. (reporting in a table that for fiscal year 2005 the Office of Drug Safety had about ninety full time employees, but projecting for fiscal year 2006 an increase to about 110 full time employees). The table, as well as the Joint Statement of Sandra Kweder and Janet Woodcock, are reproduced at U.S. Food & Drug Admin., <http://www.fda.gov/ola/2005/drugsafety0301.html>.

108. As originally enacted, the user fee legislation restricted the use of fees to the costs of “the process for the review of human 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 “[i]n 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, while other FDA programs have suffered significant funding cut-backs. *See generally* Prescription Drug User Fee Act (PDUFA); Public Meeting, 65 Fed. Reg. 47,993, 47,994 (Aug. 4, 2000).

109. *See supra* note 106.

price: the agency has vastly expanded surveillance duties that will command most, if not all, of the newly allocated resources. Thus, while the new legislation takes an important step towards re-balancing the agency's priorities so that post-approval surveillance is not the stepchild it has been in the past, it is not clear whether, even with the influx of new resources, the FDA will have the manpower it needs to meet the burdens it now faces, let alone what the IOM describes as its "increasingly challenging future."<sup>110</sup>

B. STATUTORY GAPS HAMPER THE 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 FDA 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 drugs.<sup>111</sup> Professor Richard Merrill once quipped that "[a]ll consumers of prescription drugs serve as guinea pigs for the pharmaceutical industry."<sup>112</sup> Thus, 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.<sup>113</sup>

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.<sup>114</sup> With the infusion of approximately \$400 million annually in user-fees,<sup>115</sup> 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.<sup>116</sup>

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110. See IOM REPORT, *supra* note 14, at 193; see also 153 CONG. REC. S11838 (daily ed. Sept. 20, 2007) (remarks of Sen. Burr) ("[T]he bill is a complex web of regulation. It is going to take months, if not years, for drug companies and the FDA to understand all of the new regulations.").

111. 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 subcommittee . . . [that] 'even the most extensive' clinical investigation will reveal only a fraction of the information that emerges during the course of a drug's general marketing and use." Steenburg, *supra* note 32, at 297 (footnote omitted).

112. Merrill, *supra* note 93, at 20. See generally Steenburg, *supra* note 32, at 298 & nn.23-24 (emphasizing that information about a drug continues to be discovered during the general marketing phase).

113. Steenburg, *supra* note 32, at 299.

114. *Id.* at 323-24.

115. Press Release, U.S. Food & Drug Admin., Final PDUFA Recommendations Transmitted to Congress Will Strengthen Drug Review and Drug Safety, (Mar. 23, 2007), <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01592.html>.

116. See Steenburg, *supra* note 32, 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.") (footnote omitted). Faster drug reviews, however, may spawn safety problems as well. In 2002, the General Accounting Office, now the Government Accountability Office (GAO), determined that "a

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.<sup>117</sup> Drug companies now spend over \$29 billion annually to promote their products,<sup>118</sup> including \$11.4 billion on advertising.<sup>119</sup> 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.<sup>120</sup> DTC advertising has proven to be highly successful in stimulating demand for drugs.<sup>121</sup> As a result of these developments, for many drugs there is no longer a transitional period between pre- and post-approval. Drugs that have been tested in con-

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higher percentage of drugs has been withdrawn from the market for safety-related reasons since [user fee legislation's] enactment." U.S. GEN. ACCOUNTING OFFICE, FOOD AND DRUG ADMINISTRATION: EFFECT OF USER FEES ON DRUG APPROVAL TIMES, WITHDRAWALS, AND OTHER AGENCY ACTIVITIES 4 (2002), available at <http://www.gao.gov/new.items/d02958.pdf>; see also *Ensuring Drug Safety*, *supra* note 96, at 45 (statement of Bruce Psaty) (stating that "[d]rug recalls following approval increased from 1.56% in 1993–1996 up to 5.35% for 1997–2001").

