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IMPROVING LITIGATION AGAINST DRUG MANUFACTURERS FOR FAILURE TO WARN AGAINST POSSIBLE SIDE EFFECTS: KEEPING DUBIOUS LAWSUITS FROM DRIVING GOOD DRUGS OFF THE MARKET

Howard A. Denemark*

Beneficial drugs, approved by the United States Food and Drug Administration, have been forced off the market by the current legal standards for imposing a duty on drug manufacturers to warn of adverse side effects from their drugs. Expert evidence that would not withstand scrutiny from scientific and medical peers is being used to hold drug manufacturers liable for failure to warn of potential side effects. This Article presents an approach to establishing a legal duty to warn that offers a superior resolution of the tension between concern for the existence or entry of unsafe drugs in the marketplace and concern for the loss of safe and beneficial drugs therefrom.

IN THE EARLY 1980's, a woman who complained to her doctor about morning sickness would very likely have received a prescription for the drug Bendectin.1 Bendectin was approved for this use by the United States Food and Drug Administration ("FDA")

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and remains an approved drug in our national pharmacopoeia. Today, a woman who complains to her doctor about morning sickness will not receive a prescription for Bendectin because no manufacturer makes the drug. Despite overwhelming scientific evidence that Bendectin is safe for both the mother and the unborn child, more than a thousand parents of babies with birth defects have sued Bendectin's manufacturer, making sale of the drug unprofitable. In this way, the American public has been deprived of a safe, beneficial, FDA-approved drug.

Paradoxically, therapeutic drugs are one of the most highly regulated products sold to the American public. Before any prescription or over-the-counter drug is allowed to reach the consumer, the FDA must first approve it as safe and effective. The FDA approves drugs for use after first reviewing the results of chemical and animal studies, and secondly, clinical studies on a limited number of patients. Although pre-market testing may prove the efficacy of a drug, such testing cannot prove with certainty that a drug is safe. Nonetheless, after perhaps a decade of testing a new drug, the FDA considers whether the overall health of the American public would be improved or harmed by its admission into the national pharmacopoeia.

After the experts of the FDA allow the use of a drug based upon an analysis of the total scientific knowledge they have amassed, users who believe they sustained injuries from a drug's side effects may sue the manufacturer for damages, alleging that the manufacturer did not issue adequate warnings about a possi-

2. Richardson, 857 F.2d at 824 (the FDA first approved Bendectin in 1956 and the approval has never been rescinded).


4. See, e.g., United States v. Jamieson-McKames Pharmaceuticals, 651 F.2d 532, 537 (8th Cir. 1981) (drug industry characterized as a "pervasively regulated business").

5. No new drug may be approved for use absent "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use." Food, Drug & Cosmetic Act, 21 U.S.C. § 355(b)(1) (1988)


8. Id.

ble side effect. Drug product liability lawsuits have resulted in large verdicts, particularly when, as with Bendectin, the plaintiff is a child who claims that a drug his mother used during pregnancy caused congenital birth defects.

High damage awards exert a regulatory effect on drug manufacturers. Potential liability can drive drug companies to withdraw products from the market, and discourage research into new drugs used by individuals likely to sue and receive large damage awards. Thus, the FDA's decision that a drug is safe, effective, and more beneficial than harmful can be nullified by the regulatory effect of private tort actions.

Some commentators have suggested that an FDA determination allowing the sale of a drug should preempt private suits. Most courts, however, deem the FDA's determination simply to be part of the evidence that a trier of fact may consider in reaching a judgment on liability. This article will explore the basic contours of FDA and common-law drug regulation. It will suggest a judicial approach to drug lawsuits that may help prevent private litigants from chasing FDA-approved products off the market, while preserving the right to sue when companies act contrary to the public good.

I. FDA Regulation of Drugs

Prior to January 1, 1907, when the Pure Food and Drug Act

10. See generally Annotation, Liability of Manufacturer or Seller for Injury or Death Allegedly Caused by Failure to Warn Regarding Danger in Use of Vaccine or Prescription Drug, 94 A.L.R. 3d 748 (1979) (summarizing and classifying cases where failure to warn alleged).
11. See infra notes 96-97 and accompanying text.
12. See infra notes 82-100 and accompanying text.
13. Huber, Safety and the Second Best: The Hazards of Public Risk Management in the Courts, 85 COLUM. L. REV. 277, 288-90 (1985); Ackerman, supra note 7, at 16; see infra notes 82-100 and accompanying text.
14. Walsh & Klein, supra note 9, at 193; see also Huber, supra note 13, at 334-35 (arguing that the courts should respect the determinations of expert licensing agencies); Comment, Federal Preemption of Prescription Drug Labelling: Antidote for Pharmaceutical Industry Overdosing on State court Jury Decisions in Products Liability Cases, 22 J. MARSHALL L. REV. 629 (1989) [hereinafter Comment, Prescription Drug Labelling] (arguing that the supremacy clause and the relative expertise of agencies as compared to jurors dictates that FDA determinations should preempt state court suits).
15. See, e.g., Hurley v. Lederle Laboratories Div. of American Cyanamid Co, 863 F.2d 1173, 1176-78 (5th Cir. 1988) (FDA approval does not preempt civil suits but is admissible as evidence); id. at 1176 n.2 (listing other cases).
became law, medicines sold in America were regulated by the common law. While Upton Sinclair's book, *The Jungle*, was convincing legislators and the American public that the meat packing industry was selling unhealthy products, a young journalist named Samuel Hopkins Adams was publishing fiery articles in popular magazines about the dirty business of patent medicines. Adams' writings record an era when "doctors" of dubious credentials promoted secret formula potions guaranteed to cure cancer, paralysis, opiate addiction, or, sometimes, every human affliction from colds to impotence. Particularly common were supposed cures for tuberculosis, a debilitating, highly communicable lung disease which causes its victims to waste away and die. In fact, the supposed cures were powerless, and no effective drug treatment for tuberculosis existed before 1944, when streptomycin was introduced.

