

The Role of Litigation in Defining Drug Risks

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IN THE PAST DECADE, SEVERAL WIDELY USED PRESCRIPTION medications have been observed to cause life-threatening adverse effects, and some have been removed from the market. When an approved medication is found to be unsafe, the courts are sometimes called on to determine fault and allocate remedies for injured parties. But in modern prescription drug cases, litigation has taken on additional significance. There are often important gaps in the ascertainment and reporting of adverse effects associated with prescription drugs, and the balance of information presented to physicians about the risks and benefits of medications may understate the former and inflate the latter.¹ However, once it approves a drug, the US Food and Drug Administration (FDA) has limited authority to mandate further collection of data to better define adverse effects or to ensure compliance with suggested alterations in marketing practices.² In this environment, litigation brought by government agencies and individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in drug regulatory systems.³ Litigation can exert its effect through the discovery process, in which each side shares previously unavailable information relating to the issue in dispute, as well as by motivating proper disclosure initially by presenting the possibility of substantial damages in cases of misconduct.

However, some have argued that such litigation adds to the risk and cost of medication development and is a poor way to influence patient care decisions or health policy. Given this controversy, we sought to explore the role of litigation in uncovering new information concerning drug-induced illness and the impact of litigation on drug policy. We evaluated several products recently subject to involvement of the legal system: rofecoxib (Vioxx), cerivastatin (Baycol), dexfenfluramine (Redux), paroxetine (Paxil), troglitazone (Rezulin), cisapride (Propulsid), valdecoxib (Bextra), and olanzapine (Zyprexa) (TABLE). Litigation strategies reviewed included individual and class-action lawsuits against pharmaceutical manufacturers and government investigations of pharmaceutical manufacturers for potentially illegal business practices or financial market manipulation. We sought to define the intersections among the civil justice system,

the regulatory apparatus, and the science of pharmacoepidemiology, including the effects of those interactions on drug safety research, clinical knowledge, and regulatory policy.

Sources of Knowledge About Drug Safety

Most physicians and patients learn about prescription drugs from publications of clinical trials or case reports, promotional materials or alert letters provided by pharmaceutical manufacturers, and formal documents such as the FDA-approved label. These sources, however, sometimes provide a limited perspective on a drug's benefits and risks. For example, a drug's label can vary in its completeness and balance and may not be updated in a timely way to reflect new data.

In both the premarketing and postmarketing stages, lawsuits have helped uncover important and previously unavailable data about major adverse events. For example, the selective cyclooxygenase inhibitor valdecoxib was submitted for approval in 2001 for treatment of dysmenorrhea, osteoarthritis, rheumatoid arthritis, and acute pain. The FDA approved the drug, but only for the first 3 indications. At the request of the manufacturer, the agency then refused to release safety and efficacy data from the pain-related trials, arguing that this information constituted a trade secret, even though physicians were widely expected to use the drug "off label" for that purpose. Only when the consumer group Public Citizen initiated a lawsuit did the FDA release most of the contested safety information. According to Public Citizen, the redacted information revealed that the FDA medical officer found "an excess of serious adverse events including death."⁴ Valdecoxib was withdrawn from the market a year later.

Litigation has also helped the medical community reassess drugs by bringing to light new information about adverse effects. In the case of the selective serotonin reuptake inhibitor antidepressant paroxetine, New York Attorney General Eliot Spitzer found that GlaxoSmithKline had failed to make public clinical trial data that found an increased risk of suicide in adolescent patients taking the drug. The company claimed that the FDA had not specifically approved the use of paroxetine in adolescents, so it was "under significant restraints imposed by federal law in communicat-

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ing with physicians about those studies.”⁵ The government lawsuit and investigations led GlaxoSmithKline and other selective serotonin reuptake inhibitor manufacturers to release the data. An FDA health advisory followed that warned physicians to “carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality” and emphasized that only fluoxetine had been approved to treat pediatric major depressive disorder.⁶

For the antipsychotic olanzapine, studies emerged a few years after its approval linking it to weight gain and diabetes⁷; a series of patient-initiated lawsuits in early 2003 charged that Lilly did not adequately warn about these adverse effects. By September 2003, the FDA required that olanzapine’s label be changed to provide a more prominent warning about diabetes-related adverse effects. In June 2005, the manufacturer announced a \$690 million settlement of more than 8000 olanzapine lawsuits. The settlement required that documents revealed during the discovery process—including data on the actual rates of such adverse effects—not be disclosed publicly. However, documents recently made public from concurrent olanzapine litigation reveal that Lilly long downplayed and kept secret research that linked use of the drug to weight gain and hyperglycemia, telling its salespeople, “Don’t introduce the issue!!!”⁸