117. See, e.g., Julie M. Donohue, Marisa Cevasco & Meredith B. Rosenthal, *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 NEW ENG. J. MED. 673, 674 (2007); Robert Langreth, *FDA Approval of Vioxx Allows Merck To Compete with New Arthritis Drugs*, WALL ST. J., May 24, 1999, at B3 ("[T]he battle [between Vioxx and Celebrex] will ultimately be decided by marketing clout . . ."). Merck, for example, trumpeted the FDA's approval of Vioxx with what it proclaimed to be its "biggest, fastest, and best launch ever." MERCK & CO., INC., 1999 ANNUAL REPORT (1999), available at <http://www.merck.com/overview/99ar/pdf/99ar.pdf> (placing quoted text on cover of annual report).

118. Donohue, Cevasco & Rosenthal, *supra* note 116, at 675.

119. KAISER FAMILY FOUND., PRESCRIPTION DRUG TRENDS 2 (2007), available at [http://www.kff.org/rxdugs/upload/3057\\_06.pdf](http://www.kff.org/rxdugs/upload/3057_06.pdf).

120. A 2005 study found that \$4.2 billion was spent on DTC advertising annually, or 37% of total pharmaceutical advertising. *Id.* To put these expenditures in context, the pharmaceutical industry now spends nearly as much money on advertising as the tobacco industry spends on all of its product promotion (including price reductions and samples). Compare *id.*, with FED. TRADE COMM'N, FEDERAL TRADE COMMISSION CIGARETTE REPORT FOR 2003, at 1 (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. NAT'L INST. FOR HEALTH CARE MGMT., PRESCRIPTION DRUGS AND MASS MEDIA ADVERTISING, 2000, at 5 (2001), available at <http://www.nihcm.org/nihcmor/pdf/DTCbrief2001.pdf>.

121. 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 "[t]he number of prescriptions for the 50 most advertised drugs rose 24.6% from 1999 to 2000, compared to an increase of 4.3% for all other drugs combined[.]" although this study did not take into account the fact that these drugs are also heavily promoted to doctors. See NAT'L INST. OF HEALTH CARE MGMT., *supra* note 119, at 2; see also GOV. ACCOUNTING OFFICE, PRESCRIPTION DRUGS: FDA OVERSIGHT OF DIRECT-TO-CONSUMER ADVERTISING HAS LIMITATIONS 16 (2002), available at <http://www.gao.gov/new.items/d03177.pdf> ("Surveys . . . consistently show that DTC advertisements have an impact on whether consumers request and receive a specific brand-name prescription"). The FDA also has problems regulating the content of these ads, some of which the FDA has found misleading. See *id.* at 23 ("[R]eviews 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").

trolled 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.<sup>122</sup> And make no mistake, the FDA Amendments Act is likely to open the DTC advertising floodgates because, for the first time, the law explicitly permits DTC advertising and gives companies a safe haven if they submit their advertisements to the FDA for advance approval.<sup>123</sup>

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.”<sup>124</sup>

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 assess how the drug performs when given to large numbers of patients over a period of a year or more.<sup>125</sup> Indeed, recent

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122. Almost 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, Feb. 25, 2007, at D1. During the five years Vioxx was on the market, over 100 million prescriptions were written for the drug for an estimated 20 million patients. *See In re Vioxx Prods. Liab. Litig.*, 501 F. Supp. 2d 776, 779 (E.D. La. 2007).

123. The DTC provisions of the FDA Amendments Act are complicated. Title I, Section 104, establishes a system of user fee funding for the FDA’s Division of Drug Marketing, Advertising, and Communications—the entity within FDA responsible for monitoring marketing and advertising practices. User fees will permit the FDA to add resources to this Division. Title IX of the Act, Section 901, explicitly permits DTC advertising and also adds Section 503B to the FDCA, FDAAA, tit. IX, sec. 901, § 503B, 121 Stat. 823, 939 (2007), which permits FDA to require submission of television DTC ads forty-five days before the dissemination to allow FDA to review the ad. Although the Act does not give the FDA the power to direct changes, *see id.* § 503B(c), 121 Stat. at 939, it does provide that no manufacturer may be assessed a civil penalty if the ad was reviewed by the FDA and the manufacturer accepted the FDA’s proposed changes. *See id.* § 503B(g)(4)(A), 121 Stat. at 941. Implementation of these provisions will require the FDA to (a) promulgate regulations identifying the side effects and contraindications that must be disclosed in DTC advertising and how they must be presented, *see* § 503B(f)(3), 121 Stat. at 940, and (b) prepare a report to Congress on DTC ads and the ability of DTC ads to reach “subsets of the general population,” *see id.* § 503B(g)(6), 121 Stat. at 942.

