



FDA Preemption and Patient Welfare in *Wyeth v. Levine*

By John E. Calfee

Wyeth v. Levine, which will be heard by the Supreme Court on November 3, 2008, is a lawsuit at the boundary between the state tort liability system and Food and Drug Administration (FDA) regulation of pharmaceuticals. The essential question is whether a pharmaceutical firm that fully complies with FDA regulations, including the provision of safety information, can be sued in state courts for failure to warn about drug safety, side effects, and other concerns. Patients will be better off if FDA preemption is upheld by the Supreme Court, but the path to that conclusion lies in the facts of the case itself, in the nature of the liability system, and especially in certain features of the FDA.

On April 7, 2000, Diana Levine, an artist, was suffering from severe nausea as a result of a migraine headache. (For useful summaries of the facts and issues, see Liptak 2008 and Beck and Hermann 2008, who draw on the numerous *amicus* briefs cited below.) A physician's assistant at a clinic twice administered a treatment to which Levine was accustomed: Demerol for pain and Phenergan for nausea. Phenergan is an antinausea drug that has been on the market since 1955. It is effective in treating extreme nausea, a dangerous condition, but it also involves a signal danger: if it enters an artery rather than a vein, it can cause pain and other symptoms, the most serious of which is gangrene. If Phenergan is administered by intravenous infusion instead of injection, the risk is greater, but relief presumably arrives more quickly. Fortunately, gangrene is a very rare side effect, apparently first reported in 1967. Nonetheless, it is prominently described in four different places on the two-page, FDA-approved label that accompanies the drug (Wyeth 2007, 6–8).

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Levine received Phenergan twice on that April day, first by injection and later, after her symptoms failed to subside, by the “push” form of infusion. During infusion, the drug entered an artery, causing gangrene and eventually the amputation of her right forearm. Levine sued the physician's assistant, the supervising physician, and the clinic for malpractice; the parties settled for \$700,000. She also sued Wyeth, Phenergan's manufacturer, alleging that Wyeth should have added to the FDA-approved label a specific warning not to use the push method of infusion. Wyeth made four primary arguments: it had complied with all FDA regulations, FDA regulation preempts state tort liability lawsuits that conflict with those regulations, preemption is necessary in order for the FDA to meet its regulatory mandate, and preemption is therefore implied by the supremacy clause of the Constitution. A Vermont jury sided with Levine, awarding her \$6.8 million, and this verdict was upheld on appeal by the Vermont Supreme Court. Wyeth appealed the preemption issue to the U.S. Supreme Court.

Wyeth v. Levine has elicited great interest in the business and health care communities.

Numerous *amicus* briefs have been submitted to the Court on both sides. I submitted one of the pro-preemption briefs in June with several other economists, incorporating legal drafting and other work by Ted Frank, a resident fellow at the AEI Legal Center for the Public Interest, and Eric Lasker of the law firm of Spriggs and Hollingsworth (Calfée et al. 2008). A few months later, antipreemption briefs arrived from diverse individuals and groups, including members of Congress, state legislators, medical associations, unions, and academics. One of these briefs (Carpenter et al. 2008) was devoted to rebutting mine.

The Legal Debate

When the FDA makes decisions on new drug approvals, label warnings, and other matters, it seeks to balance risks and benefits. The balancing task is often complex, requiring considerable immersion in science and clinical practice. Conflicting standards among the various states would force firms to pursue varied marketing and even drug development strategies, and it would complicate greatly the dissemination of information about recommended medical practice. Congress was mindful of this when, in 1976, it passed the Medical Device Amendments, which gave the FDA formal authority over medical devices like syringes, X-ray machines, artificial hips, and so on. That law preempted state laws in conflict with FDA regulations, but it did not explicitly refer to tort liability lawsuits. A 1996 Supreme Court decision (*Medtronic v. Lohr*) ruled that state tort lawsuits were not preempted for devices approved through the FDA's "substantial equivalence" provisions, wherein new devices similar to earlier generations are approved without clinical trials. Earlier this year, however, the Court ruled in *Riegel v. Medtronic* that liability lawsuits are preempted for products that traverse the FDA's rigorous "premarket approval" provisions. Legislation to remove this preemption has been introduced in Congress, however, with support from within the medical community (Curfman, Morrissey, and Drazen 2008a, 2008b; Gostin 2008).