Effect of Litigation on Corporate Behavior

Several lawsuits have provided insights into the practices of manufacturers regarding organization and reporting of adverse event data. One common theme in the cases reviewed was delay in revealing adverse event data, often accompanied by attempts

to minimize their prevalence or severity. For example, cerivastatin was removed from the market after being linked to 31 deaths and many more hospitalizations caused by adverse effects, particularly rhabdomyolysis. Litigation documents revealed that its manufacturer, Bayer, had received reports suggesting a 10-fold greater risk of rhabdomyolysis compared with other statins as early as 1999 but did not process all of them.⁹ A memorandum from a company official stated, “If the FDA asks for bad news, we have to give, but if we don’t have it, we can’t give it to them.”¹⁰ The plaintiffs presented this communication as evidence that the manufacturer tried to obscure unfavorable results in its data. Through the same process, plaintiffs’ attorneys learned that the company instructed its sales representatives not to tell physicians about these problems.¹¹

In the case of rofecoxib, the manufacturer was charged with many of the same practices, including efforts to diminish the impact of reported cardiovascular adverse effects by not publishing adverse events and failing to include complete data on myocardial infarctions that occurred during a key clinical trial. The information came to the attention of the public through a subpoena 5 years after the article’s publication, when rofecoxib was already off the market.¹²

Other court cases have drawn attention to how postmarketing adverse events are conveyed to the FDA and publicized. When a pharmaceutical manufacturer receives voluntary reports from health care professionals or patients about adverse events, specific rules govern how it must communicate these data to the FDA. However, in the case of troglitazone, an oral hypoglycemic found to cause liver failure, the company minimized its presentation of adverse

Table. Details of Cases Addressing Drug Safety

Area Addressed by Litigation	Description of Case	Outcome and Policy Implications
Making data public on risks found in preapproval studies Valdecoxib (Bextra)	Clinical trial data considered trade secrets by manufacturer and FDA and not released	Manufacturer persuaded to release data documenting cardiovascular risks
Ascertainment of postmarketing adverse events Olanzapine (Zyprexa)	Manufacturer initially understated weight gain and diabetes associated with use	Drug labeling and promotion revised to clarify risk
Paroxetine (Paxil)	Data not made public about suicide risk early in therapy and in pediatric populations	Manufacturer persuaded to release clinical trial data; FDA issued health advisory, clarified label; contributed to demand for registration of clinical trials
Manufacturer practices Cerivastatin (Baycol)	Studies minimized risk; adverse event reports not processed	Manufacturer paid >\$1 billion in settlements
Troglitazone (Rezulin)	Data reported in a way that did not fully reveal risks	FDA made more sensitive to presentation format of adverse drug reaction data; monetary settlements by manufacturer
Rofecoxib (Vioxx)	Drug-related myocardial infarctions omitted from published reports	Medical journal and public perception of industry-funded studies changed; monetary judgments
FDA policies Dexfenfluramine (Redux)	International reports of adverse events not rigorously pursued	FDA pressured to improve adverse event report surveillance system
Cisapride (Propulsid)	Delayed label changes exposed patients to risk	FDA more likely to publish health advisories in a timely fashion
Paroxetine (Paxil)	Withdrawal reaction reported by patients prompted lawsuits	FDA required label revision

Abbreviation: FDA, US Food and Drug Administration.

effects by not considering the reason patients dropped out of placebo-controlled clinical trials. According to one expert at the trial, "Twenty of the withdrawals from the Rezulin [troglitazone] group were due to elevated liver function tests, while almost none of the withdrawals from the placebo group were."¹³ In addition, elevations of hepatic enzymes in early testing were initially depicted simply as "≥3-fold," obscuring the fact that some enzyme elevations were more than 20-fold greater than normal and that several patients developed severe liver failure. The company did not acknowledge this clinically important difference until more than a year after the drug was marketed.¹⁴

The cerivastatin, rofecoxib, and troglitazone cases revealed the danger of inappropriate proprietary control of clinical trial findings and helped clarify the need for public registration of clinical trials. These cases also led medical journals to reconsider their policies on industry-funded studies and examine submitted manuscripts more closely for financial and other conflicts of interest.¹⁵ The multimillion-dollar court verdicts and settlements may influence companies to reexamine the practices targeted in the suits.

Effect of Litigation on Regulatory Behavior

Drug-related litigation has also influenced the regulatory process, both directly and indirectly. Some cases helped lead to changes in the FDA's official position regarding specific products. After paroxetine's approval in 1991, case reports appeared of patients who experienced uncomfortable adverse effects when discontinuing the medication. A group of patients initiated a lawsuit in August 2001 challenging the manufacturers' promotion of the drug as "non-habit-forming" in television advertisements and convinced a judge to temporarily bar the advertising, which had received FDA approval.¹⁶ Three months later, the manufacturer, under the direction of the FDA, revised its label to include reports of withdrawal-like symptoms following drug discontinuation.