124. IOM REPORT, *supra* note 14, at 153.

125. Prior to the FDA Amendments Act, the FDA’s authority to mandate Phase IV studies was 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 were barred by ethical issues, or where the use of an approved drug for children required study. 21 U.S.C. § 356(b)(2) (2000) (for “fast-track” drugs); 21 U.S.C. § 355c (Supp. IV 2004) (for pediatric studies); 21 C.F.R. §§ 314.610(b)(1), 601.91(b)(1) (2006) (for drugs that protect against chemical, radiological, and nuclear materials). *See generally* Steenburg, *supra* note 32, at 343–44. In those cases in which the FDA wanted a company to engage in a Phase IV study of a drug that did not fall into one of these categories, the agency generally imposed the Phase IV study as a condition of approval. The FDA claimed 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, empowered the agency to require Phase IV studies whenever it saw fit. That interpretation of section 505(k) had been questioned by drug company lawyers. *See* Steenburg, *supra* note 32, at 343.

studies show that the FDA requires Phase IV testing in nearly three-quarters of all new drug approvals.<sup>126</sup> 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.<sup>127</sup>

The FDA Amendments Act tries to address this problem in two ways. First, the Act gives the agency clear authority to require, as a condition of approval, Phase IV studies, so long as the agency does so to assess a “known serious risk” or “signals of a serious risk” related to the drug, or to “identify an unexpected serious risk.”<sup>128</sup> The Act also gives the FDA authority to require Phase IV studies for drugs already approved if the FDA makes a determination that “new safety information” shows an unexpected risk that cannot be addressed through other controls.<sup>129</sup> Second, the Act requires manufacturers to set timetables for the completion of Phase IV studies and to file periodic status reports to enable the FDA better to track the progress of Phase IV studies.<sup>130</sup> While the agency may, in theory, seek to have civil money penalties imposed against companies that do not take these obligations seriously, manufacturers are entitled to “demonstrate good cause” as a defense.<sup>131</sup> What constitutes “good cause” is undefined in the Act and is left to the FDA’s discretion.<sup>132</sup> It remains to be seen whether these provisions will spur better compliance with Phase IV study obligations.

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) and its “MedWatch” program. Under the AERS, companies have a duty to report adverse reactions to the FDA; also, those that are serious or life-threatening must be reported quickly.<sup>133</sup> MedWatch extends the reporting program, on a voluntary basis, to health professionals and

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126. Tufts Ctr. for the Study of Drug Dev., *FDA Requested Postmarketing Studies in 73% of Recent New Drug Approvals*, IMPACT REP., July–Aug. 2004, at 1–2, available at <http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/SampleIssue2005.pdf>.

127. GAO DRUG SAFETY, *supra* note 16, at 28. 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 it may be reluctant to force the issue. *See supra* note 124. For another, once a drug is approved and is then accepted by physicians, it becomes more difficult for a manufacturer to find participants meeting necessary criteria who are willing to enroll in the study (and thereby risk getting a placebo) and more difficult to secure institutional review board approval for a double-blind study with a placebo group. *See Steenburg, supra* note 32, 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* note 14, at 115–16.

128. FDAAA, tit. IX, sec. 901(a), § 505(o)(3)(B), 121 Stat. 823, 923 (2007).

129. *Id.* sec. 901(a), § 505(o)(3)(C)–(D), 121 Stat. at 923.

130. *Id.* sec. 901(a), § 505(o)(3)(E)(ii), 121 Stat. at 924.

131. *Id.*

132. *Id.*

133. 21 C.F.R. § 310.305 (2006).

consumers.<sup>134</sup> Even with these programs in place, most adverse reactions go unreported.<sup>135</sup> As a result, many serious adverse reactions escape the FDA's attention.<sup>136</sup> 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; therefore, the agency may have difficulty determining the incidence of a given adverse reaction.<sup>137</sup>

The FDA Amendments Act tries to strengthen the agency's ability to conduct post-approval surveillance, but it is far from clear whether these efforts will bear fruit. As mentioned above, the Act requires the FDA to make use of existing patient electronic databases to detect adverse events. But it will take considerable time for the FDA to get the system up and running, and given the recognized under-reporting of adverse events, it remains to be seen whether this increased surveillance will help the agency to recognize emerging safety problems more quickly.<sup>138</sup>

