The Liability Maze

The Impact of Liability Law on Safety and Innovation

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CHAPTER EIGHT

Prescription Drug Safety and Product Liability

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ASSESSING THE effects of product liability on the safety of prescription drugs is a complex and, in some respects, "mission impossible" task for many reasons.[1] There are, for example, a host of pharmacological and clinical questions, and attendant regulatory, legal, and sociological questions, about what one means by "safety" in the context of drugs and their uses. Given the properties of drugs, to borrow from the late René Dubos's statement about our pursuit of the "mirage of health," the idea of a drug that is both perfectly safe and effective, at least with our present knowledge, "is but a dream remembered from imaginings of a Garden of Eden designed for the welfare of man."[2]

Medically, then, the development, prescribing, and taking of drugs involves the question of "safe in relation to what?"—a calculus that opens onto the more-than-scientific matter of risks and how they are attributed, perceived, assessed, communicated, and managed. The fact that drugs do have adverse effects was legally recognized in 1965, in the American Law Institute's "Restatement (Second) of Torts." Comment k of the "Restatement" holds that prescription drugs belong to a class of "unavoidably unsafe products" because they are "incapable of being made safe for their intended and ordinary use" and therefore should not be viewed as "unreasonably dangerous" per se.[3] However, as will be seen, the varying interpretations of Comment k by courts and legal scholars, including the key question of whether it applies to all prescription drugs (hereafter,

1. Except in passing, I do not deal with the bearing of product liability law on the safety of vaccines. For discussions of this topic, see Mariner 1986, 1989; Mariner and Clark 1986; Mariner and Gallo 1987.

2. Dubos 1987, 2.

3. American Law Institute 1965, sect. 402A, Comment k.

drugs), has been one of the main uncertainties besetting attempts to decipher how product liability law and litigation affect drug safety.

A second confounding factor is that pharmaceuticals are one of the most tightly regulated industries in the United States. As a former director of the Food and Drug Administration's (FDA) Bureau of Drugs observed, "The drug industry is unique among American industries in having both its marketed products and its research on new products under federal regulation."[4] Under the authority of the FDA, drugs are subject to detailed regulatory requirements governing virtually every aspect of their testing, formulation, manufacture, marketing, and distribution. Given the pervasiveness of FDA regulations, it is difficult to neatly fence off an arena called "the effects of product liability on drug safety."

Third, there is the problem of data. There are many anecdotes, opinions, claims and counterclaims, and some limited case studies and survey reports about the effects of product liability on prescription drug safety but virtually no solid data. If such data exist—and it is interesting to wonder how policy is made in their absence—they certainly are not accessible to those outside industry.

With these caveats, this chapter deals with four principal topics that together try to provide some understanding of the ways that product liability law, and litigation or the fear of litigation, *may* affect drug safety. These topics have been examined through an extensive search and review of the literature and interviews with a small but highly knowledgeable group of persons involved with drugs and product liability, against a background of prior work I have done on historical, sociological, and policy aspects of pharmaceuticals and the development of patient education materials.

First, given the arguments by the pharmaceutical industry, among others, about the need for product liability tort reforms, I touch on the arguments, opinions, and sparse evidence on the nature and effects of the purported "litigation explosion" and product liability "crisis" for pharmaceutical manufacturers. Second, since drug safety is under the purview of both federal regulation and tort law, I consider the objectives and nature of these two systems of social controls and some of the ways they interact. Third, I examine safety-risk considerations with respect to the *design* of drugs, focusing on scientific and legal issues about what it means to safely design an "unavoidably unsafe" product.

Fourth, I discuss the topic that most experts agree is central to product

4. Crout 1976, 241.

liability and drug safety: labeling, the information about a drug's uses, contraindications, risks, and so on, that is distributed by the manufacturer, subject to FDA requirements and approvals. In part because the "Restatement (Second) of Torts" defines drugs as unavoidably unsafe products, liability law and litigation have focused primarily, though not exclusively, on the adequacy of a manufacturer's *warnings* as conveyed in drug labeling. Traditionally, the question whether a manufacturer has met or breached his duty to warn has been judged by the information provided to physicians, whom the law defines as the "users" of prescription drugs because they are the "learned intermediaries" who dispense these products to patients. In recent years, however, patients or consumers have begun to share the stage with physicians with respect to the duty to warn and labeling, owing to some legally mandated exceptions to the learned intermediary doctrine, expanding sources and types of information geared for consumers, and the controversial matter of direct-to-consumer advertising.

Finally, in a task reminiscent of the four blind men trying to identify the elephant, I try to weave together the strands contained in all the topics mentioned to assess whether, and if so how, product liability has significantly affected the safety of prescription drugs. That assessment, which is tenuous because of the dearth of data, suggests that product liability laws and litigation have had a marginal effect, both positively and negatively, on prescription drug safety, compared with the pervasive influence of FDA regulations and the powerful roles played by pharmaceutical company marketing decisions and by the "learned intermediary" physicians who write more than 2 billion prescriptions a year for their patients.

Prescription Drugs and Product Liability Trends

Advocates of tort reform hold that an "explosive" growth in product liability filings and awards, coupled with the absence of federal product liability standards and the vagaries of state laws and case-by-case decisions, has created a "crisis" that demands state and federal legislative reform. The Pharmaceutical Manufacturers Association (PMA) argues on behalf of its members that the following reforms are needed: enact a government standards provision; eliminate the doctrine of joint and several liability; limit punitive damages and the use of expert testimony; allow payment of large awards by installment; and give courts the au-

thority to reduce an award by the amount a plaintiff is entitled to receive from other sources.[5] These reforms, the PMA maintains, are necessary because

> there has been an explosion in the number and cost of tort cases. . . . If it works properly, the tort law system not only compensates those who are wrongfully injured, but also provides incentives that encourage proper conduct. Today, however, the tort law system has broken down. New theories have created uncertainty about what conduct will result in liability. And—exploiting these expansive theories . . . people are filing suit in record numbers and reaping huge windfalls. A lottery mentality now infects the tort system.
>
> Because of these developments, insurance underwriters have no way to predict the kinds or amounts of claims they may have to pay. The result: broad classes of liability insurance are now unavailable or unaffordable.[6]

Like most controversies, the tort reform debate, which initially focused on liability insurance, has involved deeply entrenched attitudes and beliefs and claims and counterclaims based on "the data." As Hensler and the other authors of a 1987 Rand Corporation report on tort litigation pointed out, the proponents and opponents have "appeared to hold sharply differing views of reality. . . . Each side presented statistical data that appeared to support its position. But the differences in the data cited were puzzling even to those wise in the ways of lying with statistics. Each side claimed to be accurately describing the tort litigation system, yet the two sides seemed to be talking about different worlds."[7]

The studies used to support positions about the effect of product liability on various industries have a major problem: with few exceptions, they used aggregate data for federal and state tort filings, ranges of awards, and so forth. Three studies that provide much needed exceptions to this general pattern were conducted by the General Accounting Office and the Rand Corporation.[8] In general, by disaggregating data on federal product liability filings and, to the extent possible given the nature of state reporting systems, state court filings, all three studies reach comparable conclusions that challenge the specter of a nationwide product

5. Pharmaceutical Manufacturers Association 1989.
6. Pharmaceutical Manufacturers Association (n.d.).
7. Hensler and others 1987, 1–2.
8. General Accounting Office 1988; Hensler and others 1987; Dungworth 1988.

litigation explosion across a range of products. In analyzing the growth in federal product liability filings from 1974 to 1985, for example, the GAO found that only three products were responsible for much of the increase: asbestos for 40 percent, the Dalkon Shield for 12 percent, and Bendectin for 5 percent.

The ways disaggregating data can clarify product liability trends were also demonstrated by Hensler and her Rand colleagues, who, on the basis of their analysis of federal and state filings, showed that "there is no longer, if there ever was, a single tort system. Instead, there are at least three kinds of tort litigation, each with its own distinct class of litigants, attorneys, and legal dynamics."[9] These three "different worlds" are routine personal injury suits; high stakes personal injury suits, including product liability cases; and mass latent injury cases such as the Dalkon Shield, each characterized by a different litigation growth rate, jury verdict trend, and cost profile.

A second Rand study, by Dungworth, reached the same general conclusions as the GAO study with respect to federal product liability trends. But by offering a more detailed analysis than the GAO, it is the most useful study to date for appraising the effect of product liability litigation on the pharmaceutical industry, at least for suits filed in federal district courts. In analyzing the distribution of defendants and cases by industry groups, Dungworth found that 434 companies were named in pharmaceutical suits between 1973 and 1986. Of those suits, however, five companies were the lead defendants in 72 percent, and only two companies—A.H. Robins and Merrell Dow—accounted for 60 percent, owing to the Dalkon Shield and Bendectin litigation. From his analysis Dungworth held that there are at least two main types of product liability litigation, each with a distinctive set of characteristics. The pharmaceutical industry belongs in a "highly concentrated" grouping, which comprises "epidemics" of suits involving a single product, such as the Dalkon Shield, Bendectin, or asbestos. The "dispersed litigation" group, in contrast, has many lead defendants and many cases spread throughout an industry.

Although the GAO and Rand studies have helped to provide a clearer picture of product liability trends, they do not address the effects of actual or potential litigation on manufacturers and their products. For prescription drugs and other products, the publicly extant information is fragmentary and inconclusive at best, because of the general unwillingness of companies to document their claims about a product liability crisis by

9. Hensler and others 1987, 2.

providing data about the actual effects of litigation. Industry surveys, moreover, are so methodologically weak and so generalized regarding categories of industries and products that their applicability to the pharmaceutical industry and drugs is only inferential and suggestive. The type and quality of information available from surveys are illustrated by a 1988 Conference Board report on "the impact of product liability," based on a mailed survey sent to chief executive officers of the country's 2,000 largest manufacturing companies and one sent to a randomly selected group of companies with fewer than 500 employees. Some of the more obvious shortcomings of the study—which was intended and used to bolster the case for tort reform—are the low response rate (270 and 280 usable responses, respectively); the fact that responses from the two groups are merged for most analyses; and the use of very broad categories of manufacturers and product lines—for example, pharmaceutical companies are included under "consumer nondurables." In passing, however, the report does at least note that "even the most vociferous critics of the product liability system concede that, on occasion, the system acts to improve product safety," and it devotes two of its sixty-six tables to these "beneficial effects."[10] According to the responses from 264 companies, *actual* liability experience had led 35 percent to improve the safety of their products, 33 percent to redesign their product lines, and 47 percent to make improvements in product usage and warnings. When asked about the "beneficial impacts" of *anticipated* liability experience, 19 percent of the respondents thought that it would lead to improved product safety, 13 percent to redesigned product lines, and 21 percent to improved product usage and warning.