The common law, and indeed, the common sense of the American public, did little to inhibit the commercial success of the ineffective, but lavishly promoted, medicines. Quacks not only sold medicines that were worthless as therapeutic agents and falsely advertised them, but they also sold some that were actually harmful to the unfortunate customers who took them. In part because of the success in focusing public attention on the dangerous dishonesty in the patent medicine business, new laws were enacted to protect a credulous public from unscrupulous purveyors of patent medicines.
Today, no medicine may be sold to the American public until it is proved both safe and effective.\textsuperscript{25} The proponent must prove, by "substantial evidence," the effectiveness of a drug to achieve the ends stated in its proposed labeling.\textsuperscript{26} The FDA can reject drug applications based on testing insufficiently rigorous to satisfy its scientists that the proponent's claims of efficacy are proved.\textsuperscript{27}

Unlike the substantial evidence standard for efficacy, the Food, Drug, and Cosmetic Act does not specify a standard by which drug safety is to be proved. Safety cannot be demonstrated in the same positive way as efficacy, since the use of a drug may cause long-delayed or unexpected side effects that current scientific knowledge cannot predict or detect.\textsuperscript{28} But side effects of some sort are common and expected.\textsuperscript{29} The FDA decides whether to approve a drug after it evaluates drug safety by balancing known risks against potential benefits, considering the seriousness of known side effects, the nature of the disease or condition being treated, and the availability of other treatment options.\textsuperscript{30}

The burden of proving the worth of a drug to the FDA falls on the applicant,\textsuperscript{31} typically the company with commercial rights to the drug. The company generally performs research to support the application, commissions the work at outside laboratories, or tries to interest university researchers in conducting the needed research. A great deal of money might be made if a new drug is approved, but losses in the form of unrecouped research and development expenses are likely if approval is withheld. The partisan drug company presents a drug application with research supporting claims of efficacy and safety. Lawyers play a significant role in the application process, though mostly by preparing the scientific personnel to defend their applications rather than by direct advocacy.\textsuperscript{32}

\begin{thebibliography}{9}
\bibitem{26} Id. § 355(d)(5) (1988).
\bibitem{27} See, e.g., Ubiotica v. FDA, 427 F.2d 376, 378 (6th Cir. 1970) (upholding the FDA's right to reject plaintiff's drug application for failure to prove safety and efficacy).
\bibitem{28} For example, Diethylstilbestrol ("DES"), a drug used routinely in the 1950's and 1960's to prevent miscarriages, was discovered to have caused tumors in the daughters of the women using the drug some 15 years after its use. Ackerman, supra note 7, at 13.
\bibitem{29} See infra text accompanying note 43.
\bibitem{32} Lavelle, Lawyers for New Drugs Must Practice Patience, Nat'l L. J., Jun. 27,
The FDA employs a professional staff of scientists who are capable of evaluating the research that underlies an application. The agency supplements its in-house expertise by empaneling advisory committees of experts who help evaluate drug safety and efficacy in their particular areas of expertise. The reliability of United States drug-approval procedures is illustrated by the fact that some countries approve drugs for use by their citizens based on FDA approval alone.

Testing a drug before it is marketed is not a perfect tool. Testing in animals will not always raise a suspicion of an adverse effect in humans, particularly as to whether a drug is a teratogen, that is, a drug that, when administered to a pregnant woman, can cause a birth defect in a child born to her. For example, the powerful human teratogen Thalidomide, a sedative that can cause birth defects if a pregnant woman takes even a single dose at the wrong stage of pregnancy, was tested extensively and did not reveal its teratogenicity. Conversely, there is scientific support for the generalization that any agent will be teratogenic at some dose level in some species when introduced at the proper stage of fetal development. As to human pre-market testing, an article in a recent FDA Bulletin acknowledged its inherent limits:

Even the most extensive pre-market testing can never cover all possible circumstances. Testing perhaps 3,000 people over a period of months or even a few years won't always identify a rare reaction unfolding over a long time, or affecting perhaps just one person in 10,000. Furthermore, drugs are rarely tested in such potentially vulnerable groups as the elderly, and never among pregnant women. Consequently, not every reaction can be foreseen for the entire population . . .

Given the limits of pre-market testing, it is not surprising

1988, at 20, col. 4.
34. Ackerman, supra note 7, at 16.
38. Ackerman, supra note 7, at 13.
that the FDA monitors doctors’ reports of drug side effects. The FDA Drug Bulletin, a circular sent to licensed physicians in the United States, includes a form for reporting suspected adverse drug reactions to the FDA. Reporting is optional for doctors but mandatory for drug manufacturers. The FDA receives thousands of Adverse Drug Reaction Reports annually, and is acting to encourage more health professionals to submit reports. If adverse reaction reports or other developments raise a suspicion that a drug is unsafe, the FDA has the power to withdraw that drug from the market.

In addition to rejecting any drug not shown sufficiently safe and effective, the FDA also controls the contents of package inserts and warning labels, ruling on whether enough reliable evidence exists to issue a warning about a suspected side effect.

II. DRUG SIDE-EFFECT LITIGATION

A. The Nature of Liability for Drug Side Effects

American jurisprudence has come to accept that drugs are not magic potions that do only what they are intended and nothing else. As one physician told a subcommittee of the House of Representatives:

Practically every useful drug carries with its administration the danger of one or more side effects. Essentially, the physician realizes that every time he prescribes a drug he takes a calculated risk, hoping that the beneficial effects of the preparation will outweigh any possible side effect. In this respect a drug has been aptly compared to a two-edged sword. The physician always hopes that the therapeutic edge will be sharp, while the side-effect edge will be dull. Unfortunately, the reverse sometimes takes place . . .