The Act takes one additional step to beef-up the FDA's post-marketing authority. It codifies the FDA's authority to require, as a condition of approval, a manufacturer to devise and execute a Risk Evaluation and Mitigation Strategy, or REMS.<sup>139</sup> The preparation of a REMS requires manufacturers to devise a strategy for marketing a drug that includes the provision of risk information to consumers and patients (through, for example, patient package inserts), and may include limitations on the distribution of the drug.<sup>140</sup> The FDA must then

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134. See David A. Kessler, *Introducing MEDWatch: A New Approach to Reporting Medication and Device Adverse Effects and Product Problems*, 269 JAMA 2765, 2767 (1993). 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 *id.* The MedWatch program is described in depth on the FDA's website. See generally U.S. Food and Drug Admin., MedWatch, <http://www.fda.gov/medwatch/index.html> (last visited Aug. 20, 2007).

135. *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).

136. See Steenburg, *supra* note 32, 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.*

137. This is the so-called "denominator" problem. *Id.*; see U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 11 (2005); see also GAO DRUG SAFETY, *supra* note 16, at 24–25; IOM REPORT, *supra* note 14, at 53–54.

138. FDAAA, tit. IX, sec. 905, § 505(k), 121 Stat. 823, 944–49 (2007). One thorny problem that must be resolved before the FDA can act is that the key database the FDA is supposed to use—the Medicare database—may not be lawfully used by the FDA for this purpose. Thus, until new legislation is enacted amending the Medicaid statute, the FDA will not have access to these databases. See 153 CONG. REC. S11841 (daily ed. Sept. 20, 2007) (colloquy between Senators Baucus and Kennedy).

139. FDAAA, tit. IX sec. 901(a), § 505-1(a)(1), 121 Stat. 823, 926 (2007). The REMS provisions codify many of the FDA's existing Risk Minimization Act Plans ("RiskMAP Guidance"). See Food & Drug Admin., *Guidance for Industry Development and Use of Risk Minimization Action Plans* (March 2005), available at <http://www.fda.gov/cder/guidance/6358fnl.htm> (last visited Oct. 30, 2007).

140. FDAAA, tit. IX, sec. 901(a), §§ 505-1(e)(2), 505-1(e)(3) & 505-1, 121 Stat. 823, 929–32 (2007).

approve the REMS, or propose modifications to the manufacturer. The Act gives the FDA the authority to require a new drug applicant to submit a proposed REMS if the FDA determines that a REMS “is necessary to ensure that the benefits of drug outweigh the risks of the drug,” taking into account a number of criteria relating to the potential risks of the drug and the size of the likely patient population.<sup>141</sup> The FDA may also require a REMS for a previously approved drug if the FDA “becomes aware of new safety information” and makes a determination that a REMS is necessary to ensure safety.<sup>142</sup> FDA decisions to require a REMS must be made by individuals “at or above the level of individuals empowered to approve a drug” based on a number of factors that go possible risks posed by the drug, reflecting the importance of a decision to require a REMS.<sup>143</sup> And a REMS must be periodically assessed and modified when needed.<sup>144</sup> Because the agency has been imposing these sorts of requirements for some time, it is hard to appraise whether giving the agency *statutory* authority to require a REMS will make an appreciable difference in drug safety.

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 gather information.<sup>145</sup> 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.<sup>146</sup> 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”<sup>147</sup> and adverse reactions,<sup>148</sup> and have a duty to permit the FDA to review business records during the course of a factory inspection.<sup>149</sup> But companies have no obligation to provide the FDA with the

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141. *Id.* sec. 901(a), § 505-1(a)(1), 121 Stat. at 926.

142. *Id.* sec. 901(a), § 505-1(a)(2)(A), 121 Stat. at 927.

143. *Id.* sec. 901(a), § 505-1(a)(4), 121 Stat. at 927.

144. *Id.* sec. 901(a), § 505-1(g), 121 Stat. at 932. The goal of the REMS is to detect serious risks with drugs as quickly as possible and to permit the FDA to respond with appropriate measures, including, when necessary, withdrawal of approval. The FDA instituted this program, which is codified in the Act, after it sustained a large number of withdrawals of recently approved drugs—ten withdrawn from 2000 to 2006—by the drug's sponsors. GAO DRUG SAFETY, *supra* note 16, at 10.