Another, very small, sampling of the range of opinions, specific to the effects of product liability on pharmaceutical manufacturers and the safety of prescription drugs, is provided by interviews I conducted between January and March 1990:

> *Health law professor specializing in drug product liability:* Liability attorneys for pharmaceutical companies talk and worry about the unpredictability of the courts and juries, and the unpredictability of the law; they're afraid that state laws are changing in ways that will increase

10. McGuire 1988, 1, 20. Similar findings regarding "management action in response to product liability" were reported by risk managers for 232 corporations in a 1987 Conference Board survey report: about one-third said their company had improved the safety design of a product, and over one-third that liability had led to improved product labeling. See Weber 1987, 15.

their company's liability. But it's not clear that liability law is a good deterrent for safety problems, or enhances drug safety, because we just don't have the data.

Attorney in private practice specializing in pharmaceuticals: You will not get hard data on the effects of product liability on drug safety from manufacturers or insurers. But in thirty years of legal practice and government work, with the exception of Bendectin and oral contraceptives, I can't think of an instance where liability or the prospect of liability has affected anything but labeling. Product liability is just not the driving force for the industry. What does worry me, however, is that we seem to be drifting away from a national marketing system for drugs. Because of the effects of state-by-state litigation decisions, and states setting up their own labeling requirements for foods and drugs, we are Balkanizing the system, and I think it will be a disaster.

Senior attorney with a pharmaceutical company: For certain classes of drugs, liability concerns have probably led to safer products, in conjunction with FDA requirements. Companies do worry about li ability because of the uncertainty; we understand and can work witl the FDA regulations, and the FDA can only disapprove, not sue. I think that liability litigation is always a deep pockets issue for a company. But I personally don't think that the litigation threat is that serious, except for DES-type products where potentially significant risks are discovered well after the drug has been introduced. I believe—though it's heretical—that the liability crisis is largely a myth when one looks at available information such as the actual number of cases. The threat of a runaway jury often makes a company settle before a trial, and most huge jury awards are reduced down the line. The real hassle is the "nuisance money" settlement process. Other than DES-type cases, the tort system for drug product liability "ain't broke," and the tort reform proposals go way beyond what is needed to fix it. Tort law is a law of what ought to be—compensation for injury and, when warranted, punishment.

Product liability litigation attorney with a pharmaceutical company: Overall, I think liability has had a deterrent effect for industry with respect to drug safety; safety has been improved as a result of causes of action under negligence. For example, there has been a decrease in certain manufacturers' excesses, such as not doing an adequate job of reporting and issuing warnings about serious adverse drug reactions. From my experience, though, the vast majority of cases brought against drug manufacturers don't have merit, as seen in the number of claims

that actually get to court, and the even smaller number that are decided for the plaintiff. And, it's hard to get a quick and easy out-of-court nuisance suit settlement from a drug company; to settle this way is to condemn your entire product line, and the cost of liability insurance also makes it hard to squeeze a settlement out of a company.

Health care consumer activist: The fact that warnings have been changed and drugs and devices withdrawn from the market suggests that the deterrent effect of liability has been established more clearly for products than for malpractice. But it's hard to tell if companies have really learned yet, because most of the big payouts have just been in the last few years, and the financial costs of irresponsible behavior with respect to warnings and design safety are just coming home to roost. Pharmaceutical companies are really dumb if they haven't learned some lessons, but you also have to recognize that marketing divisions are the tail that wags the company dog.

Controls over Drug Safety: Federal Regulations and Tort Law

From a social controls perspective,[11] efforts to ensure the safety of drugs rely primarily on three entities: the pharmaceutical manufacturer and two external agencies with legal powers over the manufacturer—the FDA through its regulatory authority and the courts through product liability actions under tort law. An understanding of the objectives and powers of these two external control systems, and the ways they interact, is thus an important ingredient in attempting to evaluate the effects of product liability on drug safety.

FDA Regulations: The Government as Guardian

As the FDA's regulatory authority has evolved under congressional legislation, particularly the food and drug acts of 1906, 1938, and 1962, it has had three main objectives concerning the drug industry: "to assure . . . that clinical research on drugs meets appropriate ethical and scientific standards, . . . that all marketed drug products meet certain standards of safety, effectiveness, and quality, and . . . that all marketed drug products

11. For the classic analysis of social controls, see Janowitz 1976.

are labeled accurately and promoted honestly."[12] In the words of the historian J. H. Young, the intent of these regulatory thrusts has been for the government to serve as "guardian" of the public's health by trying to "protect [its] citizens from dangers associated with their . . . drug supplies."[13]

As Young has shown in his studies, the major drug (and food) legislation in the United States has followed a pattern. Six factors have been prominent: "change, complexity, competition, crusading, compromise, and catastrophe," with catastrophe playing an especially critical role.[14] Regulatory controls over the safety of prescription drugs came in the wake of the chemotherapeutic revolution and were triggered by the death of more than 100 people from the diethylene glycol used as a solvent for one of the new wonder drugs, marketed as Elixir Sulfanilimide. Largely because of the outcry over this event, Congress included a "new drug" section in its 1938 Food, Drug, and Cosmetic Act. This provision required, for the first time, that the FDA evaluate a manufacturer's evidence for a new drug's safety before its marketing and approve the drug as "safe for use" for the conditions listed in its labeling.[15]

Safety issues again became prominent in the late 1950s and early 1960s owing to another landmark catastrophe, thalidomide,[16] and have remained in the forefront of industry, legislative and legal, medical, and public-interest concerns about prescription drugs. Attention has centered on such matters as the inherent design safety of drugs, the integrity of drug manufacturers and their willingness to self-regulate, the labeling information provided to physicians and patients, the prescribing habits of physicians, and the adequacy of the FDA's safety-related regulations and decisions. Physicians have received substantial attention regarding their

12. Crout 1976, 241. For accounts of the 1906, 1938, 1962 food and drug acts see Temin 1981 and Young 1982.

13. Young 1982, 11. Young also points out that the United States was the last industrialized country to adopt the guardian role. Currently, under the impetus of federal technology transfer policies, some analysts are concerned that the FDA is becoming a "promoter" of certain drugs and devices rather than a guardian. See Annas 1989.

14. Young writes, "As to catastrophe, in the United States, at least, food and drug bills seem to have required the shock of a major public health crisis to convert them into laws. The crisis atmosphere also influenced provisions in the laws, as well as the psychology of government officials given authority to enforce them" (1982, 11).

15. See Anderson 1946. Under the 1906 Pure Food and Drug Acts, Young points out, "enforcement did not take place until after foods and drugs had been marketed, and the law put the burden of proof upon government officials to show that products were violative" (1982, 12).

16. Kaitin 1988; Witherspoon 1988.

knowledge about drugs and their prescribing practices.[17] But the brunt of the concerns and criticisms that have been raised by academic physicians, conveyed to the lay public by popular articles and books like *The Therapeutic Nightmare,*[18] and investigated by consumer groups and by congressional committees, has been directed at the pharmaceutical industry and at the FDA.[19]

Whatever the shortcomings of the FDA's regulations and actions may be, however, the agency unarguably has authority over almost every aspect of a drug's development, marketing, and manufacturing. In relation to product liability, some features of the chief safety-related FDA requirements that drugs must meet include the following:[20]

The approval process. Two sets of regulations specify the types of research, submissions of data to the FDA, and regulatory reviews and approvals required for a manufacturer to receive permission to market a new drug. These regulations are for the investigational new drug (IND) exemption that allows a sponsor to ship an unapproved drug to investigators and for new drug applications (NDA). Before beginning clinical studies, a manufacturer must submit an IND application that includes safety data on the drug's toxicity from animal tests and any human use data from the United States or abroad. If the agency grants an IND, the sponsor next conducts three phases of clinical testing, which also involve regulations for research with human subjects. Phase I studies, with a small number of human subjects who are usually normal volunteers, are done to establish the safety of the drug at different dosages and to obtain certain basic pharmacologic data; if warranted by phase I results, phase II studies are done with small numbers of patients to test the drug's clinical safety and efficacy. If these initial clinical data indicate that the drug is effective and safe for its intended use, the sponsor then proceeds with phase III trials, involving wider clinical testing with larger numbers of patients.

On completion of phase III testing, the sponsor compiles the data into the voluminous document called an NDA, which the FDA's reviewers evaluate to determine if the manufacturer has provided "substantial ev-

17. Lesar and others 1990; Soumerai, McLaughlin, and Avorn 1989.

18. Mintz 1965. Print and electronic media, both nonfiction and fiction, play an important and often professionally underestimated role in shaping public attitudes, beliefs, and behavior with respect to prescription drugs.

19. Herzog 1977.

20. For discussion of and citations to the FDA regulations dealing with investigational new drugs, new drug applications, postmarketing safety requirements, and good manufacturing practices, see Grabowski and Vernon 1983; Gibbs and Mackler 1987; Walsh and Klein 1986.

idence" of the product's safety and effectiveness through "adequate and well-controlled studies." Of particular relevance to product liability actions, the NDA review includes the drug's proposed *labeling*, which covers all types and forms of information about the product prepared and distributed by the manufacturer. Besides the detailed, technical package insert provided to physicians and pharmacists, labeling information includes the content of press releases, promotional kits, written or verbal advertisements, and material such as pamphlets or brochures prepared for patients.

