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Prescription Drugs, Products Liability, and Preemption of Tort Litigation

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THE BENEFITS AND RISKS ASSOCIATED WITH PHARMACEUTICAL agents and medical devices have received increasing attention from the medical community, the public, and government agencies. Serious concerns about US Food and Drug Administration (FDA) capabilities and oversight for ensuring accurate determination of safety and efficacy, appropriate mechanisms and decisions regarding drug and device approval, and effective postmarketing surveillance have prompted investigations by the Institute of Medicine¹ and by an FDA blue ribbon commission.² Major legislation³ has been enacted to improve the agency's ability to fulfill the daunting responsibility of ensuring that pharmaceutical products and medical devices approved for marketing are safe.⁴

Even though the evaluation of new drugs and devices is technically rigorous, the current approach of basing drug approval decisions on clinical trials of efficacy that include relatively small numbers of patients virtually guarantees that the full risks and complete safety profile of these drugs will not be identified at the time of approval.⁵ Rather, the full safety profile and effectiveness only manifest as each drug is used in the wider population of patients who are less carefully selected than participants in clinical trials.

The article by Giezen and colleagues⁶ in this issue of *JAMA* is an important example of this well-known phenomenon. In an analysis of 174 biological products (eg, antibodies, hormones, enzymes) approved from January 1995 through June 2007, including 136 agents approved in the United States, 105 approved in the European Union, and 67 approved in both regions, the authors found that 82 safety-related regulatory actions (including 19 "black box" warnings) were issued for 41 of the 174 different biologicals (23.6%). The probability of a biological agent having a first safety-related regulatory action was 14% at 3 years and 29% at 10 years after approval, with first approved agents in a biological class especially prone to safety-related regulatory action.

Given the current imperfect process for approval and the flawed postmarketing surveillance system, the drug and device regulation process is at best an inexact and incomplete science. Until these deficiencies in the system are remedied, some patients inevitably will continue to experience harm from the use of newly marketed products as well as from use of other

approved medications. Just as with other consumer products that cause harms, consumers (ie, patients) who are injured by defective medical devices or by pharmaceutical products with inadequate warnings of potential harms may have to resort to legal action as recourse for their injuries. According to Gostin,⁷ litigation and state tort law "provides a system of civil justice designed to compensate patients, deter unreasonably hazardous conduct, and encourage innovation in product design, packaging, labeling, and advertising."⁷

Thus, tort law serves in effect as a way to close regulatory gaps in the FDA premarketing approval process and to provide a mechanism for postmarketing surveillance.^{7,8} Moreover, litigation has been a rich source of information about how drug and device manufacturing companies behave, such as with off-label promotion, ghost and ghost authorship, and reporting of safety findings.^{9,10} Without the information revealed by the public release of documents in tort liability actions, many of these behaviors would remain unknown, some drug manufacturers' judgments about safety issues would be hidden from view, review, or oversight, and the FDA would not be able to uncover them either.

A critically important upcoming US Supreme Court case, *Wyeth v Levine*, will determine whether patients should be permitted to bring claims against pharmaceutical manufacturers for harms resulting from "failure to warn" of potential risks, even though the product label and prescribing information was approved by the FDA. The case involves a 62-year-old woman who was given an intramuscular injection of promethazine hydrochloride (Phenergan; Wyeth Pharmaceuticals Inc) and then later was given an "intravenous push" of the drug for treatment of symptoms related to migraine headache. However, the second injection of the drug reportedly involved arterial contact, resulting in vascular compromise and progression to gangrene and, ultimately, amputation of her hand and forearm.

The Supreme Court of Vermont had affirmed a Superior Court ruling that found Wyeth was negligent and had failed to provide adequate warning about the known dangers of direct intravascular injection of promethazine, and the court awarded the patient \$6.8 million.¹¹ Wyeth contends that the lawsuit should be banned because the prescribing information had been approved by the FDA. At issue for the Supreme Court is whether FDA approval of prescription drug labeling "preempts" state law products liability claims against a pharmaceutical manufacturer whose products are later found to have safety risks and cause harm. Specifically, the issue is whether a manufacturer

See also p 1887.