Accordingly, the law recognizes that a drug, even when properly

40. See Ackerman, supra note 7, at 13-15.
42. The FDA’s authority to control drug warnings is not absolute. Agency rules allow a drug manufacturer that is aware of some hazardous side effect to insert a warning without FDA approval. 21 C.F.R. § 201.57(e) (1989). One commentator, however, has suggested that the drug companies are not able to make use of this provision in light of their ongoing dependence on the FDA’s good will. Cooper, Drug Labeling and Products Liability: The Role of the Food and Drug Administration, 41 FOOD DRUG COSM. L.J. 233, 236 (1986).
designed, manufactured, and administered, may cause side effects. The Restatement (Second) of Torts holds that, although one in the business of selling dangerous products should be liable for harms the products cause to consumers despite the seller's exercise of "all possible care," such liability should not be imposed on sellers of "unavoidably unsafe" products. "Unavoidably unsafe" products include those "which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use." Thus, the common law does not require that drug manufacturers perform the impossible task of marketing only products having no side effects, but rather, the law requires that drug manufacturers issue a warning of the risks particular to a given drug.

In the case of over-the-counter drugs, the warnings must be available directly to the purchaser of the product in the packaging materials or on the container itself. For most prescription drugs, the warning need only be given to the physician rather than the patient. The ultimate consumer of prescription drugs cannot lawfully buy the drug without a doctor's prescription. The consumer goes to a doctor who may prescribe a drug as one aspect of providing health care. Thus, in general, it is not the consumer's desire that brings about a purchase, but the doctor's expert advice. Inherent in the doctor's choice of a drug is a balancing of risks and benefits that doctors are trained to understand in a context of the patient's individual health needs. Some courts have recognized that doctors stand between drug vendors and consumers, controlling access to drugs, and have ruled that drug warnings issued to doctors discharge the manufacturer's duty to warn about harmful side effects. However, some drugs, although dispensed

44. The Supreme Court of the United States recognized this fact in United States v. Rutherford, 442 U.S. 544, 555 (1979) ("Few if any drugs are completely safe in the sense that they may be taken by all persons in all circumstances without risk.").
45. Restatement (Second) of Torts § 402A & comment k (1965).
46. Id. § 402A comment k (1965).
47. Id.
49. Brushwood & Simonsmeier, Drug Information for Patients: Duties of the Manufacturer, Pharmacist, Physician, and Hospital, 7 J. of Legal Med. 279, 286 (1986).
50. See, e.g., Stevens v. Parke, Davis & Company, 9 Cal. 3d 51, 65, 507 P.2d 653, 661, 107 Cal. Rptr. 45, 53 (1973) ("In the case of medical prescriptions, "if adequate warning of potential dangers of a drug has been given to doctors, there is no duty by the drug manufacturer to insure that the warning reaches the doctor's patient . . . "). There is an exception to this rule that reinstates the duty of drug manufacturers to insure that the
by prescription, involve little individual consideration by the prescribing doctor. For example, birth control pills are often dispensed to women at their request as a means of contraception rather than being prescribed as a therapeutic drug. In such a circumstance, some courts have extended the duty to warn to include directly informing the user of the drug.

The failure to issue an appropriate warning, whether to the consumer or the community of physicians, is a necessary focus of a product suit against a drug manufacturer. A manufacturer that issues a warning to the appropriate party, adequately setting forth the danger of side effects, enjoys protection from suits alleging that the drug caused those side effects. Suit may be brought under the rubric of negligence, breach of a duty to warn, breach of warranty, or strict liability, alleging a failure to include a warning adequate to make the product safe, but a suit brought under any of these theories necessarily turns on precisely the same issue: Whether the manufacturer issued an adequate warning about the possible harmful side effects of a given drug.

A failure to warn becomes actionable only if the drug manufacturer knew or should have known of the side effect in question. *Griggs v. Combe, Inc.* illustrates this point. In *Griggs*, the Supreme Court of Alabama answered a certified question posed by sympathetic patients that drug warnings are often disregarded.

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52. See, e.g., *id.* (manufacturer of oral contraceptive found liable for failing to directly warn user of potential side effects).

53. Felix v. Hoffmann-LaRoche, 540 So. 2d 102, 105 (Fla. 1989) (manufacturer of drug Acutane not liable for birth defects suffered by user's child since warning provided by manufacturer was adequate to convey to physicians the dangers of the drug to pregnant women); Serna v. Roche Laboratories, 101 N.M. 522, 524, 684 P.2d 1187, 1189 (1984) (drug manufacturer not liable when user suffering side effects presents no evidence of inadequate manufacturer warnings); Eiser v. Feldman, 123 A.D.2d 583, 583-84, 507 N.Y.S.2d 386, 387-88 (N.Y. App. Div. 1986) (oral contraceptive manufacturer not liable for visual impairment suffered by user since manufacturer provided express warnings to physicians and patients in package insert).

54. E.g., *Griggs v. Coombe, Inc.*, 456 So. 2d 790, 791-93 ( Ala. 1984) (discussing possible theories of recovery for injuries due to drug side effects); see *Werner v. Upjohn Co.*, 628 F.2d 848, 858 (4th Cir. 1980), cert. denied, 449 U.S. 1080 (1981) (stating "the issue under either theory [negligence or strict liability] is essentially the same: was the warning adequate?"). *But see* Hamilton v. Hardy, 549 P.2d 1099, 1106 (Colo. Ct. App. 1976) ("Although we agree the evidence which proves a failure to warn is the same under both theories, we disagree that the theories are identical.").

55. 456 So. 2d 790 (Ala. 1984).
the United States Court of Appeals for the Eleventh Circuit, asking whether any theory available under Alabama law allowed recovery by a user of an over-the-counter topical analgesic for failure to warn, where the manufacturer neither knew nor should have known that the active ingredient was capable of producing a strong adverse reaction. The active ingredient, benzocaine, had been in use as a topical treatment since 1903 and the plaintiff's serious adverse reaction to the drug was apparently the first reported incident.