Before a drug has been approved for marketing, agency regulations sharply restrict promotional claims about its effectiveness or safety. As summarized by a former head of the FDA's Division of Drug Advertising and Labeling, this preapproval constraint

> is related to FDA's mandate to ensure that full information regarding [safety] be presented concurrently and in fair balance with efficacy claims. . . . The sponsor's natural tendency to look on the bright side means that preapproval promotion can be expected to portray a view of the new drug's therapeutic usefulness that is more optimistic than the view that may be finally reflected in the approved labeling [and] without knowledge of an important warning, contraindication, or adverse effect.[21]

Reflecting these concerns, the NDA review of the proposed labeling's format and content has two main foci. First, are the indicated uses for the drug confined to those for which the manufacturer has established substantial evidence of safety and effectiveness? Second, does it meet the agency's specifications for stating the relevant safety information, such as known precautions, warnings, contraindications, and directions for proper use? Failure to conform with the detailed regulations governing labeling can constitute misbranding of the product, on the grounds that its safety and effectiveness have been mischaracterized, a deficiency with potentially severe product liability as well as regulatory consequences.[22]

Postmarketing: adverse drug reaction reports and labeling changes. In relation to safety and product liability, two of the most important sets of FDA regulations governing prescription drugs after they have received marketing approval involve requirements for reporting adverse drug re-

21. Rheinstein 1982, 331.
22. Gibbs and Mackler 1987, 232.

actions (ADRs) to the agency and those dealing with changes in the product's approved labeling. In 1985 and 1987 the FDA issued amendments that strengthened its ADR reporting system. The requirements now include quarterly reports for all drugs during the first three years postmarketing and annually thereafter and an ADR alert report that must be filed within fifteen days after the manufacturer receives information about any "adverse experience" that falls within the agency's definition of "serious." Other aspects of the amendments and related guidelines include the specification of sources that manufacturers are expected to monitor for relevant ADR information, such as a list of "designated journals," and marking a major regulatory shift, requirements for the inclusion of ADR information from foreign sources.[23]

The effects of the new ADR reporting regulations on product liability have yet to be determined. In promulgating the 1985 regulations, Shulman and Ulcickas pointed out, "the FDA specifically repudiated any intent to affect the liability of manufacturers . . . [and] authorized the inclusion of a disclaimer on the ADR report form to the effect that filing the report did not constitute an admission of causality or association between the drug and the adverse event." "However," they reasoned, "it seems fair to say that the increased scope and stringency of the regulations as a whole translate into increased vulnerability to liability claims."[24]

Manufacturers often make labeling changes after a drug has been marketed, primarily to reflect new warning information or new indications for use. New indications must be approved by the FDA before they can be added to the label. But since 1984 the agency has "authorized drug manufacturers to strengthen label warnings, modify dosage in a manner enhancing product safety, and delete unsupported effectiveness claims without prior approval."[25] Indeed, particularly when serious ADRs are recognized, the FDA encourages a manufacturer to issue a warning to physicians as rapidly as possible, although he must advise the agency of an intended labeling change by filing a "supplemental new-drug application providing a full explanation of the basis for the changes."[26] For the most part, however, as Gibbs and Mackler observe, the regulations

23. Shulman and Ulcickas 1989; see also Faich 1986. Shulman and Ulcickas note that the FDA's interest in foreign ADR data was due in part to two criminal prosecutions in the United States, against Smithkline Beckman and Eli Lilly, for failing to report foreign information on serious adverse effects (p. 93).

24. Shulman and Ulcickas 1989, 99.

25. Gibbs and Mackler 1987, 233–34. For the labeling regulations see 21 CFR 314.8.

26. Walsh and Klein 1986, 186, n. 71.

"do not specify the circumstances which compel a manufacturer to modify its labeling to reflect . . . increased knowledge [about risk]."[27] This lack of specificity, as will be seen, is a recurrent issue in product liability cases with respect to the timeliness and adequacy of new warning information.

Manufacturing practices. The FDA also has detailed, extensive regulations for good manufacturing practices (GMPs). These regulations "establish minimum criteria for buildings, personnel, equipment, control of components, processing controls, labeling controls, quality controls, and record keeping. . . . [A] sponsor must demonstrate in its NDA . . . that its product will be manufactured in accordance with GMPs. After product marketing begins, noncompliance with GMPs causes the drug . . . to be deemed 'adulterated.' "[28]

New regulatory issues. Two recent aspects of FDA regulation will bear watching by those concerned with the effects of product liability on prescription drug safety. The first is a high-court ruling that makes the FDA, as well as pharmaceutical manufacturers, potentially liable for design or warning defects. In 1988 a unanimous U.S. Supreme Court decided in *Berkovitz* v. *United States* that "the federal government may be held liable under provisions of the Federal Tort Claims Act . . . for failing to study the necessary safety data before issuing a license to market a vaccine. The Court also ruled that the federal government may be liable for licensing the distribution of a vaccine even though the vaccine did not comply with certain government regulatory standards."[29]

A second aspect of FDA regulations that warrants monitoring, for many reasons besides product liability, is its controversial 1987 regulations for the treatment use and sale of investigational new drugs for certain diseases such as AIDs and cancer.[30] In effect, the "treatment IND" provisions have created a parallel track of clinical trials and therapeutic use for some experimental drugs. Arguments abound over whether the benefits of the treatment IND track will outweigh its potential risks to patients, the extent to which standards for ensuring the safety and effectiveness of new drugs will be compromised, and the degree to which the IND

27. Gibbs and Mackler 1987, 232.

28. Gibbs and Mackler 1987, 213, n. 126, 229. The GMP regulations are in 21 CFR 211.

29. Coben, Romney, and Panichelli 1989, 409. Although this is a single decision, involving a vaccine, Coben and others point out its far-reaching liability implications for the FDA. "The cornerstone to liability [in various instances]," these commentators believe, "will be whether or not government employees failed to comport with statutory, regulatory, or agency policy which is both objective and obligatory in nature" (p. 410).

30. 21 CFR 312.34.

track represents a transformation of the FDA from a consumer protection to a drug promotion agency.[31] On the liability front, attorneys are speculating about the ways that "treatment use of investigational drugs under the new regulations may increase product liability exposure for sponsors." These drugs, for example, "may not receive even the limited [tort liability] benefit of whatever protection marketed drugs receive from FDA-approved labeling." Another prospect is tort suits charging manufacturers with "failure to use due care in selecting qualified investigators" who, under the regulations, are also the treating physicians.[32]

Product Liability Law: Objectives and Causes of Action

Both federal regulations and tort doctrine in the United States are concerned with the safety of a drug manufacturer's product. There are some important differences, however, in the social policy objectives of these two systems of control, which bear on the ways they interact and the extent to which one influences the other. As noted, the general role of the FDA can be characterized as guardian of the public's health through detailed regulations intended to ensure the safety and effectiveness of drugs and other products under its purview. As product liability law has evolved as a part of American tort doctrine, it has sought to fulfill a broader range of objectives, but as Mariner noted, "There is little consensus on the specific overall goals of tort law, much less strict liability and negligence. Most commentators refer to the deterrence of harm, corrective justice or retribution, or compensation for injury. A more practical rationale is that of risk spreading, pursuant to which responsibility for injury should be placed on the person who is in the best position to prevent harm or who can best absorb and recoup the cost of injury."[33]

For whichever objective a product liability action is brought, establishing a "defect" is the key factor, and for prescription drugs it can be a thorny matter to define and determine. The law recognizes three types of product defects that can give rise to a liability claim, usually under a

31. Annas 1989; Johnstone 1988; Marshall 1989.

32. Johnstone 1988, 539. Although I am far from expert in product liability law, it seems to me that *Berkovitz* suggests scenarios for the potential liability of FDA regarding approvals for sale and use of experimental drugs under the treatment IND regulations, and for NDA approvals based in part on parallel track data.

33. Mariner 1989, 29.

negligence or strict liability cause of action.[34] The first is a *manufacturing* defect that "creates a flaw in the individual product that differentiates it from the normal product produced by the manufacturer."[35] "Historically," Gibbs and Mackler comment, "demonstrating a specific flaw in the manufacturing process in finished goods has been quite difficult for an injured plaintiff."[36] For this reason, coupled with the stringency of the FDA's GMP regulations and the importance that the agency attaches to them for ensuring quality control, manufacturing defect litigation is rare for prescription drugs. As a product liability attorney for a pharmaceutical company commented, "There have been almost no manufacturing defect claims against our company and, I suspect, all other drug companies as well."[37]

The second type is a liability action that can be brought on the grounds that a product has a defective *design*. Many product liability authorities believe that design defect cases will increase for prescription drugs. But to date there have been relatively few such cases, given the Comment k view that these are unavoidably unsafe products and the related fact that "there are considerable uncertainties as to how the concept of design defect ought to be elucidated".[38] The third type, and the most frequently alleged in drug cases, is a *warning* defect. For drugs, such defects involve the content of the label, which, as noted earlier, takes various forms and which is tightly controlled by the FDA.

34. When a product is alleged to be defective, litigation is usually based on one of three main causes of action under common law: negligence, strict liability, and breach of contract. For prescription drugs, litigation has predominantly meant charges of negligence or strict liability. Shulman and Ulcickas provide a concise summary of the differences between these two causes of action: "In a negligence suit, the defendant's conduct is central. To succeed, the plaintiff must establish the following: first, that the manufacturer owed a duty to the plaintiff to act reasonably; second, that the manufacturer breached that duty by acting in a way that falls below the standard of the reasonably prudent manufacturer; third, that the plaintiff has suffered actual harm; and fourth, that the harm was proximately caused by or flowed directly from the breach of the manufacturer's duty. . . . In a strict liability analysis, the initial emphasis is product-oriented, focusing on the safety of the drug rather than the reasonableness of the manufacturer's conduct. Fundamental to a strict liability argument is proof by the plaintiff that the product was defective, that the defect existed when the product left the manufacturer's control, and that the defect caused the plaintiff's injury" (1989, 94). For a review of other liability doctrines, such as market share liability in DES cases, see Goldblatt and others 1989; Wilner and Gayner 1989. See Schwartz 1987 for a concise discussion of contributory and shared negligence in product liability cases.