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that complies with FDA warning requirements can be held liable under state tort law for not supplying adequate warnings.

Preemption, also known as federal preemption, is one of the most controversial issues in US products liability law. Preemption is the concept that federal law takes precedence over state or local law, such that the federal government can prevent states from regulating at all in the same subject. Federal supremacy holds that federal law bars or “preempts” conflicting state regulation when there is a federal law regulating the particular subject.

The source of federal preemptive power is in the Supremacy Clause of the US Constitution, which stipulates that federal laws “shall be the supreme Law of the Land.” Under this clause, courts are obligated to follow an unambiguous instruction in a federal statute that preempts state law. In essence, preemption means that the federal regulatory scheme is the controlling law and is one of the most commonly used defenses in products liability.

Another 2008 case examining preemption, *Riegel v Medtronic*,¹² involved a claim of products liability for a medical device by a patient who was seeking damages for injuries that resulted from an angioplasty catheter during a percutaneous coronary procedure. The Supreme Court held that the patient’s claims were preempted under the 1976 Medical Device Amendments (MDA)¹³ to the 1938 Federal Food, Drug, and Cosmetic Act (FDCA).¹⁴ The MDA effectively bars litigation that challenges the safety or effectiveness of a medical device that received premarket approval from the FDA and is marketed in the form that received that approval.⁷ The MDA expressly preempts any state “requirement” that is “different from, or in addition to” any federal requirement or that “relate to the safety or effectiveness of the device” under federal law.⁷ Immediately after the *Riegel* ruling, lawyers defending medical device manufacturers filed motions in state and federal courts to dismiss plaintiffs’ claims under preemption.¹⁵

In the upcoming *Wyeth v Levine* case, with opening arguments scheduled for November 2008, the Supreme Court will determine whether the FDCA, which governs regulation of pharmaceutical agents and has no express preemption clause, has implied preemption of state tort litigation. Just as with the FDCA, the recently enacted FDA Amendments Act³ also does not include a provision for preemption. Nonetheless, while the previous FDA positions have supported tort liability as an important mechanism for drug safety, providing a “distinct layer of consumer protection,” the current FDA position is one that favors preemption. However, according to Kessler and Vladek,¹⁶ the FDAAA appears to undermine this current pro-preemption stance by codifying 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 codification 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.”¹⁶ Accord-

ingly, in response to newly discovered risks, drug manufacturers have the authority and responsibility to modify labeling when hazards manifest and may do so without securing prior approval from the FDA.¹⁶ Risks discovered before drug approval or after product marketing that are known to investigators or drug manufacturers ought to be disclosed to the FDA, the public, physicians, and pharmacists as quickly as possible, and there should be no reward or incentive for delay. Isn’t state tort preemption just that?

The *Wyeth v Levine* ruling will have far-reaching and profound implications for patients and drug safety. If the court rules in favor of Wyeth, endorsing preemption, patients will lose an irreplaceable method for seeking remedies for injuries resulting from pharmaceutical agents that were approved by FDA. As with the medical device preemption ruling, such a decision would likely result in thousands of lawyers defending drug manufacturers to file motions in state courts to dismiss plaintiffs’ claims under preemption. In a recent products liability lawsuit, a Philadelphia judge ruled that the federal National Childhood Vaccine Injury Act preempts tort claims of design defects and failure to warn,¹⁷ effectively immunizing vaccine manufacturers against liability claims.