The Supreme Court of Alabama held that no legal theory, including "negligence, strict product liability, breach of implied warranty of merchantability, or duty to warn" justified a recovery. Benzocaine caused a condition in the plaintiff known as "Stevens-Johnson Syndrome." In severe cases, Stevens-Johnson Syndrome can be fatal. The Court refused to declare the product "defective" or "unreasonably dangerous," as is required for a plaintiff's verdict under Alabama product liability doctrines, because the danger could not be known through human foresight. Similarly, since the manufacturer lacked foreknowledge that this type of injury could result, it was not negligent to omit a warning. In deciding a similar suit based only upon the theory of negligent failure to warn, the Missouri Court of Appeals summed up the law with great precision: "If [an adverse drug] reaction had never occurred before, [the drug manufacturer] could not know about it or in the exercise of the required degree of care, could not have found out about it, and absent knowledge of such reaction, there could be no duty to warn."

Similarly, where the manufacturer knows of a possible side effect and issues an adequate warning, an action against the man-

56. Id. at 791.
57. Id. at 791-92.
58. Id. at 791.
59. Id.
61. Griggs, 456 So. 2d at 792.
62. Id.
63. Johnston v. Upjohn Co., 442 S.W.2d 93, 97 (Mo. Ct. App. 1969) (citation omitted). In Johnston, the court held that plaintiff did not make a sufficient case against a drug manufacturer for failure to warn because the manufacturer had neither knowledge nor the means of knowing that the plaintiff might suffer a severe reaction to a particular antibiotic. The plaintiff's reaction was the first reported instance of a serious side effect from use of the drug. Id. at 95.
manufacturer will not lie. Summary judgment dismissing claims against a manufacturer should be granted where the court can find, as a matter of law, that the manufacturer warned in clear language about the risks of suffering the harm later claimed by the plaintiff. Thus, issuing an adequate warning gives manufacturers a strong defense to side-effect litigation.

B. The Role of Expert Testimony

The issue of whether a given drug caused the physical problem from which a plaintiff suffers is an element of proof in any side-effect litigation. This element is not satisfied merely by showing that an individual used a drug and later suffered ill health, or in the case of a teratogen, gave birth to a damaged baby. Courts have held that "[w]ithout more, [a] proximate temporal relationship will not support a finding of causation." The "more" is inevitably provided by medical or scientific expert witnesses who testify that there is reasonable medical or scientific certainty that


66. One jurisdiction has particularized adequacy as follows:

1. the warning must adequately indicate the scope of the danger; 2. the warning must reasonably communicate the extent or seriousness of the harm that could result from misuse of the drug; 3. the physical aspects of the warning must be adequate to alert a reasonably prudent person to the danger; 4. a simple directive warning may be inadequate when it fails to indicate the consequences that might result from failure to follow it and . . . ; 5. the means to convey the warning must be adequate.

Serna, 101 N.M. at 524, 684 P.2d at 1189 (citing Richards v. Upjohn Co., 95 N.M. 675, 679, 625 P.2d 1192, 1196 (N.M. Ct. App. 1980)). Similarly, the Supreme Court of Florida has held that it can dismiss a suit as a matter of law if a "warning is accurate, clear, and unambiguous." Felix, 540 So. 2d at 105.


68. Hasler, 718 F.2d at 205.
the drug caused the damage. Naturally, the plaintiffs' will seek out experts whose views support a finding that the drug caused the damage, and the defendants will counter with experts who reach the opposite conclusion.

Normally, expert testimony is accepted as admissible. For example, the Federal Rules of Evidence favor the admission of expert testimony when proffered. The intent of Federal Rule of Evidence 702 itself and the advisory committee note to the rule, is to allow for the liberal admission of expert testimony.69

There is a growing concern in both the legal and scientific communities, however, that the selection of experts for trial may not be a benign process of finding a legitimate doctor or scientist whose opinions most closely parallel the desired proof.70 Rather, the supposed experts may be individuals whose views are well outside the mainstream of their disciplines, or worse, "experts" who tailor their testimony with little concern for accuracy, for the benefit of the parties that retain them.71

Dr. Robert Brent, a teratologist who has served on occasion as an expert witness, believes that scientific experts are tempted to give unreliable testimony not only for money, but for the ego gratification of being the respected center of attention.72 Dr. Brent maintains that experts are willing to express opinions in the courtroom they would not air in a scientific forum.73 Testimony given in court is unlikely to find its way back into the scientific community, where careless, unprofessionally biased, or false statements would damage an expert's professional reputation.74 Indeed, Dr. Brent suggests that experts would be more responsible if depo-

69. Fed. R. Evid. 702 & advisory committee's note; see also Habecker v. Copperloy Corp., 893 F.2d 49, 51 (3rd Cir. 1990) (case law, in addition to the rule and the advisory committee supporting the liberal admission of expert testimony).
71. See Brent, supra note 70, at 755.
72. Id. at 760.
73. See id. at 755.
74. See id. at 761. For a recent example of the backlash that can follow the announcement of inadequately supported findings in the scientific community, see Broad, 'Cold Fusion' Claimants Review Puzzling Results, N.Y. Times, Apr. 3, 1990, at C8, col. 2.
tion and trial testimony were exposed to peer review. This reform has not been implemented, and there remains a belief that one can find an "expert" to support any proposition, no matter how contrary to the truth. Courts are not bound to accept all expert evidence the parties proffer. Even the testimony of expert witnesses with appropriate credentials may be rejected as unpersuasive if the court determines that their opinions are not based on appropriate foundations. For example, at least three courts have found unpersuasive the testimony by Dr. Alan K. Done, a physician who is among a minority of scientific voices proclaiming that the drug Bendectin causes human birth defects. At a time when the vast majority of scientific opinion held that the drug is entirely safe for the fetus when taken by the mother, Dr. Done was prepared to testify on behalf of parents of damaged babies that Bendectin caused the harm, citing studies that birth defects in some animals can be induced by doses of Bendectin. Epidemiological studies on humans — statistical analyses of the incidence of human maladies with a goal of identifying their causes — have failed to reveal a teratogenic hazard from Bendectin. While the overwhelming majority of teratologists and medical experts are convinced that this evidence refutes the earlier animal studies, Dr. Done apparently remains unconvinced.