35. Schwartz 1987, 23.

36. Gibbs and Mackler 1987, 229.

37. Personal interview, Feb. 27, 1990.

38. Schwartz 1987, 25.

Of Floors and Ceilings: Federal Regulations and Product Liability Law

Opinions differ, sometimes sharply, on how the external controls provided by FDA regulations and product liability law interact: which, as a matter of law and social policy, should be determinative when safety is questioned; and how, in fact rather than theory or myth, they individually and jointly affect pharmaceutical manufacturers and their drug products. For this chapter, however, the salient point about the relation between FDA regulations and state tort law is that in drug product liability cases judges and juries have recurrently defined federal drug safety standards as a baseline or floor, not as a ceiling. A finding of *noncompliance* by a manufacturer with an FDA regulation is a "strong sword" for a plaintiff,[39] because it is evidence of negligence or can constitute negligence per se with a presumption of liability. But the converse finding does not apply: *compliance* with the regulations may be accepted as evidence of due care by a manufacturer, but it is at best a "weak shield" in defending against a product liability action.[40] The "judicial response" to a manufacturer's use of what is called the government standards defense—that compliance with the regulations "rebuts allegations of negligence or product defects"—"has been consistent and unresponsive."[41] In short, as Paul Rheingold, a leading authority on drug product liability law, wrote, "While drug statutes and regulations form the everyday basis for the conduct of the drug supplier, they are of little importance when it comes to determining whether liability exists or not in a suit for personal injury."[42]

Prescription Drugs and Design Defects

"The debates and actions about risky drugs," a prominent attorney and former FDA official declared, "involve their labeling, not their [design]

39. The apt images of "strong sword" and "weak shield" are used by Gibbs and Mackler 1987.

40. As Gibbs and Mackler pointed out, the courts "do not . . . explain why noncompliance should always be far more probative than evidence of compliance. Nor do they articulate how much significance a jury should attach to FDA approval relative to other trial evidence" (1987, 223).

41. Shulman and Ulcickas 1989, 98. On this point see, for example, the opinion in *Wells* v. *Ortho Pharmaceutical Corp.* 788 F.2d 741, 745–46 (11th Cir. 1986).

42. Rheingold 1985, 135, n.1.

safety as such. Because, given the molecular nature of drugs, you can't just develop a new widget to make their design safer."[43] This remark underscores an important basic aspect of pharmacology and therapeutics: the indeterminate and probabilistic nature of our knowledge about drugs and their effects. As Mitchell and Link pointed out, "safety" in this context is a problematic term and concept:

> There are . . . legitimate scientific disagreements over the actions of drugs. More and better science can only reduce this range of uncertainty. It cannot eliminate it. Thus, when somebody wants to find some instances of lack of safety or efficacy, he has an uneasy time of it. Unfortunately, as Dr. Wardell put it, "the term 'safety' is giving the public the wrong idea of what is to be expected from drugs." Both regulatory authorities and drug manufacturers agree that there is no such thing as a 100% safe drug, and the public would be better off if this term were abolished and replaced by references to degrees of risk or hazard.[44]

The risk-laden nature of drugs, as noted before, was recognized in the "Restatement (Second) of Torts," which states that certain products like prescription drugs are "unavoidably unsafe" because they are "incapable of being made safe for their intended and ordinary use." Thus, according to Comment k, a prescription drug is neither unreasonably dangerous nor defective under product liability law *if* it was properly designed and is properly labeled.

"If" turns out to be a very big word for drug litigation involving a design defect, for reasons of both fact and law. There are pronounced differences of opinion between courts, litigation attorneys, and legal scholars, for example, on the following points: (1) Should all prescription drugs be legally deemed unavoidably unsafe, or should the applicability of Comment k be determined on a case-by-case basis? (2) For purposes of deciding liability, how should the *proper* design for a drug be determined, and correlatively, (3) what standards and tests should be applied to determine whether a design is defective? (4) Which common law causes of action should be used for a design defect case? And (5) does an inadequate warning constitute a type of design defect?

While a thorough discussion of these product liability law issues is

43. Personal interview, Mar. 7, 1990.
44. Mitchell and Link 1976, xvi.

beyond the scope of this chapter,[45] the ways in which courts deal with them will obviously be very important to both the pharmaceutical industry and litigants. "In recent years," Schwartz pointed out, "increasing numbers of claims have challenged the design of prescription drugs under Section 402A."[46] Thus far only one federal appeals court has upheld a jury's verdict that a prescription drug–in this case, an oral contraceptive—

45. For discussion of product design issues in prescription drug liability cases, including topics such as the Comment k defense, whether "state of the art" should apply to the time of manufacture or the time of use, the risk-utility test, and strict liability or negligence as causes of action, see Birnbaum and Wrubel 1985; Coben, Romney, and Panichelli 1989; Gibbs and Mackler 1987; Mariner 1989; McClellan, Tate, and Eaton 1981; Rheingold 1964; Schwartz 1988a; Twerski and others 1976; Wade 1983.

Although these product liability law questions are largely beyond the scope of this chapter, three points do merit a brief mention. First, understanding, much less adjudicating, the design of a product like a prescription drug—and many other technically complex products—is exceedingly difficult. Since even experts often disagree on what constitutes a "proper design" in relation to the state of the art when a product was developed or used, it is little wonder that there are persisting concerns about the ability of judges or juries to decide whether a product was properly or improperly designed. Second, and not unrelated to the problem of technological complexity, there are legal uncertainties over what standard or test should be applied to determine whether a design is defective. Both the two major standards, the consumer expectation test and the risk-utility or risk-benefit test, have been problematic when applied to drugs and vaccines, as various commentators and courts have noted. Some of the problems that arise with these standards in the case of prescription drugs, for example, were addressed in 1988 by the California Supreme Court in *Brown* v. *Superior Court*, one of the many DES product liability cases (44 Cal. 3d 1049, 245 Cal. Rptr. 412 [1988]). The "consumer expectation" test asks whether a product performed as safely as the ordinary consumer would expect it to when used in its intended manner. But for prescription drugs, the *Brown* court held, this test is inappropriate because, under the learned intermediary doctrine, the prescribing physician is the "consumer," and physicians know that all prescription drugs have inherent risks, both known and unknown. The court also felt that the more widely used risk-utility test is not appropriate for prescription drug cases, because this standard assumes that a safer alternative design is feasible.

Third, a body of court decisions and analyses by legal commentators suggest that distinctions between design defects and warning defects have become vanishingly small, apace with the problems that courts are having in maintaining distinctions between strict liability and negligence in such cases. In 1984, for example, the New Jersey Supreme Court, in *Feldman* v. *Lederle Laboratories*, held that under strict liability an inadequate warning can constitute a design defect, because both types of alleged defects involve the same question: "whether, assuming the manufacturer knew of the defect in the product, he acted in a reasonably prudent manner in marketing the product or in providing the warnings given. Thus, once the defendant's knowledge of the defect is imputed, strict liability analysis becomes almost identical to negligence analysis in its focus on the reasonableness of the defendant's conduct." 97 N.J. 429, 479 A.2d 385 (1984).

The *Feldman* court also took issue with the Comment k position that all prescription drugs, by definition, are unavoidably unsafe. "Drugs, like any other products, may contain defects that could have been avoided by better manufacturing or design. Whether a drug is unavoidably unsafe should be decided on a case-by-case basis." 479 A.2d 383.

46. Schwartz 1988a, 33.

was defective in design.[47] However, the "net effect" of this decision, coupled with the variances in the ways in which other courts have dealt with drug design defect cases, "is that the law governing prescription drug liability is perhaps more unsettled today than it was a decade ago."[48]

For the present and the forseeable future, then, pharmaceutical manufacturers must live not only with the indeterminancy surrounding the pharmacology and therapeutics of their drugs but also with the problems of uncertainty surrounding potential liability for the design of those drugs. Some slight and primarily qualitative evidence suggests that the possibility of design defect liability is affecting manufacturers' decisions about their products in three spheres: the introduction of "me too," or follow-on, drugs, the withdrawal of certain drugs from the market for safety reasons, and the steps being taken to maximize the safest possible use of highly risky drugs that are marketed.

In each of these decisionmaking arenas, manufacturers, much like the FDA and the courts, engage in a risk-benefit or risk-utility analysis that includes economic factors and value judgments as well as technical scientific and medical components.[49] For both regulatory and liability purposes, manufacturers weigh such factors as "the likelihood and severity of the risks created by the design, the benefits of the design, and the feasibility and costs of alternative designs or products that could serve the same purpose but pose fewer risks."[50] Using these types of balancing act assessments, manufacturers, as well as regulators, physicians, and patients, may decide that a greater degree of design-related risk is acceptable for a pioneer or innovator drug (the first of its kind that is effective for a given condition) than for subsequent drugs in the same class: the me-too, or follow-on, drugs with usually minor modifications in chemical structure or in their physiologic effect or mechanism of action.[51]

The knowledgeable people interviewed for this chapter all felt that the

47. *Brochu* v. *Ortho Pharmaceutical Corp.*, 642 F.2d 652 (1st Cir. 1981). In *Brochu* a federal appeals court, applying New Hampshire law, held that strict liability standards should apply to a prescription drug design claim. The plaintiff, who had suffered a paralytic stroke allegedly caused by taking Ortho-Novum 2, claimed that this oral contraceptive was unreasonably dangerous in its design because it had a higher level of estrogen and posed a greater risk of stroke than other equally effective oral contraceptives marketed by the company.