As shown in the study by Giezen et al,⁶ many safety problems are identified only after drug approval. The human body is in a constant state of change and the effects of some drugs will manifest only after exposure over time. Furthermore, some serious adverse drug effects are quite uncommon and require use of the drug in large numbers of patients to become evident. The safety of drugs in a clinical trial, the study type used for FDA approval, is based on specific participant types, numbers, and design that cannot ensure the true safety of a drug. In addition, manipulation of study results by the drug manufacturers (who almost always sponsor studies used for decisions about drug approval) can obscure the true safety profile of a drug.⁹

While, laudably, Congress recently allocated the FDA more money and other resources, and the FDA announced plans to increase its workforce by more than 1300 physicians and scientists,¹⁸ the agency is still limited by the very nature of determining drug safety. The current postmarketing surveillance system has several fundamental shortcomings and flaws, including the voluntary, passive collection of adverse drug reactions; unreliable denominators in calculating rates of adverse effects; and difficulty in determining whether the adverse effect is due to the drug or the condition for which the drug is used. It is unreasonable to expect that the agency that approves drugs will also take on the responsibility for the identification of all postmarket safety problems.

Even though the current postmarketing surveillance system might not yet be effective, vigilant, and trustworthy enough to completely protect the public,⁵ how much worse would it be to eliminate the system completely? Patients (consumers) would be left at the mercy of a system that cannot possibly determine the safety of drugs if left as it is. If the court rules for preemption in *Wyeth v Levine*, congressional action will be necessary to remove preemption of state tort litigation in-

volving claims of products liability for prescription drugs. Otherwise, the current system of FDA approval of drugs would have to be changed to preserve the health of the public. Under this alternative approach, no drug could be fully approved until long-term studies with large numbers of participants had been completed and marketing would have to be greatly limited until full FDA approval is achieved. Surely, the drug manufacturers would not be pleased with such a system; however, without such safeguards, patient safety would be jeopardized. Either way, Congress, not the Supreme Court, seems better suited to decide public policy on patient safety, and it is telling that many members of Congress have joined amici briefs to remind the court that Congress already has decided not to grant preemption to drug manufacturers.

One of the most important ways to ensure the health of the nation is to be certain that medical devices and pharmaceutical agents are safe. The FDA is not infallible and the recently increased resources do not include a crystal ball. Therefore, unless and until the FDA drug approval process and the postmarketing surveillance system improve significantly, patients must have a means to seek recourse through tort litigation against product manufacturers. Anything less may well preempt the well-being and safety of the public.

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Health of the Nation 2008 and Beyond

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BASED ON SEVERAL FACTORS, THE CURRENT GENERAL health of the United States is considerably less than optimal. The nation remains involved in a protracted war in Iraq, which has been costly in terms of financial expenditures, but even much more importantly, in the thousands of lives lost and many more individuals severely injured. Numerous regions of the country are just beginning to recover from recent devastating tropical storms that caused extensive property damage and severe flooding. The nation's financial systems are in crisis, requiring an unprecedented \$700 billion federal bailout in an attempt to stabilize the economy.

The nation's health care system also remains suboptimal. Despite the United States having the world's highest per capita health expenditures, the numbers of uninsured and underinsured remain high, estimated at 45.7 million and 25 million, respectively.^{1,2} Health care costs continue to in-

crease in terms of higher premiums, higher deductible levels, and higher out-of-pocket expenditures, with some employer-based health insurance plans eliminating or reducing levels of employee coverage and shifting more costs to employees. The aging of the US population and escalating costs of medical care are threatening the long-term viability of government-based insurance systems such as Medicare.

This theme issue of *JAMA*, devoted to the Health of the Nation, was intended to “focus additional attention on and continue the momentum of interest in this pressing topic.”³ This issue includes several research articles and scholarly commentaries on various important aspects of this complex topic.

In a study examining health insurance coverage of children and using national data from the 2002-2005 Medical Expenditure Panel Survey, DeVoe and colleagues⁴ estimated that approximately 11.8% of US children were uninsured each year, including 3.3% of children who were uninsured even though they had at least 1 insured parent. In a study of nearly 150 000 patients with myocardial infarction treated at 449 medical cen-

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