Federal law contains no such preemption provision for drugs. The FDA used to argue that state tort liability lawsuits were unlikely to conflict with FDA regulation (Porter 1997; Levine 2007), but, in recent years, the FDA's lawyers have argued in court that preemption is an essential component of FDA regulation. This view was formally advanced in a January 2006 preamble to a *Federal Register* notice of revised rules for the format of

drug labels (FDA 2006, 3934). The FDA argued that without preemption, carefully balanced FDA regulations could be upset by juries that are neither trained nor motivated to look beyond the facts of a sympathetic plaintiff to give reasonable weight to the overall costs and benefits of drugs and of information about drugs. One might think that an extra warning cannot do any harm and may even do a little good. But the FDA learned long ago that prohibiting warnings is almost as important as requiring them. Otherwise, drug labels would be burdened with even more warnings and other details than they already are. This could lead to "overwarning," as emphasized in the *amicus* brief submitted by the U.S. Department of Health and Human Services (HHS 2007).

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A vast and growing literature analyzes preemption of federal regulation generally and FDA regulation in particular (Buzbee 2007; Nagareda 2006; Epstein 2006; Kessler and Vladeck 2008; Sharkey 2007a, 2007b). The Bush administration is pushing for preemption for regulation by many federal agencies, including the Consumer Product Safety Commission (Mundy 2008; Mundy and Wang 2008). After state courts reached conflicting conclusions in pharmaceutical liability litigation cases involving FDA preemption, the Supreme Court agreed to hear *Wyeth v. Levine*. This case raises numerous legal issues. One is about when manufacturers can add warnings to a drug label without FDA approval, as Levine claimed Wyeth should have done (HHS 2007, 12ff). The FDA normally preapproves every element in drug labels, but it provides an exception for new warnings based on newly discovered information. Opponents of preemption, however, argue that the FDA regulations permit the addition of unapproved warnings based upon old information, such as that involving Phenergan and inadvertent arterial exposure.

Another issue is whether FDA regulations provide only a regulatory "floor" but not a "ceiling," thus leaving states free to enforce stricter standards—perhaps established through litigation—but not weaker ones. The FDA itself maintains that its regulations are both a floor and a ceiling (HHS 2007, 10). Therefore, when litigation like that in *Wyeth v. Levine* treats FDA regulation as a

floor but not a ceiling, it causes state law to conflict with federal law in violation of the supremacy clause of the Constitution. Hence, HHS and Wyeth argue that the Constitution supports implied preemption of state law by FDA regulation.

The Policy Debate

The debate over drug liability preemption parallels an earlier debate over medical devices (Curfman, Morrissey, and Drazen 2008a; Korobkin 2007; Gostin 2008; Piwinski and Fitzpatrick 2008). The two leading general practice medical journals—the *New England Journal of Medicine* (NEJM) and the *Journal of the American Medical Association* (JAMA), both of which exert extraordinary influence over Congress and the press—have published editorials and other opinion pieces vigorously opposed to preemption (Curfman, Morrissey, and Drazen 2008a, 2008b; Glantz and Annas 2008; Kesselheim and Avorn 2007; DeAngelis and Fontanarosa 2008). Their core arguments are that the FDA cannot adequately monitor safety and that FDA regulation is usefully supplemented by litigation and its byproducts. (Korobkin 2007 is a refreshingly neutral exception.)

These analyses largely ignore three crucial points. First, the liability system is a clumsy tool that can easily do more harm than good, and its record in the pharmaceutical market is particularly bad. Second, the FDA faces powerful incentives to overregulate and overwarn, meaning that warnings and contraindications imposed by litigation will usually impede—rather than improve—medical care. Finally, contraindications imposed through litigation (as in *Wyeth v. Levine*) are especially likely to leave patients worse off. The next three sections address the liability system, FDA regulation, and contraindications.

What the Liability System Can and Cannot Do

The JAMA and NEJM articles that support liability lawsuits as a bulwark to FDA regulation pay almost no attention to the possibility that tort litigation can actually do harm. NEJM editors DeAngelis and Fontanarosa (2008), for example, criticize a recent federal court decision protecting childhood vaccine manufacturers from liability lawsuits without even mentioning that Congress passed a law to do exactly that after litigation nearly destroyed the child vaccine market in the 1980s (Manning 1996; Offit 2008). The journal authors say

that litigation can be harnessed at little to no cost in order to advance three goals: improving information and regulation, deterring unsafe behavior by pharmaceutical firms, and compensating victims. Their arguments rely mainly on anecdotes, most of them familiar to anyone who has been following the FDA in the past few years, along with appeals to the sparseness of FDA resources. None of these arguments, however, are persuasive.