48. Schwartz 1988a, 33.

49. On risk assessment, see Bradbury 1989; Inman 1987b; Nelkin 1983.

50. Schwartz 1988a, 34–35.

51. Wastila, Ulcickas, and Lasagna 1989.

potential of design defect liability is having its greatest effect on the pharmaceutical industry in connection with the risks that seem acceptable for a me-too drug. In the opinion of a product litigation attorney with a leading pharmaceutical company, "If a major opportunity exists for a plaintiff to file a design defect claim, it's with a me-too drug, because a safer alternative design probably was available."[52] Similarly, a senior attorney with another major company believes that "for me-too drugs, the safety profile is more important than the effectiveness profile when the company decides whether to go ahead with testing and marketing. The hook for these drugs is better safety than the predecessor or competitor drugs; a safety profile that looks worse than other drugs in its class will be a me-too drug's death knell."[53] Much the same view was offered by a senior official with the FDA, from his perspective as a regulator and his sense of what manufacturers worry about with respect to drug design liability issues: "Serious risks are what people worry about with a follow-on drug. It's a question of relative economic gain versus economic risk or liability for a company, and that assessment has to include both known hazards with the drug and the odds of someday encountering unexpected problems."[54]

Once drugs have been marketed, different safety-related factors can trigger a decision to withdraw a product. Like a physician's decision to prescribe or a patient's decision to take a drug despite its hazards, a decision by the FDA or a manufacturer to withdraw a drug entails judgments for which, medically, legally, and sociologically, there are no simple guidelines: what constitutes an "acceptable" risk?[55] Because of both the pharmacology and therapeutics of drugs and the relatively small clin-

52. Personal interview, Feb. 27, 1990.

53. Personal interview, Jan. 30, 1990.

54. Personal interview, Feb. 21, 1990.

55. In discussing what constitutes an acceptable risk, Dr. W. H. W. Inman, director of England's Drug Safety Research Unit, points out that "a patient may tolerate a reduced quality of life in order to prolong it. . . . [or] [h]e may risk shortening his life in order to improve the quality of what remains. . . . Should the [acceptable] risk of a fatal ADR be more than one in ten thousand, one hundred thousand, or one million? Should it be ten or a thousand times less than the risk of a fatal outcome to the disease? [Take, for example, rheumatoid arthritis.] This horrific, almost malignant disease may shorten life-expectation from the time of diagnosis by at least one third. I know of no drug which is too dangerous to use in rheumatoid arthritis. Several NSAIDs have been removed from the market when the best estimates of annual mortality due to ADRs were between one hundred and ten thousand times less than the annual mortality from the complications of the disease. Certainly it might have been reasonable to curtail their use in lesser illnesses, but not to remove them completely" (1987a, 18).

ical data base on which a marketing approval is based, serious adverse effects may not be identified until a drug has been in use for months or years. In some instances a marketed drug's known risks, even if mild or moderate, may become greater than its benefits if a competitor drug appears with a better safety profile and equivalent efficacy.

The various kinds of risk-benefit factors and decisionmaking processes involved in a manufacturer's decision to remove a drug from the market, however, are seldom fully discoverable by "outsiders." Thus, for example, it can be difficult to determine whether a given drug was withdrawn "only" because it became economically unviable for its manufacturer as newer competitor drugs gained a greater share of the market,[56] rather than because of serious hazards. And when serious adverse effects are the issue, it is not always clear whether a withdrawal is due to impending regulatory action, a regulatory decision, actual litigation, the fear of litigation, or some combination of all of these.[57]

The sparse literature analyzing drug discontinuations does show that only a small percentage of the new chemical entities introduced into the U.S. market are withdrawn for safety reasons. Bakke and his colleagues, for example, examined drug discontinuations for safety reasons in the United Kingdom and the United States for the period 1964–83, with "safety" referring to toxicity problems that caused a drug's risks to outweigh its benefits.[58] For that period they found that a total of twenty-four drugs were discontinued in both countries for safety reasons, amounting to only 2 percent of the new chemical entities that had been introduced. From their data the authors concluded that "drugs that reach the market under the prevailing regulatory systems [of the U.S. and the U.K.] are seldom associated with unacceptable toxicity."[59]

In the absence of solid data on the extent and nature of litigation involving drug design safety issues, apart from decided cases and the GAO and Rand analyses of the "tort epidemic" generated by Bendectin, it is impossible to make even a "best guesstimate" about how that litigation compares with the small percent of drugs withdrawn for safety

56. Weintraub and Northington 1986. As examples in this article show, some drugs that are withdrawn because they are no longer economically beneficial to a company are subsequently reintroduced because of pressure from physicians and patients.

57. The discussion in this section, and in the section on warning defects, does not deal with the separate issue of manufacturers who engage in fraud or the tort of deceit by ***knowingly*** withholding information about design defects.

58. Bakke, Wardell, and Lasagna 1984. A similar pattern of safety withdrawals was found from 1977 to 1987. See Kaitin and others 1989.

59. Bakke, Wardell, and Lasagna 1984, 559.

reasons. Nor, correspondingly, can one evaluate the extent to which liability concerns per se have led to discontinuations or to efforts to find safer alternative drugs for specified conditions.

However, the sparse evidence available, which includes some case studies, does suggest that product liability law, litigation, and concerns play at least some role in enhancing the design-related safety of drugs. Manufacturers' awareness of or experience with product liability issues can affect the fact that certain drugs never reach the market because of toxicity problems and that others are withdrawn because their medical risks turn out to exceed their benefits. There is, however, a downside element to the role of liability concerns vis-à-vis the basic hazards of drugs. Two examples are discussed by Lasagna in this volume: the first is a uniquely effective drug like Bendectin being withdrawn because of litigation even though no conclusive evidence of serious adverse effects was found; the second is the high probability that several new, uniquely effective uses for thalidomide will never be used outside an IND framework.[60]

To me, however, one of the most interesting facets of design-safety issues does not involve decisions to keep a drug from reaching the market or to discontinue it once marketed. Rather, it is the decisionmaking by the various actors engaged in the marketing and use of drugs that are known to be highly effective but extremely hazardous. These actors comprise the manufacturer, aware of the potential and perhaps likely liability attached to such a marketing decision; the FDA; the physicians and their patients, who, presumptively, are informed about the drug's serious hazards but deem them "acceptable"; and, waiting and watching on the sidelines, consumer activist organizations and litigation attorneys.

Three examples of such drugs are Roche's Accutane (isotretinoin), Sandoz's Clozaril (clozapine), and G. D. Searle's Cytotec (misoprostil). Accutane, prescribed for severe recalcitrant cystic acne, received its NDA approval from the FDA in 1982, with full recognition of the fact that it can cause major fetal abnormalities and thus should not be used by women during or just before pregnancy. "The message to physicians [about the drug's strong teratogenic potential] was and continues to be clear and forceful."[61] But by 1988 severe birth defects in sixty-two infants had been attributed to the use of Accutane during pregnancy, and the FDA's Ep-

60. For more detailed discussions of bendectin and thalidomide, see Barash and Lasagna 1987; Kaitin 1988; Witherspoon 1988.

61. Shulman 1989, 1565.

idemiology Unit estimated that the drug might have caused up to 1,300 birth defects nationwide between 1982 and 1988. Subsequently, on the recommendation of an FDA advisory committee, Roche's physician package insert was supplemented by a pregnancy prevention program kit, containing an instructional videotape for physicians, brochures for patients, an informed consent form, and a true-false test to be completed by the patient so that her doctor can evaluate how well she understands Accutane's risks. The manufacturer is also sponsoring an epidemiological monitoring program.

These steps have been undertaken by the manufacturer in an effort both to avert birth defects and to protect against liability actions. Nonetheless, the liability consequences of Accutane's marketing have been considerable, for, in the wake of thalidomide, the drug has been branded as a "prescription for birth defects."[62] In 1988 the American Trial Lawyers Association formed the Accutane Litigation Group, composed of lawyers representing "victims of Accutane." By that time between ten and twenty lawsuits were pending for birth defects ascribed to the drug, and about the same number of cases alleging serious side effects in adult users such as vision loss and eye, gastrointestinal, cardiac, and central nervous system disorders.[63]

Because of the lasting and powerful memory of thalidomide, many people familiar with Accutane's history are puzzled by the medical and legal risk-benefit calculus in Roche's decision to develop and market a potent teratogen for a disfiguring but not life-threatening condition, and by the FDA's IND and NDA approvals. And given the litigation that has followed its use, many also are puzzled that Roche has not withdrawn Accutane from the market or at least sought FDA permission to restrict its distribution solely to men. Said a former FDA official, "Accutane's marketing and now its litigation illustrates my belief that, although there are some crazy liability decisions, liability has not had a major effect on drug development and marketing."[64]

Clozaril and Cytotec have much shorter development and marketing histories than Accutane but illustrate the same kinds of questions in search of answers about the decisionmaking processes related to the approval, marketing, prescribing, and taking of effective but medically and litigiously risky drugs. Clozaril was approved by the FDA in October 1989

62. Nygaard 1988.
63. Nygaard 1988.
64. Personal interview, Mar. 7, 1990.

for the management of severe schizophrenia in patients unresponsive to standard and less toxic antipsychotic drugs. Before receiving marketing approval in the United States, the drug was available for restricted use in about thirty other countries, because of side effects including seizures and a potentially lethal agranulocytosis, a severe decrease in white blood cells that increases a patient's susceptibility to infection. Owing to these known risks, and clinical data indicating that it was no more effective than already available drugs, the FDA disapproved an initial NDA by Sandoz in 1984. The 1989 approval to market the drug, according to the agency, was based on additional clinical data showing that Clozaril was effective in patients who do not respond to or have intolerable side effects from conventional psychotropic drug treatment. Because of its severe risks and the inability of those taking the drug to understand or consent to those risks, Clozaril's approved labeling makes it available to physicians and their patients on a restricted distribution basis, which includes "a special program that has been developed for safety monitoring. Under the program a home health care company will both deliver the prescribed clozapine tablets and collect blood samples each week to be sent to a national laboratory for analysis. Patients and physicians will be notified of the results. If the results indicate that the patient should stop taking the drug, his or her physician will be notified immediately by telephone."[65] The "Clozaril model," several knowledgeable persons have commented to me, seems like a good idea in terms of restricted distribution and close safety monitoring of a drug with this type of risk-benefit profile. As such, it will be an interesting case to follow, from product liability, regulatory, and clinical perspectives.

G. D. Searle's Cytotec, marketed in 1989, will also be an interesting drug to follow from the same three perspectives, as well as because of its sociopolitically volatile nature. The drug is indicated for the prevention of gastric ulcers induced by the nonsteroidal antiinflammatory drugs (NSAIDs) widely used to treat arthritis. Besides protecting high-risk NSAID users from gastric ulcers and their often serious complications, however, Cytotec is an abortifacient. In seeking approval to market Cytotec, Searle was very aware of the implications of a drug that, while an effective new agent for a prevalent and serious side effect of other widely prescribed compounds, can also induce complete or partial abortions. The company anticipated strenuous opposition from pro-life political groups, the possibility of Accutane-like labeling requirements and "preg-

65. Nightingale 1990.

nancy prevention" strategies being required or "persuasively recommended" by FDA, and the prospect of litigation. Some pro-life opposition to the drug's marketing did develop, but not as much as had been anticipated. As part of its NDA application, the company prepared proposed labeling with contraindications and warning language and formatting that was stronger than the FDA felt it needed to be. Their product liability concerns, however, may be realized, since litigation claims reportedly have been discussed.[66]

These three examples, to which others could be added, suggest the sociological and social policy knowledge that could be gained from in-depth case studies of the "real" decisionmaking factors and processes connected with the marketing and use of drugs that are at once highly effective and highly hazardous. One thing that even a cursory knowledge of such agents does underscore, however, is the importance of labeling, both to protect patients by maximizing the safety of a drug's use, and to serve a "damage control" function that attempts to protect manufacturers against liability.