145. Kesselheim & Avorn, *supra* note 69, at 310.

146. Federal Food, Drug, and Cosmetics Act, § 505(b)(1)(A)–(F), 21 U.S.C. § 355(b)(1)(A)–(F) (2000 & Supp. IV 2004). 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.” § 505(b)(1)(A).

147. 21 U.S.C. § 355(k) (2000).

148. *See supra* notes 132–33.

149. *See* Federal Food, Drug, and Cosmetics Act § 704.

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, it by no means has comprehensive authority.

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 trial lawyers have—the right to subpoena relevant information from any source.<sup>150</sup> A few examples drawn from the litigation over Vioxx and Celebrex illustrate 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.<sup>151</sup> That study showed a statistically significant increase in heart attacks.<sup>152</sup> 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.<sup>153</sup> The advisory committee recommended a warning be added to the labeling for Vioxx, Celebrex's main competitor.<sup>154</sup> But unaware of the Pfizer study linking Celebrex to increased heart attacks and strokes, the committee did not make a similar recommendation for Celebrex.<sup>155</sup>

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

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150. Compare FED. R. CIV. P. 26, 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. FED. R. CIV. P. 27. 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, 633–35 (2001) (explaining the comparative advantage plaintiff's lawyers engaged in civil litigation have in information-gathering over agency officials).

151. See Alex Berenson & Gardiner Harris, *Pfizer Says 1999 Trials Revealed Risks with Celebrex*, N.Y. TIMES, Feb. 1 2005, at C1.

152. See *id.*

153. See *id.*

154. See *id.*

155. See *id.* An equally telling example is reported regarding the antipsychotic medication olanzapine. Lawsuits filed after the drug's approval alleged that the manufacturer, Eli Lilly, recognized that the drug was linked to weight gain and diabetes, but did not warn patients about the risks. Kesselheim & Avorn, *supra* note 69, at 309. 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. *Id.* 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!!!" *Id.* For a detailed treatment of the Celebrex incident, see MCGARITY, *supra* note 9 (manuscript at ch. 1, pp. 7–13).

not provided to the FDA.<sup>156</sup> 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;<sup>157</sup> otherwise there would be a “substantial chance that significantly higher rates” of cardiovascular disease would show up in the Vioxx group.<sup>158</sup> An internal e-mail similarly warned that if Vioxx patients did not receive aspirin, “you will get more thrombotic events and kill [the] drug.”<sup>159</sup> 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.”<sup>160</sup> Evidence uncovered in litigation also revealed the fact that Merck scientists in 2000 were considering combining Vioxx with other agents to reduce the risk of heart attacks and strokes.<sup>161</sup>

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; this process led the FDA to take Halcion, Zomax, and ephedra off the market, and encouraged the agency to regulate tampons more rigorously.<sup>162</sup> 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.<sup>163</sup> 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 without effectively treating their depression.<sup>164</sup> 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, encouraging sales representatives to tell doctors that “Paxil demonstrates remarkable efficacy

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156. 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.

157. *Id.*

158. *Id.*

159. *Id.*

160. *Id.*; MCGARITY, *supra* note 9 (manuscript at ch. 1, p. 13).

161. *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).

162. Wagner, *supra* note 17, at 709 n.73, 711 & nn.79–82.

163. *See* Gardiner Harris, *Spitzer Sues a Drug Maker, Saying It Hid Negative Data*, N.Y. TIMES, June 3, 2004, at A1; *see also* Press Release, Office of the N.Y. State Att’y Gen., Settlement Sets New Standard for Release of Drug Information (Aug. 26, 2004), available at [http://www.oag.state.ny.us/press/2004/aug/aug26a\\_04.html](http://www.oag.state.ny.us/press/2004/aug/aug26a_04.html).