Litigation has also helped identify regulatory policies that can keep unsafe prescription medications on the market. Litigation involving the diet drug dexfenfluramine revealed that as early as 1995, Belgian pharmacovigilance authorities had informed the FDA about reports of heart valve abnormalities in women using diet drugs. This aspect of the dexfenfluramine case highlighted the danger that can arise from not requiring reports of adverse events identified in non-US marketing experience unless the events are "serious and unexpected."¹⁷ The FDA's failure to consider the earliest cases was due to a number of factors; for example, the agency did not stay adequately abreast of adverse effects reported to overseas counterparts, and the manufacturer did not provide case reports to the FDA because the company may not have considered the valvulopathy "serious" unless patients' clinical status was compromised.¹⁸

Lawsuits have also exposed important limitations in the FDA information collection and dissemination procedures. Company documents obtained during the dexfen-

fluramine litigation revealed the manufacturer's active campaign to resist FDA efforts to place a "black box" warning on the official label concerning the risk of pulmonary hypertension.¹⁹ The warning was never included, but the drug was taken off the market more than a year later when its risk of causing cardiac valvulopathy and pulmonary hypertension was determined to outweigh its very modest capacity to promote weight loss. Similar protracted labeling negotiations took place regarding cisapride, a prokinetic agent linked to potentially fatal cardiac adverse effects. Documents obtained in litigation revealed that the FDA engaged in negotiations with the manufacturer for 5 years over changing the drug's label to include adverse event data that had been submitted to the agency but not made fully available to the public.²⁰

Scientific and Policy Relevance of Drug Safety Litigation

Certainly, not all changes in the use or labeling of the drugs studied were entirely attributable to the involvement of the legal system. Other developments occurred simultaneously, including the emergence of new clinical trial data and accumulating clinical experience with these agents. But in each case, the legal system played an important role in spurring change in regulatory or corporate procedures, as well as extending knowledge about drug risks by adding to the evidence available for evaluation by physicians, patients, and regulators.

The impact of litigation on defining drug safety problems is not always positive. The anti-nausea medication pyridoxine/doxylamine (Bendectin), a widely used and probably safe drug, was withdrawn from the market because lawsuits based on flawed scientific foundations charged that it caused fetal anomalies.²¹ Critics have also claimed that tort litigation, or the threat of it, can discourage the development of new products. In 2004 and 2005, the US House of Representatives passed legislation that would prevent the awarding of punitive damages in drug product cases unless the products failed to comply with FDA standards or the manufacturer knowingly presented fraudulent data to obtain regulatory approval.²² Neither bill was approved by the Senate.

The FDA has in recent years submitted numerous briefs supporting drug manufacturers in cases brought by patients who experienced adverse effects for which the companies issued inadequate warnings. The agency sided with the manufacturers in arguing that the courts should not expect the industry to provide any risk information beyond what is contained in the drug's official label.²³ In January 2006, the FDA greatly extended this position, promulgating a new regulation stating that its decisions should preempt nearly all action in any state (including state courts) concerning drug safety.^{24(p3969)} In May 2006, one federal district court cited the FDA's position as a rationale for dismissing a case against a pharmaceutical manufacturer for not adequately warning about suicidal ideation associated

with paroxetine use.²⁵ Although the case is being appealed, if the FDA's preemption position is widely accepted by the courts, FDA approval of a drug would absolve companies of responsibility for failing to adequately evaluate or report the risks associated with their products.

Curbing frivolous lawsuits is a worthy goal, but limiting legal involvement in the prescription drug arena is likely to increase the nation's problem of poorly defined or inadequately presented drug risk information.² These case studies indicate that clinical trials and routine regulatory oversight as currently practiced often fail to uncover important adverse effects for widely marketed products. In each instance, the litigation process revealed new data on the incidence of adverse events, enabled reassessments of drug risks through better evaluation of data, and influenced corporate and regulatory behavior. In performing these tasks, lawyers and their clients often find themselves serving as drug safety researchers of last resort.

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EDITORIALS

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Adjuvant Therapy for Pancreatic Cancer One Small Step Forward

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THE GREAT TRAGEDY FACING THE MAJORITY OF PATIENTS with newly diagnosed adenocarcinoma of the pancreas is the persistent high rate of lethality: most newly diagnosed individuals will die within a year.¹ Approximately 20% of patients are considered for surgical therapy; however, only about half of these individuals

undergo successful resections.²⁻⁴ Surgery remains the only opportunity for cure and can be performed with significant reduction in rates of operative morbidity and mortality, particularly at experienced high-volume centers.⁵ Use of neo-adjuvant strategies in the preoperative setting to improve surgical resectability remain experimental. Adjuvant therapy

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