Read the Label: Liability for Warning Defects

Most prescription drug liability suits against pharmaceutical manufacturers allege negligent failure to warn about risks, rather than negligence or strict liability for design, testing, or manufacturing. In warning defect cases the key issue for plaintiffs and defendants is what constitutes "adequate warning" or "reasonable disclosure" about a drug's risks, including those known at the time the drug was marketed and those discovered through postmarketing use and research.[67] For, as Shulman and Ulcickas wrote, while all drugs may be "unreasonably dangerous" per Comment k, or may be determined to be so on a case-by-case basis, "the protection of Comment k is forfeited . . . if the warnings accompanying the prescription drug are inadequate."[68]

66. Personal communications.

67. Postmarketing research by a manufacturer, initiated by the company or done at the FDA's request, can be undertaken "defensively," to identify toxicity problems, or to study some aspect of a drug's efficacy, including new indications for use. See Medicine in the Public Interest 1985.

68. Shulman and Ulcickas 1989, 95. As this article also points out, the distinction between negligence and strict liability "fades" on the question of what constitutes an adequate warning. "In both causes of action, an examination of the reasonableness of the manufacturer's conduct is required. The language of Comment j of the Restatement, al-

The FDA, as noted, has regulations that strictly control the content and format of the principal source of labeling information, the package insert for physicians and pharmacists that must accompany each drug.[69] Under the regulations labeling is also more broadly defined to include many other forms and types of information conveyed by the manufacturer; for example, replications of the package insert in the form of product cards or sources such as the *Physicians' Desk Reference*, written or verbal advertisements, promotional materials like press releases and promotional kits, "Dear Doctor" letters, and the oral representations made by company detail men.[70]

For product liability purposes, FDA labeling regulations, like other aspects of its public guardian role, set a floor of minimum standards rather than a ceiling. A manufacturer's compliance with labeling regulations does not preempt the holdings of the common law duty to warn, nor, as Gibbs and Mackler pointed out, did the FDA intend it to. "In adopting the [labeling] regulations, the FDA specifically disavowed any intent 'to influence the civil tort liability of the manufacturer or the physician. Rather, it is the agency's intent to ensure that a complete and accurate explanation of the drug is provided to the medical community.' "[71]

What Constitutes an "Adequate" Warning?

Court decisions on alleged warning defects have dealt with the *content* of the physician package insert and other forms of labeling, the *timeliness*

though part of strict liability theory, is equally applicable within the context of a negligence action. A manufacturer is required to warn of dangers 'if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge' of the risk" (p. 95).

69. The courts, with one exception, have held that pharmacists do not have a legal duty to warn or counsel patients directly about prescription drugs. See Brushwood and Simonsmeier 1986, 300–25.

70. There are a number of warning defect cases and FDA actions concerning the various forms of labeling other than the physician package insert. In terms of FDA enforcement activity regarding prescription drug advertising, for example, between 1971 and 1983 the agency sent pharmaceutical companies 1,069 letters requesting corrective action, canceled 858 ads and 968 instances of promotional labeling, and held 1,728 advisory conferences. See Fisherow 1987, 231. Consumer activist groups like the Public Citizen Health Research Group play a watchdog role for what they consider misleading advertisements and often petition the FDA to have such ads withdrawn or modified. For discussion of and citations to warning defect cases involving "Dear Doctor" letters sent by manufacturers to physicians about newly identified adverse effects, and liability for detailmen's warnings and overvigorous promotion, see Hirsh 1987, 402–03, and McGarey 1984, 118–19 and note 5.

71. Gibbs and Mackler 1987, 232, quoting from 44 *Federal Register* 37437 (1979).

of warnings, and the question of *to whom* the manufacturer owes a duty to warn. Some of the key points that have emerged in failure-to-warn cases have been the following:

—Pharmaceutical manufacturers have a legal obligation to "utilize methods of warnings which will be reasonably effective, taking into account both the seriousness of the drug's adverse effects and the difficulties inherent in bringing such information [in a timely] manner to the attention of a group as large and diverse as the medical profession."[72]

—The duty to warn is a "continuous one, requiring the manufacturer to keep abreast of the current state of knowledge of its products as gained through research, adverse reaction reports, scientific literature, and other available knowledge."[73]

—The duty to warn "does not arise until the manufacturer knows or should know of the risk."[74]

—A warning must be issued as soon an adverse effect is discovered.[75]

—A drug must not be so overpromoted (for example, by detail men) "that an otherwise adequate warning becomes inadequate."[76]

—Manufacturers can be liable for failing to warn of risks, including rare adverse reactions, associated with but not confirmed to be caused by use of their product.[77]

Two aspects of prescription drug warning defect decisions have been particularly problematic in terms of the regulatory intent and hoped-for effectiveness of labeling information. The first is the extent to which this information should or must incorporate "unsubstantiated" medical evidence about possible hazards. FDA regulations permit manufacturers to issue warnings when new ADRs are documented, without prior approval of such a labeling change. But the agency holds that "the most important feature of the package insert, the one that distinguishes it from other sources of information and makes possible its use as an authoritative reference source, is that its content must be based on substantial evidence.

72. *McEwen* v. *Ortho Pharmaceutical Corp.*, 270 Or. 375, 528. P. 2d 529 (1974).

73. Fern and Sichel 1985, 13, citing *Lindsay* v. *Ortho Pharmaceutical Corp.*, 637 F. 2d 91 (2d Cir. 1980).

74. Fern and Sichel 1985, 13, citing *Ortho Pharmaceutical* v. *Chapman*, 180 Ind. App. 33, 388 N.E. 2d 541 (1979).

75. *Feldman* v. *Lederle Laboratories*, 97 N.J. 429, 479, A. 2d 388–9 (1984).

76. McGarey 1984, 119, citing *Stevens* v. *Parke Davis. & Co.* 9 Cal. 3d 51, 67, 507 P. 2d 653, 662, 107 Cal. Rptr. 45, 54 (1973).

77. *Wooderson* v. *Ortho Pharmaceutical Corp.*, 235 Kan. 387, 681 P. 2d 1038 (1984), *cert. denied*, 105 S. Ct. 365 (1984). In *Wooderson*, the plaintiff was awarded punitive as well as compensatory damages, marking the first punitive damage decision in a pharmaceutical company failure-to-warn case. See Fern and Sichel 1985.

The labeling cannot simultaneously meet this requirement and be fully up to date. It cannot be both authoritative and avant-garde."[78]

A second concern is that product liability decisions, or attempts to ward off litigation, may lead manufacturers to include so much information in the label that it causes a "sensory overload." The potentially detrimental effects of too much warning information has been discussed by some courts as well as by the FDA, legal commentators, and writers concerned with risk-benefit assessments and the expertise and roles of physicians and patients in making such assessments.

> A potential but real consequence of imposing liability for failure to warn of all suspected reactions will be to convert the package insert into a cluttered unintelligible list containing virtually every disease which might be suspected to be an adverse reaction to the product. This "overkill" would be the manufacturer's attempt to shield itself from liability. Unfortunately, promiscuous or unwarranted warnings cast doubt upon and undermine those warnings which reflect real potential hazards that the FDA requires to be listed on the label.[79]

The Duty to Warn: Physicians as the Learned Intermediary

A unique legal characteristic of prescription drugs is that, in contrast to over-the-counter (OTC) drugs and other "normal" consumer items, the manufacturer's duty to warn is owed to the physician rather than to the patient who is the drug's end-user. Under 1938 and 1951 regulatory changes intended to protect the public from the potential hazards of uncontrolled access to certain classes of drugs, the FDA required that such drugs could be obtained only through a physician and that adequate information about the use of such drugs needed to be written in medical terms "not likely to be understood by the ordinary individual."[80] With some exceptions, the courts have agreed with this regulatory philosophy,

78. From a 1974 article by Robert Temple, FDA Bureau of Drugs, on "Legal Implications of the Package Insert," quoted in Fern and Sichel 1985, p. 15. FDA labeling regulations also emphasize that the label for a given drug is not intended to be a "dispositive treatise."

79. Fern and Sichel 1985, 16.

80. The FDA first stated this position in 1938 (3 *Federal Register* 3168). Subsequently, in the 1951 Durham-Humphrey Amendment to the Food, Drug and Cosmetic Act, which officially authorized the FDA to establish the prescription or nonprescription status of all drugs, "a practitioner licensed by law" was required to administer prescription drugs (65 Stat. 648 [1951]).

which makes physicians the gatekeepers who control access both to prescription drugs and to information about those drugs. In a term first used in a 1966 judicial opinion, the physician is the "learned intermediary" who stands between the user of a prescription drugs and its manufacturer.[81]

The rationale for the physician's primacy in prescription drug use, as Shulman wrote, "is a familiar one. The physician is considered to be in the best position to weigh the risks and benefits of a specific drug for individual patients. The courts [and regulators] also are persuaded by arguments that direct communications from manufacturer to consumer may be too difficult, could unduly interfere with the doctor-patient relationship, and might frighten or confuse the patient, discouraging compliance with the prescribed therapy."[82]

Under both statutory and common law precepts, then, the effects of product liability law on the safe use of prescription drugs should come about through manufacturers' efforts to better inform physicians about the risks and proper use of their products. Presumptively, physicians will both read and carefully heed the labeling information,[83] and in prescribing a drug they will explain its indications, risks, and proper administration so that the patient can informedly consent to its use. "In practical concept," Rheingold wrote, "a sort of 'Norman Rockwell' practice of medicine was envisioned by [the learned intermediary] decisions—the ignorant, reliant patient, sitting in the presence of the all-knowing doctor."[84]

Erosions of the Learned Intermediary Doctrine

Since the mid-1970s, however, several social currents have been eroding the learned intermediary doctrine and strengthening the position that patients, too, should have access to intelligible information about the

81. *Sterling Drug Inc.* v. *Cornish,* 370 F.2d 82 (8th Cir. 1966). For citations to and discussions of other cases upholding the learned intermediary doctrine, see Brushwood and Simonsmeier 1986; Grant 1988; Rheingold 1964 and 1985.