As noted earlier, the testimony of experts is liberally admitted. Thus, while not impossible, it currently is very difficult to convince a court to exclude the proffered testimony of an individual who has adequate scientific credentials and offers to testify about the results of tests which, like animal studies, are accepted

75. Id. Dr. Brent's proposed remedy also includes better education of experts as to their roles in litigation, as well as other steps toward enforcing greater responsibility; see also Milunsky, supra note 70, at 2, (arguing for certification of expertise by committees of scholars in the relevant fields).
78. Richardson, 649 F. Supp. at 801.
80. Richardson, 649 F. Supp. at 802.
81. See supra text accompanying note 69.
C. Incentives and Results of Tort Suits

Suits alleging that a drug caused birth defects have the potential to generate a multi-million dollar verdict for even a single, bench-tried case. For example, in Wells v. Ortho Pharmaceutical Corp., a federal district judge awarded over five million dollars to a mother and child where the child was alleged to have suffered multiple birth defects from her mother's use of a contraceptive spermicidal jelly.

When the damage awards are high enough, tort suits regulate business decision-making. Perhaps the most dramatic example of the regulatory power of tort actions is litigation over the drug Bendectin. Although morning sickness is often a non-acute condition, in severe cases, it can cause starvation, ketosis, dehydration, and metabolic disturbances that can force a choice between abortion to prevent irreversible metabolic damage and maternal death. Thus, Bendectin is a drug that can make the burden of pregnancy lighter and in some cases, safer.

There is a broad consensus in the medical community that Bendectin does not cause birth defects. Indeed, of all drugs about which birth defect research has been done, "Bendectin stands in its own place as the agent about which there is the greatest degree of certainty on its safety." Notwithstanding the overwhelming medical opinion that Bendectin is a safe drug, lawsuits brought by parents of children with birth defects are legion. Mounting a defense can be prohibitively expensive, and in 1983, Merrell Dow, the manufacturer of Bendectin, withdrew the drug from the market. A Merrell Dow spokesman recently explained that the company "find[s] that marketing products for use

83. Id. at 296-98.
84. See supra note 1.
86. See id.; Shepard, supra note 79, at 255.
87. Shepard, supra note 79, at 255.
88. See Richardson, 857 F.2d at 824. (Over 1500 Bendectin lawsuits were consolidated with the Richardson case for pretrial proceedings in the Southern District of Ohio).
89. Ross, supra note 3, at A19, col. 2.
during pregnancy is just an invitation to litigation.”

The “invitation to litigation” was widely distributed in the case of Bendectin. In 1979 alone, the drug was prescribed to one million new users. Doctors estimate that the background rate of major congenital malformations, that is, the percent of children born with a major malformation not attributed to a particular cause, is two to five percent. Thus, of the million women who took Bendectin during 1979 to combat morning sickness during pregnancy, approximately 20,000 to 50,000 could be expected to bear a child suffering from birth defects even if Bendectin does nothing to increase the likelihood of a defect. Since a chemically-induced defect may be indiscernible from a defect of genetic or unknown cause, a drug company faces the seemingly inevitable prospect of defending against a multitude of claims for defects its product did not cause. A drug manufacturer undertakes a substantial risk in such litigation, since “[t]he sight of a helpless mutilated youngster may evoke emotion along with the corresponding wish to make somebody pay for his or her plight . . . [so] the presence of handicapped youngsters could render a jury ‘unable to arrive at an unbiased judgment.’ ”

A plaintiff’s emotional advantage in birth defect litigation undoubtedly contributes to high damage awards. For example, in 1987, when even though an overwhelming medical consensus supported Bendectin’s safety to the unborn, a jury assessed $20 million compensatory and $75 million punitive damages in a single

90. _Id._ at A19, cols. 2-3.
91. _See_ _Lynch v. Merrell-National Laboratories_, 830 F.2d 1190, 1194 (1st Cir. 1987).
93. This analysis assumes the one million prescriptions were all for morning sickness and that the women for whom the drug was prescribed took it. The range of 20,000 to 50,000 birth defects is merely a rough estimate since it ignores miscarriages, multiple births, and any other confounding factors. Despite these inaccuracies, the estimate illustrates the magnitude of the threat of litigation a company faces when marketing a drug that may be used during pregnancy. Moreover, it was estimated in 1981 that over 30 million women had taken Bendectin. Kolata, _Jury Exonerates Bendectin in Mekdeci Case_, 212 _SCIENCE_ 647 (1981). This suggests that the number of potential plaintiffs worldwide is between 600,000 and 1.5 million persons.
94. _See_ _Ross, supra_ note 3, at A19, col. 6.
95. _Lynch_, 830 F.2d at 1196; (quoting _In re_ Richardson-Merrell, 624 F. Supp. 1212, 1224 (S.D. Ohio 1985) (“It is clear that the presence at trial . . . of children suffering form severe visible birth defects is inherently prejudicial.”)), _aff’d in part and vacated and remanded in part_, 857 F.2d 290 (6th Cir. 1988), _cert. denied_, 109 S. Ct. 788 (1989).
96. _Huber, supra_ note 13, at 323.
case brought on behalf of one child against the defendant manufacturer of Bendectin. Even though the typical award is much less, the knowledge that selling the drug may create 50,000 potential plaintiffs, even if using the drug does absolutely nothing to increase the probability of a birth defect, makes lawsuits a powerful disincentive to market a drug. One lesson of the Bendectin litigation is that these suits can drive a drug off the market, even when the scientific community pronounced it safe and doctors prescribed it to a million new users in 1979 alone.

The message manufacturers may receive from the filing of actions for failure to warn and the high damage awards may not be that they must respond to new information by issuing warnings, but that it is a mistake to sell drugs for use during pregnancy. Despite FDA approval of the drug Bendectin and its warning information, and a strong scientific consensus that it is not a teratogen, the regulatory power of private tort actions forced it from the market. Put another way, the FDA's decision that a drug should be added to the nation's pharmacopoeia was reversed by the economic force of lawsuits brought against the overwhelming weight of scientific evidence that Bendectin does not cause birth defects.