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Information and Regulation. Litigation can uncover previously nonpublic information, but the most important information—clinical trial results, adverse events, and so on—is nearly always already in the hands of the FDA, and it typically has been taken into account by the agency. Because all the essential information about Phenergan was already well known to the FDA—and to anyone reading the label—there is no reason to think that litigation improved the information about the drug. This situation is hardly unique. For example, a detailed and largely favorable assessment of the role of litigation in pharmaceutical markets noted that Vioxx litigation has done little or nothing to improve knowledge about that drug (Bernstein 2007, 1055).

In fact, litigation can actually cause harm by disclosing or increasing the prominence of information. Perhaps the most vigorous wave of criticism of the FDA alleging inadequate warnings in recent years arose in connection with “suicidality”—suicidal thinking, roughly speaking—among youthful users of the selective serotonin reuptake inhibitor (SSRI) class of antidepressants. This episode started with litigation (NYOAG 2004). Facing relentless criticism from litigators, politicians, popular press editorialists, and elite medical journals, the FDA implemented its strongest “black box” warning for all antidepressants, not just for SSRIs. (There was little reason to think that older drugs, which can cause fatal overdoses, were safer.) Subsequent research has found that SSRI use is strongly associated with lower, not higher, suicide rates, and that the highly publicized warnings probably did more harm than good by reducing antidepressant use (Shogren 2004; McKeown, Cuffe, and

Schulz 2006; Ludwig, Marcotte, and Norberg 2007; Brent 2007; Gibbons et al. 2007; Lubell et al. 2007; Bridge et al. 2007; Pfeffer 2007; Bridge et al. 2008).

Rather than revealing valuable new information, litigation seems more likely to arrive in the wake of distressing new information, such as FDA-imposed drug withdrawals, with results that are anything but encouraging. Litigation over the “fen-phen” diet drug combination, for example, was triggered mainly by drug withdrawals and has caused some \$15 billion to change hands while generating a vast amount of fraud and little, if any, useful health information (Brickman 2008). Similar patterns have characterized breast implant and Vioxx litigation. Even the vast and extended tobacco litigation has uncovered little useful new information on health hazards as opposed to provocative behind-the-scenes facts about the industry (Schuck forthcoming, n108, citing Rabin 2001), even though this market has nothing like the FDA to collect and analyze information for government.

Compensation. The inefficiencies of the tort system as a compensation mechanism are well known and, indeed, inevitable, given that legal costs typically absorb something on the order of half of liability litigation awards. (For the most studied case, asbestos litigation, see Carroll et al. 2005.) Again, one may look at fen-phen and breast implant litigation, in which the chase for extravagant compensation undermined science and bankrupted otherwise valuable firms. (Schuck forthcoming, n19, provides useful summaries of problems with compensation through litigation.)

Deterrence. Using the liability system to deter unsafe behavior by pharmaceutical firms makes sense if regulation is weak. But the firms face quite the opposite situation, and the discussion thus turns to essential features of FDA regulation.

The Influence of Politically Driven FDA Risk Aversion*

The single most important factor in *Wyeth v. Levine* is the peculiar nature of the FDA as an institution. The FDA is an extraordinary agency in three respects. First, its regulatory scope is exceptionally broad and highly intensive, encompassing virtually every aspect of

pharmaceutical development, manufacturing, and distribution. Second, the agency is permitted wide regulatory discretion, which it often exercises through surprisingly informal means. The FDA can do this because it can leverage its power in one sphere (such as new drug development and approval) to exert literally unchallenged influence elsewhere (such as marketing and manufacturing). Third—and most important in our discussion—the FDA, to a degree far greater than almost any other agency, is held responsible by the public for harms from the products it regulates. The three factors interact because the potency and comprehensiveness of FDA power makes it easy for the agency to intensify its regulation in response to criticism, especially from Congress.