82. Shulman 1989, 1566.

83. If the labeling is adequate but has not been read or not been heeded by physician before she or he issues a prescription, the physician's failure to follow adequate instructions constitutes misuse that under product liability law, bars a plaintiff's recovery. See Grant 1988. See chapter 7 in this book for a discussion of the relation between malpractice and product liability. As Tancredi and Nelkin suggest, one reason that physicians seldom seem to be defendants in prescription drug product liability cases may be that limitations on malpractice awards in many jurisdictions shift litigation to the "deep pockets" of industry.

84. Rheingold 1985, 136.

safety, effectiveness, and proper use of their prescribed medications. Developments favoring more patient- or consumer-oriented drug information have included a number of court decisions holding, on a case-by-case basis, that there are exceptions to the learned intermediary rule, and some regulatory rulemaking and trends more favorable toward the provision of labeling information to patients. These legal and regulatory moves have been fostered by congressional support for patient or consumer-directed information, questions and concerns about the extent to which physicians approximate the ethical and legal standards for informed, voluntary consent to treatment when they prescribe or administer prescription drugs, and the increasingly active and influential consumer rights movement in the United States. The growing support for and availability of multisource rather than physician-based single-source information, in turn, raises a number of product liability questions, including the viability of the common law position that the pharmaceutical manufacturer's duty to warn is owed only to the physician.

MANDATED EXCEPTIONS. Judicial and regulatory exceptions to the learned intermediary rule have been made for two main categories of prescription products. The first is vaccines used for mass immunizations, which may be dispensed in a setting where no physician provides an individualized balancing and communication of the risks and benefits.[85] The second category includes oral contraceptives, estrogen products, progestational drugs, and intrauterine devices. According to FDA rulemaking and several court cases, the rationales for exempting such products from the learned intermediary rule are that they are used electively by large numbers of healthy women, they are potentially dangerous, and they are prescribed "with no assurance that the users [are] being adequately warned about their dangers."[86]

In 1975 the FDA issued a notice of proposed rulemaking about extending its patient package insert (PPI) program, and then in 1979 issued proposed regulations to require PPIs for all nonelectively used prescription drugs.[87] The history of the proposed PPI program, especially the

85. McGarey 1984, 131.

86. McGarey 1984, 132.

87. The proposed regulations (44 *Federal Register* 40016 [1979]) were based on several considerations. These included studies of the effectiveness of the FDA's four mandated PPIs, a review of the literature on consumer information for prescription drugs, awareness that restricting information solely to physicians did not encourage the safe use of prescription drugs, and a growing political recognition of the consumer rights movement. On the history of the PPI program, see Dorsey 1977; McGarey 1984.

roles played by consumer groups, the medical profession, the pharmaceutical industry, Congress, and the Reagan administration, is a fascinating and instructive sociopolitical study in its own right. Officially, the agency's plans and preparations for instituting a comprehensive program of consumer- or patient-directed information ended in 1982, when final regulations that had been promulgated but not yet implemented were withdrawn as part of the administration's deregulatory thrust.[88]

VOLUNTARY PATIENT EDUCATION AND CONSUMER INFORMATION. For both political and budgetary reasons, it seems unlikely that any type of federally required patient information program will be resurrected. But in the judgment of an FDA official closely involved with the PPI initiative, the "original goal in proposing the program has worked, because a great deal of prescription drug information for patients is now available through many publications and other resources."[89] The 1980s indeed saw a profusion of written and audiovisual materials providing general and specific information about prescription drugs, issued by government agencies, health professional and consumer groups, and industry.[90]

Consumer-directed information about prescription drugs is not intended to *replace* the physician's role in making prescription decisions and discussing them with patients. Rather, its intent is to help remedy long-recognized deficits in the prescribing process and in the use of drugs. The "broader message" of the experience with a drug like Accutane is the need for physicians to give, and patients to receive from their doctor or other sources, better information to help them understand the risks, benefits, and proper use of prescription agents and what steps to take when they experience side effects.[91] The extent to which prescription drug information written for laypersons will accomplish the goals of a multisource rather than single-source drug information system remains to be seen. Studies of PPIs and other printed materials show they can be effective learning tools, especially if used in concert with verbal information or counseling from a health professional.[92] However, their long-

88. Notice of the program's cancellation was published in 47 *Federal Register* 39148 (1982). In December 1982 the FDA was directed by the assistant secretary for health to form a Committee on Patient Education (COPE), to coordinate efforts to educate consumers about prescription drugs and to encourage private sector efforts.

89. Personal interview, Feb. 21, 1990.

90. National Council on Patient Education (n.d.)

91. Shulman 1989.

92. See, for example, Johnson and others 1986; Regner, Herman, and Reid 1987; Sands, Robinson, and Orlando 1984.

term effects on knowledge and actual drug usage, and the degree to which they improve doctor-patient interactions dealing with prescribing, are uncertain.[93]

The bearing of product liability law on consumer-oriented information provided by a pharmaceutical manufacturer is equally uncertain at this juncture. McGarey pointed out in 1984 that "the most serious inadequacy of the case-by-case approach to the single-source [learned intermediary] problem is that it fails to provide a method for improving the safety of prescription drug use."[94] If a prediction made in 1985 by no less an authority than Paul Rheingold proves accurate, however, liability decisions may well be making the learned intermediary an endangered species, at least under product liability law. Rheingold's prediction was that "cases will continue to appear creating what the courts regard as exceptions to the black letter rule [the learned intermediary doctrine]. . . . After that . . . the exceptions will swallow the rule . . . [and] manufacturers will be placed under a general duty to warn the public directly, and that exceptions will relate to those few occasions when such a warning is not due."[95]

At present, product liability concerns seem to be hindering the pharmaceutical industry's voluntary efforts to provide patient-directed information about prescription drugs. Unless required by administrative rulemaking or the courts, manufacturers have no affirmative duty to provide labeling information written for patients, and no regulatory sanctions or product liability is imposed if they do not provide it. Some manufacturers are reluctant to develop prescription drug information for patients because their product liability attorneys fear that any such materials, in lieu of the physician package insert, greatly increase a company's risk of liability. Those manufacturers who have ventured into the patient education arena, in turn, recognize the wisdom of having their literature reviewed and approved by the FDA, which defines it as promotional labeling. And because of concerns about potential liability, companies are extremely conscious of the content and precise wording of patient information materials about specific prescription drugs. In my experience, such concerns can help to ensure the accuracy of the information that is conveyed. But fears of liability can also clutter patient information materials with boilerplate statements and impede the presentation of certain

93. As Tietz (1986) points out, there have been remarkably few informed consent suits involving prescription drugs.

94. McGarey 1984, 139.

95. Rheingold 1985, 144.

types of useful information.[96] One hedge against liability used by industry is to distribute patient-oriented material to the physician, who in turn provides it to his or her patient as part of the prescribing process. But in the opinion of several attorneys, including litigation specialists for industry, there is a question whether a learned intermediary defense would hold up in court in a case involving information written for patients, because the physician could be viewed as just a "pass through" or conduit.[97]

DIRECT-TO-CONSUMER ADVERTISING. Besides industry-sponsored patient information programs, the 1980s saw the beginnings of a more controversial venture by pharmaceutical manufacturers: drug advertising directed to the lay consumer rather than to the physician prescriber and pharmacist dispenser. Beginning with mass media ads for soft contact lenses in 1978, and then advertising campaigns for several prescription drugs in the early 1980s, the industry began to "test the waters" to see if direct-to-the-consumer promotion would be an effective marketing strategy to help them meet "changing market conditions."[98]

Direct-to-consumer advertising promises to be a continuing source of controversy during the 1990s. Opinions differ, often sharply, within and between industry, health professionals, laypersons and consumer organizations, the FDA, and attorneys about the ethical propriety and economic costs and gains of such advertising, its effects on patients and physicians and their interactions, and its product liability implications.

The FDA was given statutory authority in 1963 to regulate prescription drug advertising. These regulations have never prohibited industry from advertising specific prescription drugs to the public once they have received an NDA marketing approval as long as promotional materials include the same "brief summary" labeling information required for

96. This statement is based on my experience preparing prescription drug informational materials for patients for a pharmaceutical company.

97. Personal interviews.

98. Discussing direct-to-consumer advertising at a conference in 1983, Felton Davis, Jr., senior vice president of Government and Public Affairs for Ciba Geigy, stated: "A host of marketing conditions have required a rethinking of our approach. Because the time of patent protection on prescription products has shortened considerably over the last years, market penetration has become even more important. Also, increased restrictions are being placed on prescribers and dispensers, so we thought that we might have a new market by advertising directly to patients. The requirement that we deal only with physicians caused the industry a large problem, because no one knew anything about the industry as an industry. We have always been on the defensive, and we're still defending ourselves against charges. We have never been able to speak directly and positively to the public, and we hope to be able to do so now." Medicine in the Public Interest 1984, 42.

professional advertisements and do not mention an FDA "seal of approval."[99]

Nonetheless, some agency staff, among others, have been concerned about various implications of this marketing approach.[100] Proponents of prescription drug consumer advertising argue that it has an educational as well as a sales function: such ads can provide people with useful information that will make them more informed and compliant users of their medications. Opponents are equally convinced that such advertising will make people "yearn, not learn,"[101] and that industry and its supporters are simply being disingenuous when they argue educational merits. Those concerned about direct-to-consumer advertising worry that it will help "trivialize" prescription drugs, drive up their cost, pressure people to ask their physicians for drugs they do not need, undermine the physician-patient relationship, and confuse laypeople because of the inherent oversimplification in ad messages.[102]

Because it is a relatively new and evolving venture, the effects of consumer advertising on the industry's risks for product liability actions, and, conversely, the effects of liability on such advertising, remain speculative. In 1985 Rheingold predicted that litigation involving consumer advertising will be another area where "the courts may fashion an exception to the black letter [learned intermediary] rule because the drug company has reached out to the public deliberately."[103] He described two consumer advertising situations that might lead a manufacturer to be held liable. The first is when an affirmative representation has been made in an ad that is found to be negligently or intentionally misleading even if the package insert is accurate. Second, even if manufacturers "make no representations of safety in their public advertising . . . the very act, however, of promoting the drug to the public and creating a demand will probably be used by some courts to impose a duty on the supplier to issue warnings directly to the consumer. . . . The purpose of promotion

99. Two types of ads, whether geared for health professionals or laypersons, are not required to include the technical brief summary information: ads that present only price information, with no mention of what the product is used for, or how it is used; and what are termed "institutional ads" that discuss a particular medical condition such as arthritis or diabetes but do not mention a specific product.