The same process that made Bendectin unavailable to women suffering from morning sickness can be brought to bear against other drugs. Plaintiffs' attorneys are alert to possible new drug suits and, after identifying an allegedly dangerous drug, have been known to seek clients by advertising for them. One result is a current concern that the threat of litigation based on ephemeral scientific evidence has reduced the contraceptive options available to Americans. This same process may remove other FDA-ap-

98. See Ross, supra note 3, at A19, cols. 2-3.
99. Beardsley, Drug not Guilty, Says Court, 314 NATURE 209 (1985) (discussing the fact that some attorneys continue to advertise for cases involving women who took Bendectin during pregnancy and gave birth to children with birth defects); Kolata, supra note 93, at 647 (same).
100. Isaacs & Holt, Drug Regulation, Product Liability, and the Contraceptive Crunch: Choices are Dwindling, 8 J. LEGAL MED. 533, 539 (1987); Rosenfield, Modern Contraception: a 1989 Update, 10 ANN. REV. OF PUB. HEALTH 385, 394, 398 (1989); see also A No-Choice Policy on Birth Control, U.S. NEWS & WORLD REP., Feb. 26, 1990 at 14, 15 (suggesting that the reduction from nine U.S. corporations doing contraceptive re-
proved drugs from the marketplace.

III. THE DEBATE OVER PREEMPTION

Debate over lawsuits for failure to warn about possible side effects often focuses on whether FDA approval of a drug should preempt tort actions. Several scholarly, well-written articles have advocated preemption, while others have opposed placing the final decision in the regulators' hands.¹⁰¹

The advocates of preemption point out that a lay jury is not as capable as the scientists and doctors of the FDA at identifying the side effects of drugs. According to these advocates, preemption advocates argue that FDA approval should preclude lawsuits for failure to warn because the experts have already decided the drug does more good than harm.¹⁰⁴

Opponents of preemption point out that the FDA approval process is not focused on the rights of individuals who are injured by drug side effects, or that, despite expertise in pharmacology or medicine, the FDA makes its choices without a popular mandate.¹⁰⁶ When a drug poses risks different from its benefits, as with the first oral contraceptives which prevented pregnancy and preserved sexual spontaneity but carried slight risks of blindness or even death, scientific expertise may be less useful than jurors' consciences.¹⁰⁷ The former chief counsel of the FDA, Richard A. Merrill, expressed particular skepticism at the notion that mathe-

¹⁰¹ E.g., Huber, supra note 13, at 288-90 (discussing one manufacturer's reluctance to produce a drug because the manufacturer has been held liable for damages alleged to have resulted from that drug and calling for preemption of tort suits for FDA-approved drugs and federal regulation to reduce tort liability); Walsh & Klein, supra note 9, at 179 (advocating federal preemption as a solution to restore product liability law to its original purpose); Comment, Prescription Drug Labeling, supra note 14 (advocating preemption based on supremacy clause and expertise concerns).

¹⁰² See, e.g., Cooper, supra note 42, at 233 (stating that value judgments about product liability are better left to the courts than the FDA); Merrill, Risk-Benefit Decisionmaking by the Food and Drug Administration, 45 GEO. WASH. L. REV. 994, 1008-12 (1977) (discussing the difficult task facing the FDA in the approval process); Comment, Federal Preemption and the FDA: What Does Congress Want?, 58 U. CIN. L. REV. 263 (1989) (relying on an absence of express preemptive language by Congress).

¹⁰³ See Huber, supra note 13, at 335; Walsh & Klein, supra note 9, at 193.

¹⁰⁴ See Huber, supra note 13, at 332-35; Walsh & Klein, supra note 9, at 193.

¹⁰⁵ See Cooper, supra note 42, at 234.

¹⁰⁶ See Merrill, supra note 102, at 996.

¹⁰⁷ Cf. id. at 1011 (asserting that choice between risks and benefits should be made through "procedures that permit public participation").
matical or medical expertise helps the FDA make choices where the risks and benefits of a drug are not comparable.\textsuperscript{108} Further, some authors note that the threat of litigation may make manufacturers refine their drugs to achieve greater safety.\textsuperscript{109}

The threat of private litigation may be more effective than FDA regulation at insuring that drug companies reveal research results to the FDA. For example, one drug manufacturer withheld adverse research results from the FDA concerning triparanol, a drug sold to reduce blood cholesterol sold under the name "MER/29."\textsuperscript{110} The jury found that the manufacturer withheld from the FDA results of studies done cooperatively with two other pharmaceutical companies that had reported eye damage in research monkeys.\textsuperscript{111} In fact, the drug can cause cataracts and some skin problems in humans.\textsuperscript{112} One woman on the research team resigned rather than endorse the false report.\textsuperscript{113} Her husband related the story of the falsification to an FDA inspector with whom he carpooled, and a federal investigation was launched.\textsuperscript{114}

Three Merrell employees pleaded \textit{nolo contendere} to criminal charges, and the company was fined the maximum allowed by law, $80,000.\textsuperscript{115} Meanwhile, civil suits against Merrell "ultimately cost the company between $45 and $55 million."\textsuperscript{116} Thus, the impact of civil litigation can be a vastly more powerful financial incentive for honesty than an inconsequential maximum fine.