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Critics have charged the FDA with slighting safety because it lacks the resolve and resources necessary to track safety (Curfman, Morrissey, and Drazen 2008b, 2; Kessler and Vladeck 2008; Carpenter et al. 2008; Kennedy and Kessler 2008). Such criticism has been given far too much weight. Prominent among the attacks is a celebrated Institute of Medicine report highly critical of the FDA. But the report stated at the outset that “[t]he committee did not attempt to document whether or not a drug safety crisis exists, and this report should not be interpreted as commenting on that claim one way or the other” (IOM 2006, 1-1). Neither the Vioxx episode nor contentious episodes involving SSRIs and other drugs have revealed any tendency for the FDA to downplay safety (Calfee 2007; see also Goldfine 2008 on recent analysis of another widely discussed drug, Avandia).

More attention should be paid to the long history of FDA risk aversion in its handling of new drug approvals and drug safety. The FDA staff faces a deeply biased incentive structure. This arises directly from a disparity in how different kinds of regulatory errors are penalized. FDA staff know that if they commit what is often called a Type I error—the approval of a drug that turns out to be, or appears to be, insufficiently safe once marketing begins—their error will usually become known publicly. A Type I error often generates impassioned criticism of the agency, as we have seen repeatedly in the past few

* This and later sections draw extensively on the *amicus* brief (Calfee et al. 2008) that I coauthored.

years. But a Type II error—the failure to permit marketing of a drug that would, in fact, provide benefits in excess of harms—is typically detected by relatively few people, and its deleterious effects can persist more or less indefinitely. The effect is to bias even the most well-intentioned FDA regulators toward excessive caution and testing. This has been documented in research on the “drug lag” between the United States and Europe in the 1960s, the 1970s, and succeeding decades, as well as in the effects of the user fee system adopted in the 1990s that sped up drug approval decisions (Peltzman 1973, 1974; Wardell and Lasagna 1975; Kaitin and Brown 1995; Bakke et al. 1995; Philipson and Sun 2008).

The FDA became even more cautious after the Vioxx uproar began in October 2004 (Harris 2005). The FDA has recently been unreceptive to a variety of promising new drugs for advanced cancer—including Provenge, Genasense, and others—and, most recently, to new drugs for pain, fibromyalgia, psychosis, and osteoporosis (Goldstein 2008). The agency has also moved toward requiring new drugs to demonstrate superiority over existing treatments, rather than the usual standard of “safe and effective,” and it is rethinking the use of “surrogate markers” in testing and approving drugs for chronic conditions (Favole and Mundy 2008).

Of course, being slow to approve new drugs is not the same thing as paying excessive attention to safety and warnings. In fact, most of the intense criticism in the past few years has charged the FDA not with inappropriate approvals but with a slighting of drug safety, including inadequate warnings (IOM 2006). There is no systematic research on whether the FDA tends to overwarn, but the same incentive logic continues to apply. When deciding about the contents of new drug labels and changes in labels for approved drugs, the FDA knows it might err either by requiring too little information and too few warnings or by requiring too much. If patients are harmed by what was not explicitly warned against, the agency may find itself the target of vigorous criticism. Far less criticism is likely to occur if the label warns too strongly about harms that, in fact, almost never occur or if the label contraindicates uses that would probably be beneficial on net but will not be seen because of physicians’ respect for contraindications.

Thus, as with new drug approvals, the FDA has an incentive to err on the side of caution in its drug labeling policy. On the whole, the agency is more likely to include more warnings than are justified by the actual balance of costs and benefits than it is to fail to include

necessary warnings. For example, the label for the rotavirus vaccine Rotateq was recently amended to include a warning against intestinal blockage, even though extremely large clinical trials involving tens of thousands of subjects had revealed no excess likelihood of blockage from the vaccine compared to a placebo (Loftus 2008).

The result is a strong tendency toward clutter and overwarning rather than sparseness and underwarning in FDA decisions about drug labels. This has been exacerbated by the lack of established FDA preemption. As the FDA and others have long recognized, manufacturers may seek to supply warnings about virtually all possible harms because the absence of a specific warning might form the basis for a lawsuit (FDA 2006, 3935). For example, a series of *Wall Street Journal* articles published in 2005 noted that the three erectile dysfunction drugs on the market each carried labels more than twenty pages long (Hensley 2005a, 2005b). A glance at almost any recent issue of *NEJM* or *JAMA* reveals ads that contain two or more pages of detailed “warnings,” “precautions,” and “adverse events,” occupying far more space than the very limited information about the drugs’ benefits.