164. *See* Harris, *supra* note 162.

and safety in the treatment of adolescent depression.”<sup>165</sup> Three months later, GlaxoSmithKline settled the case by, among other things, agreeing to make its data public.<sup>166</sup> 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.<sup>167</sup>

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.<sup>168</sup> 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.<sup>169</sup> In May 1990, the FDA called for the makers of silicone gel breast implants to provide safety information for their products, which the companies did not do.<sup>170</sup> After giving the implant manufacturers several extensions, the FDA ultimately withdrew the implants from the market.<sup>171</sup> The agency took this drastic step, not because there was evidence proving that the implants were unsafe (although there was evidence raising safety concerns),<sup>172</sup> but because the industry failed to submit evidence showing that the implants did not pose an unreasonable risk when used as intended.<sup>173</sup> Whatever one might think about the breast implant product liability litigation,<sup>174</sup> there is no doubt that the litigation “was uniquely success-

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165. *See id.*; *see also* Press Release, Office of the N.Y. State Att’y Gen., *supra* note 162.

166. *See* Press Release, Office of the N.Y. State Att’y Gen., *supra* note 162.

167. *See supra* note 90; *see also* Shankar Vedantam, *Depression Drugs To Carry A Warning; FDA Orders Notice of Risks to Youths*, WASH. POST, Oct. 16, 2004, at A1.

168. 21 U.S.C.A. §§ 351–360m (West 1999 & Supp. 2007).

169. 21 U.S.C. § 351(f) (2000) (requiring manufacturers of medical devices to submit health and safety data to the FDA once the FDA issued regulations calling for the submission of the data).

170. General and Plastic Surgery Devices; Effective Date of Requirement for Premarket Approval of Silicone Gel-filled Breast Prosthesis, 55 Fed. Reg. 52,568 (May 17, 1990) (to be codified at 21 C.F.R. pt. 878). *See generally* Teich v. Food & Drug Admin., 751 F. Supp. 243 (D.D.C. 1990).

171. *See* Vladeck, *supra* note 149, at 636–37.

172. 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 WKLY., 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. *See* J.S. Marotta et al., *Silicone Gel Breast Implant Failure and Frequency of Additional Surgeries: Analysis of 35 Studies Reporting Examination of More Than 8,000 Explants*, 48 J. BIOMEDICAL MATERIALS RES. 354, 359 & fig.1 (1999). In 1999, a study by the Institute of Medicine did not find a greater risk of chronic illness in women with silicone implants. INST. OF MED., SAFETY OF SILICONE BREAST IMPLANTS 10–11 (Stuart Bondurant et al. eds., 2000), available at <http://www.nap.edu/books/0309065321/html>.

173. David A. Kessler, *The Basis of the FDA’s Decision on Breast Implants*, 326 NEW ENG. J. MED. 1713, 1714–15 (1992). Even Marcia Angell, a critic of the breast implant litigation, acknowledges that these legal interventions led to long-delayed scientific research on implants. *See* 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).

174. *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* note 171, at 19–21.

ful 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.<sup>175</sup>

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. The FDA Amendments Act may help close those gaps somewhat, but they remain substantial. Nothing in the Act gives the FDA comprehensive authority to obtain whatever records it deems necessary to do its work. 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. Even with the additional resources provided for under the Act, the FDA faces resource constraints. It is still a small “David” facing dozens of “Goliaths.” That is not about to change. As the Senate's chief sponsor of the Act warned, “the resources of the drug industry to collect and analyze postmarket safety data vastly exceed the resources of the FDA, and no matter what we do, they will always have vastly greater resources to monitor the safety of their products than the FDA does.”<sup>176</sup> Failure-to-warn litigation brings to light information that is not otherwise available to the FDA, doctors, other health care providers, or consumers. The benefits of this litigation should not be discarded lightly, and, as we have said, we see no benefit to the FDA or the public in finding failure-to-warn litigation preempted.

#### CONCLUSION

The point of this Essay is not to denigrate the job the FDA does in protecting consumers. The talented 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 safeguard our nation's drug supply on its own. Even with the added authority of the FDA Amendments Act, the agency will not have immediate access to data enabling it to pinpoint problems as they emerge, the personnel and other resources to deal effectively and swiftly with newly discovered hazards, and the insulation from political and other forces that often seek to apply pressure to influence agency decision-making. For that reason, we believe it would be a mistake to 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, physicians, health care providers, and patients, and provide redress to consumers injured through no fault of their own.

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175. Wagner, *supra* note 17, at 715.

176. 153 CONG. REC. S11832 (daily ed. Sept. 20, 2007) (remarks of Sen. Kennedy).