Courts, though, have been unwilling to preempt, on the basis of FDA approval of a drug, state tort actions for failure to warn.\textsuperscript{117} FDA approval of warning language has been viewed as a minimum standard manufacturers must meet, and not as an indicator of all warnings a reasonable manufacturer would issue.\textsuperscript{118}

\begin{itemize}
  \item \textsuperscript{108} See \textit{id.} at 1008.
  \item \textsuperscript{109} Isaacs \& Holt, \textit{supra} note 100, at 539 (citing Galen, \textit{Birth Control Options Limited By Litigation}, Nat'l L.J., Oct. 20, 1986, at 28, col. 1).
  \item \textsuperscript{110} S. Fredman \& R. Burger, \textit{Forbidden Cures} 17 (1976).
  \item \textsuperscript{111} \textit{id.}
  \item \textsuperscript{112} See \textit{id.} For a discussion of the MER/29 scandal in the popular press, see Dowie \& Marshall, \textit{The Bendectin Cover-Up}, MOTHER JONES, Nov. 1988, at 46.
  \item \textsuperscript{113} See S. Fredman \& R. Burger, \textit{supra} note 110, at 17.
  \item \textsuperscript{114} \textit{id.}
  \item \textsuperscript{115} See Dowie \& Marshall, \textit{supra} note 112, at 46.
  \item \textsuperscript{116} S. Fredman \& R. Burger, \textit{supra} note 110, at 17.
  \item \textsuperscript{117} \textit{See supra} note 15.
  \item \textsuperscript{118} See Brochu v. Ortho Pharmaceutical Corp., 642 F.2d 652, 658 (1st Cir. 1981) ("approval by the FDA of the [warning] language involved is \textit{not necessarily conclusive} on the question of the adequacy of the warnings."); Walsh \& Klein, \textit{supra} note 9, at 185-88 (discussing state court decisions premised on this point).
\end{itemize}
Thus, a company may be liable for omitting to print warning language the FDA explicitly rejected for a drug's package insert.119 An inquiry into the failure to adequately warn may derive from provisions of the federal food and drug regulations which indicate that a manufacturer may strengthen its warning beyond the warning approved by the FDA.120 In practice, however, the bare legal right to make a warning more strict than the FDA requires may be illusory for a manufacturer whose livelihood may depend significantly upon maintaining the agency's good will.121 A former Chief Counsel of the FDA observed that, while a review of the applicable law would lead to the conclusion that manufacturers can act contrary to the FDA's will, the "FDA . . . retains, as a practical matter, complete control over package inserts."122

Preemption of tort suits upon FDA approval of warning language would stop approved drugs from being driven off the market by litigation. However, preemption would also stop the regulatory power of tort suits from providing manufacturers an incentive to improve drug safety and information,123 leaving the FDA as the sole arbiter of how much warning information should be issued. Even accepting as true that the experts at the FDA are the only appropriate parties to decide the proper content of warnings, there remains a question of how quickly the FDA is able to process the blizzard of new information constantly being developed about the multitude of products under FDA jurisdiction. Currently, the FDA can rely on the incentives of the tort system to encourage manufacturers to continue research, reveal research results honestly, monitor scientific literature, and request or issue appropriate warnings. Preemption would remove those incentives, and it is unclear whether the FDA could adequately review drug information under its current staffing and budget without the support of private lawsuits. Further, as the MER/29 scandal demonstrates, the threat of civil litigation by drug users who are not warned of side

119. See, e.g., Wooderson v. Ortho Pharmaceutical Corp., 325 Kan. 387, 409, 681 P.2d 1038, 1057 (1984) (warning actually included with defendant's oral contraceptive may be found inadequate even though a similar warning, sufficient to satisfy the duty to warn the plaintiff, had been previously rejected by the FDA), cert. denied, 469 U.S. 965 (1984).

120. 21 C.F.R. § 314.70(c)(2) (1989).

121. Cooper, supra note 42, at 236.

122. Id.

123. See id. at 237.
effects makes misleading the FDA a riskier proposition.\textsuperscript{124}

It may be possible to establish rules within the current litigation framework that retain the desirable incentives provided by tort actions, yet leave manufacturers confident that plaintiffs will not prevail when they fail to produce reliable scientific evidence that a warning could have been made on the basis of information then available to the manufacturers. Judges with a greater understanding of the structure of scientific proof could set more appropriate duties to warn, summarily dismissing suits that rely on evidence the relevant scientific community would find unreliable. Thus, liability in tort would occur only when the evidence presented would also be acceptable to competent experts in that field.

\textbf{IV. The Development of Scientific Knowledge}

Because there is no liability for a drug manufacturer's failure to warn users about unknown hazards,\textsuperscript{126} and because scientists around the world are adding constantly to the body of scientific knowledge, there can come a point in time before which no warning need be issued as to a given drug, and after which omission of a warning becomes tortious.\textsuperscript{126} For this reason, the timing of scientific discoveries and warnings can be crucial. In the absence of preemption by FDA approval, an understanding of how scientific knowledge is developed and disseminated is vital for the bench and bar in drug side-effect litigation.

\textbf{A. The Dissemination of Scientific Knowledge}

The principal mechanism by which scientists make their results known is through publication in scientific journals.\textsuperscript{127} The publication of research has implications for both the investigator and the scientific community. First, translating one's findings into a publishable article requires accuracy and logical thinking.\textsuperscript{128}

\begin{itemize}
\item \textsuperscript{124} See supra text accompanying notes 110-116.
\item \textsuperscript{125} See supra text accompanying notes 55-63.
\item \textsuperscript{126} Basko v. Sterling Drug, Inc., 416 F.2d 417, 426 (2d Cir. 1969) ("when chloroquine was first developed and tested, there was no known or foreseeable risk of idiosyncratic retinal damage [. but] . . . [w]hen the risk became apparent . . . a duty to warn attached.").
\item \textsuperscript{127} See Zuckerman, The Sociology of Science, in HandBook Of Sociology 515 (N. Smelser ed. 1988).
\item \textsuperscript{128} J. Ziman, Reliable Knowledge: An Exploration Of The Grounds For Belief In Science 132 (1978).
\end{itemize}
Second, the editors of most journals distribute articles submitted for publication to a panel of scientists in the relevant discipline. \textsuperscript{129} Research that is obviously flawed or unreliable may be kept out of the prestigious scientific publications this way. Third, once an article is published, it is available to the scientific community to be read, tested by further experimentation, and criticized. \textsuperscript{130} Thus, the researchers place their reputations at risk, to rise or fall with the perceived merit of their work. \textsuperscript{131} Some sociologists of science see peer review as the central mechanism insuring the reliability of scientific knowledge. \textsuperscript{132}