Litigation Dynamics and Jury-Induced Contraindications

Of particular concern is the prospect of the addition of new contraindications. Normally, a balancing process operates at two critical junctures: when the FDA decides what warnings to include on the label and how those warnings are organized, and again when physicians take account of label warnings in their prescribing decisions. If state tort liability lawsuits simply cause unfounded or excessive warnings to be added to labels, physicians can still exercise their usual role in balancing risks and benefits, albeit in circumstances made unnecessarily difficult by the extra warnings. Contraindications, however, work differently. Physicians are likely to treat contraindications as outright bans because to prescribe in the face of a labeled contraindication is to invite malpractice lawsuits and punitive damages if anything goes wrong. Contraindications therefore largely replace, rather than supplement, the usual balancing of risks and benefits.

When lawsuits involving preemption and contraindications go to trial, juries tend to focus on a highly specific personal tragedy rather than on social trade-offs, giving more weight to the harm suffered by the victim than to the benefits realized by past and future noninjured users

of the drug. There is little reason to expect the jurors' medical judgment to be superior to that of the FDA. Of course, juries do not always decide for plaintiffs, but when they do, there is an excellent chance that they will have faulted the manufacturer for failing to provide what in fact would have been cluttered overwarning, given that labels already reflect the FDA's tendency to require sufficient or excess warning information on labels. The result can be unnecessary contraindications, preventing physicians from taking due account of comparative risks and benefits in the highly fact-specific situations in which physicians often make prescribing decisions.

As the dynamics of litigation play out, contraindications in one state will likely become national because of the practical inability to limit label changes or litigation exposure to a single state. If juries in certain states or regions are especially inclined to find fault with drug labels and impose contraindications, their preferences will end up controlling physicians in other states as label changes are implemented nationwide. This will have lasting effects. Pharmaceutical firms will attempt to predict other warnings that, if added to the label, might prevent costly litigation in the future. With no way to know exactly what would be required through future litigation, firms will continue to seek the same sort of detailed clutter on labels that the FDA has worked to fend off in the past. Much, if not most, of this new warning information would have greater prominence than would be justified by the balance of risks and benefits precisely because these are warnings that the FDA previously declined to require on labels despite its tendency toward excessive warning information. The effect would be to discourage the beneficial use of drugs whose labels contain these litigation-induced warnings (cf. Viscusi et al. 1994).

Preemption and Patient Welfare

On balance, FDA preemption of state tort liability lawsuits is good for patients. Litigation is a grossly inefficient tool for achieving better information, improved regulation, or victim compensation, and jury verdicts tend to reinforce the FDA's existing incentives to give too much weight to safety and warnings at the cost of prohibiting or suppressing useful prescribing. Too often, juries in failure-to-warn lawsuits will examine behavior that is actually reasonable or even involves excess warning, not underwarning. The warnings they impose will often be excessive, and these warnings will probably be

expanded to encompass the entire nation. The force of this logic is especially distressing for contraindications, the extreme form of warning at the center of *Wyeth v. Levine*. Because physicians will be prohibited from balancing risks and benefits, litigation will exacerbate overwarning and its adverse effects with little, if any, offsetting benefit.

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Eventually, this chain of events can feed back into pharmaceutical research and development. Firms can face incentives to invest less in drugs that promise to provide substantial clinical benefits but also have significant side effects (such as many drugs for cancer and multiple sclerosis). If research firms think these side effects are likely to be exaggerated through litigation, even to the point of triggering contraindications, the financial payoff from researching these drugs and bringing them to market would be reduced, causing fewer innovative drugs to be made available to patients.

Perhaps the Court will uphold the Vermont decision in *Wyeth v. Levine*, thus removing any check on the adverse forces just described. Or perhaps the Court will decide for *Wyeth* but do so on narrow grounds, such as exactly when firms can add label warnings or the distinction between contraindications and lesser warnings. But Congress can itself decide the preemption issue, subject to a presidential signature. The next session of Congress will almost certainly take up legislation to overturn the Court's decision in *Riegel*, which essentially upheld federal preemption law for the most important medical devices. If *Wyeth* wins any sort of victory at the Supreme Court, we can anticipate that similar legislation will be proposed for pharmaceutical litigation preemption.

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