100. In 1983 the FDA commissioner, Arthur Hayes, Jr., asked pharmaceutical companies to "observe a voluntary moratorium" on direct-to-consumer advertising other than price comparisons and institutional ads, while the FDA studied various issues such as effects on patient education and on the doctor-patient relationship. See Murphy 1984, 20.

101. Miller 1983.

102. Miller 1983.

103. Rheingold 1985, 139.

is but one, to create demand, and it will be reasoned that even though the doctor had to move his hand in order for the patient to get his drug, the drug supplier departed from his reclusive role of dealing with doctors only and therefore must suffer its own adverse consequences."[104]

Whether the prospect of the kinds of liability Rheingold envisioned will act as a brake on the volume of direct-to-consumer advertising, or moderate its tone and content, is an open question. Two knowledgeable attorneys whom I interviewed were not sanguine about such effects, given the counterforce of potential profits from consumer marketing. One attorney, formerly with the FDA, commented that direct-to-consumer advertising is increasing rapidly "and is one more example of the fact that pharmaceutical companies pay more attention to marketing than liability." Another attorney, working for a pharmaceutical company, had a similar opinion, believing that consumer advertising may increase liability risks for the industry but that "such risks will be balanced by the fact that advertising pays off from a marketing vantage point."[105]

Blind Men, Elephants, and the Safety of Prescription Drugs

In the familiar oriental fable, the blind men who feel different parts of an unknown object identify them as a rope, a spear, and so forth. Each was a fair inference from the "facts" they could discern, but these did not enable them to identify the object as an elephant. Assessing the effects of product liability on the safety of prescription drugs is analogous to the blind men's task, except that there are at least two elephants we are groping to recognize. One elephant can be called "safe" prescription drugs. For, as discussed earlier, what one means by safety in the context of these pharmaceutical products, and how it is assessed, are questions that may be answered very differently by pharmacologists, physicians, patients, manufacturers, regulators, judges, and juries. The second elephant has a more unwieldy name, "the effects of various social control agents—industry, the medical profession, patients and consumer groups, regulations, product liability law, and so forth—on the safety of prescription drugs." I am not ashamed to admit that I am like one of those legendary blind men with respect to both these elephants, because I know I am in some very good company. And having failed to identify the

104. Rheingold 1985, 141.
105. Personal interviews.

elephants with any great precision or clarity, I must make my final remarks comparably tentative.

Given the pharmacological and clinical evidence that there is no such thing as a 100 percent safe prescription (or other) drug, the question is how the risks of these unavoidably unsafe products can be contained and their *safer* (as opposed to perfectly safe) use be maximized. Measures to contain the risks and enhance the safest possible use of prescription drugs fall into two broad categories. First, as a drug is developed and tested and, if approved, marketed, many types of evidence and decisionmaking processes are involved in determining its risks and in balancing those risks against its clinical benefits. Second, given the available body of indeterminate knowledge about a drug's risks and benefits, how safely and effectively it is used depends partly on the caliber of the labeling information about its indicated uses, contraindications, risks, dosage and administration, and so on. However, while proper labeling information is necessary to safe and effective prescription drug use, it is not sufficient. For such information must be read and understood by physicians, factored into their prescribing decisions, and adequately conveyed to and comprehended by patients. And once a prescription is written, the medication must be dispensed properly and used "as directed" by the patient. There can be, in short, many a slip between the cup and the lip, and however excellent the whole process is, adverse reactions or "bad outcomes" will still occur.

More than 8,000 prescription drugs (including drug combinations) are marketed in the United States, and physicians write well over 2.3 billion inpatient and outpatient prescriptions each year. Given this huge volume in relation to the number of serious adverse reactions that are known or estimated to occur—some 60,000 "adverse events" associated with drugs and biologies are reported to the FDA annually—the United States seems, on balance, to do a credible job of dealing with the risks of these basically risky products.[106] But given the imperfections and fallibilities of people and the social organizations they invent and manage, the conclusion that we could do a better job of containing the risks and maximizing the safer use of prescription drugs should be self-evident.

106. Ackerman 1988; Faich, Dreis, and Tomita 1988; Myer 1988. Most analysts feel that ADRs are underreported, largely because of the failure of physicians to report adverse effects to a drug's manufacturer or the FDA, and their unawareness of the FDA reporting system. However, the fact that nearly 24 percent of the reports received are for "severe" reactions, involving death or hospitalization, led the FDA to believe they are being notified about "grave clinical outcomes." Faich, Dreis, and Tomita 1988, 786.

Physicians do not always live up to the Norman Rockwell image of the learned intermediary described by Rheingold: they are not omniscient about diseases and treatments, including clinical pharmacology; they usually do not do a very good job of communicating with their patients; and they do misprescribe. Patients, in turn, even if knowledgeable about their illnesses and medications, do not always heed the oral or written information they receive, follow their medication regimen, tell their doctor about other drugs they are taking, and report adverse reactions.

Pharmaceutical manufacturers and their regulators, the FDA, also could do a better job in dealing with prescription drug safety. Their deficiencies, and the many reasons for them, are engraved in legal cases, congressional hearings and reports, press accounts, and so forth. Manufacturers, for example, have been known to let economic benefits outweigh risks to patients in marketing decisions, to be negligently slow to issue warnings when new adverse reactions are identified, and to engage in fraudulent misrepresentation by deliberately withholding information about a drug's hazards from the FDA or physicians or both.[107] The FDA, in its turn, has been subject to recurrent criticisms about matters such as the quality of its staff, the timeliness and the competence of its premarketing and postmarketing reviews and actions, its failures to act on ADR information, and labeling requirements that sometimes stifle manufacturers' attempts to issue warnings. Some more recent regulatory issues, as mentioned, concern the effects of the agency's 1987 IND treatment provisions on safety and effectiveness assessments of new drugs, including potential sources of liability for treatment IND sponsors.[108]

Finally, I respond to the central question I was asked to address: to what extent have product liability doctrines, verdicts, and concerns promoted drug safety? Of all the questions a blind man might be asked about any part of the two elephants, that one seems hardest to answer. For, as repeatedly noted about prescription drug design and warnings, evidence, more weighty than single cases, anecdotes and opinions, and poorly designed surveys, is either nonexistent or not available. Moreover, as has also been stressed, it is exceedingly difficult to disentangle the effects of FDA regulations and product liability on drug safety, especially given the quality and quantity of information one has to work with.

From the sketchy and insubstantial information that is available, it seems reasonable to conclude that product liability law and litigation have

107. Rheingold 1964; Schwartz 1988b, 1148–49; Weisner and Walsh 1988.
108. See Herzog 1977; Grabowski and Vernon 1983; Schwartz 1988b, 1148–49.

had only a marginal effect on the development of safer drugs. Liability is one of many factors involved in decisions not to bring new agents to the market or to withdraw marketed drugs when their risks are judged to outweigh their benefits, and it does not seem to be a paramount consideration. Design defect cases have been much less common than warning defect cases involving prescription drugs. For with those products, one is dealing with nature's molecular structures or with variations devised by "tinkering" with nature. In this context, the type of "error" that an engineer might make in designing a new widget is not a particularly appropriate construct, nor are the more usual tort law notions of "design defects" as a cause of action.

Because of the inherently hazardous nature of prescription drugs, it seems reasonable to assume that product liability would have its greatest effect on the content and timeliness of information conveyed to physicians, and to patients, through the types of materials that the FDA defines as labeling. That law, verdicts, and fear of litigation involving warning defects have helped to foster more accurate and timely information about prescription drugs, and thus by inference their safer use, was the unanimous judgment of the several experts I interviewed, and it is the "received"—though slimly documented—"wisdom" found in the literature. However, liability fears seem to be impeding the provision of patient-directed educational materials about prescription drugs by manufacturers and, to date, having no discernible effect on direct-to-consumer advertising.

Although studies such as those by the GAO and Rand support the view that the pharmaceutical industry has not suffered a litigation explosion, manufacturers are cognizant of and worried about product liability issues. Those issues include the current and emerging content, objectives, and workings of state and federal tort laws in this country and, given the multinational structure of most pharmaceutical companies, developing international trends in product liability law and no-fault compensation for drug-induced injuries.[109]

When one considers the nature of prescription drugs, the scientific and value issues involved in determining the reasons for "bad outcomes," the multiple objectives of tort law, the variety of reasons that impel patients and their attorneys to litigate, and the frequently arcane reasoning and unpredictability of juries and judges, it is not surprising that one can cite product liability laws and verdicts that seem both "proper and improper"

109. For a concise review of these international trends, see Shulman and Lasagna 1990.

for prescription drugs and their manufacturers.[110] The industry is pressing vigorously for tort reforms and often cries out at the "wounds" it receives from the "strong sword" of product liability. At the same time, some of the strategies that companies are developing as "damage control" or "preventive medicine" efforts against liability show that they recognize they *can* take steps to further contain the risks and increase the safer use of their prescription products.[111]

110. The phrase "proper and improper" is used by Epstein in discussing one of the "downside" problems of product liability law with respect to warning defect litigation: "Modern common law creates a serious bias, intensified by the discretion left to juries, toward finding all warnings inadequate when judged by the standards of hindsight. On a selective basis, the theory of improper warnings becomes an elaborate, expensive, and erratic pretext for compensating for bad outcomes alone. As every skillful trial lawyer knows, the question of adequacy of warnings is a form of reverse engineering. First find out what warnings were given, and then tailor the claim on adequacy to render them insufficient." Epstein 1987, 172.

111. Examples of such efforts include the development of "product safety programs" and educational programs for pharmaceutical company employees, designed to teach them about product liability and how to minimize it by compliance with regulations, information flow within a company, communications with physicians and patients, and so forth. See Golden 1986.

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