Other observers of science point out that the power of peer review has decreased dramatically in the past few decades. \textsuperscript{133} They note that, in the modern career of science, publications are the "basic currency of credit" for obtaining tenure, government grants, and the respect of the scientific community. \textsuperscript{134} The incentive system confronting scientists ensures that articles will be published even if they make only a very small contribution to the body of scientific knowledge. \textsuperscript{135} There is also a strong need to be the first to publish a result, as respect and grants go to the first discoverer and not to the scientists who later confirm a phenomenon. \textsuperscript{136} The drive to publish for prestige and career advancement generates a flood of articles of marginal worth in medical and scientific journals. \textsuperscript{137} Apparently, the two traditional instruments of quality control that encourage scientists to perform and publish worthy research, peer review before articles are accepted for publication and peer reaction after the work is published, are less effective today than they were just two decades ago because "the

\textsuperscript{129} Large & Michie, Proving that the Strength of the British Navy Depends on the Number of Old Maids in England: A Comparison of Scientific Proof with Legal Proof, 11 ENVTL. L. 557, 580 (1981).

\textsuperscript{130} Id.; see also J. Ziman, supra note 128, at 75-76 (noting the value of peer review even for research using good experimental technique).

\textsuperscript{131} Zuckerman, supra note 127, at 526-28; Large & Michie, supra note 129, at 580; see also Broad, supra note 74, at C8, col. 2.

\textsuperscript{132} See J. Ziman, supra note 128 at 75-76, 107-08; Zuckerman, supra note 127, at 524-25.

\textsuperscript{133} W. Broad & N. Wade, Betrayers Of The Truth 52-55 (1982).

\textsuperscript{134} Id. at 53; cf. Mills, Reporting Provocative Results: Can We Publish 'Hot' Papers Without Getting Burned?, 258 J. A.M.A. 3428, 3429 (stating that less emphasis by universities on the volume of a researcher's publications would serve to reduce the number of articles of marginal value) (1987).

\textsuperscript{135} W. Broad & N. Wade, supra note 133, at 53-54.

\textsuperscript{136} See Zuckerman, supra note 127, at 531.

\textsuperscript{137} See W. Broad & N. Wade, supra note 133, at 54.
excessive proliferation of scientific papers . . . clutter[s] up the communications system of science[,] . . . protecting bad research from scrutiny."138 For this reason, some observers of the scientific community conclude that the majority of scientific publications have "little or even zero impact on the forward march of knowledge."139

Even disregarding any erosion of the quality control on publication of scientific articles, one could not safely accept as true the conclusions of recent or path-breaking articles in even the most prominent journals. Research leads scientists down many promising blind alleys before establishing a scientific fact. Thus, while ninety percent of the science in a high school textbook is probably accurate, having withstood the tests of time in the scientific community, ninety percent of the science in the most prestigious research journals may be false.140 Nonetheless, the published literature remains the best measure of the state of scientific knowledge at a given point in time.141

Regardless of their underlying merit, scientific discoveries usually do not burst into the scientific press and gain immediate acceptance. For example, a well-designed research paper showing a strong correlation between cigarette smoking and lung cancer, today regarded as a "seminal publication in its field," met with great resistance upon release in 1950.142 Eleven years later, the question of whether smoking caused lung cancer was still sufficiently at issue to justify publishing a debate between two researchers in The New England Journal of Medicine.143 Even then, the causal connection had not been accepted widely as a scientific fact.144 The history of science is replete with examples of resistance to new findings,145 and not without cause, since erroneous

138. Id. at 221.
139. Id. at 54 (citing Cole & Cole, The Ortega Hypothesis, 178 SCIENCE 368-75 (1972)).
140. See J. ZIMAN, supra note 128, at 40.
141. See supra text accompanying notes 127-132.
144. See Little, supra note 143, at 1245.
145. For a seminal article on this issue, see Barber, Resistance by Scientists to Scientific Discovery, 134 SCIENCE 596 (1961). For an interesting discussion of a current medi-
conclusions are very much a part of the process of scientific discovery.

B. The Development of Scientific Knowledge About Teratogens

The challenge of predicting a drug's teratogenicity is particularly difficult. First, direct evidence as to a drug's effect on pregnant women is unavailable before a drug is released because drugs are never tested on pregnant women.146 Second, animal research may be of limited value because certain drugs, such as aspirin, are teratogenic to some laboratory animals but not humans,147 while other drugs may be teratogenic to man alone.148 Teratologists know that "[ex]trapolation from animal data to humans is difficult with the best of data and is very risky with poor data."149 It is axiomatic to teratologists that "any agent administered at the proper dose level, at the proper stage of development to embryos of some species will cause disturbances in the development of the embryo or the fetus."150 This axiom, known as Karnofsky's Law,151 means that any substance, no matter how safe for human use, can be made to produce defects in animal experimentation.152 Thus, a review of medical literature may include reports of teratogenicity in animals that do not imply a similar effect in humans. Third, because a percentage of babies who are not exposed to any teratogenic agents are born with defects, the best way science has devised to separate naturally occurring birth defects from those caused by drugs is through after-the-fact statisti-
cal studies of large populations. Detecting even a very potent teratogen could require a sample of as many as 200,000 births. A weak teratogen, one that causes defects in only a small percent of those babies whose mothers take the drug, might only be detected upon review of data concerning a million births or more. Birth defect data is not compiled or reviewed routinely across the United States, although some defect monitoring programs review as many as 100,000 births per year. Thus, the task of collecting the data necessary to identify a teratogenic effect might only be completed many years after a drug is released. Delays can be expected to arise from “possible incompleteness or inaccuracy of reporting, and delays in reporting of the defects, data processing, and statistical analysis.”

It is not surprising, given the pressures to publish and the difficulty of detecting or predicting teratogenicity, that scientific articles have incorrectly suggested teratogenicity in agents not currently believed to cause birth defects. Significantly, a study that purports to identify a formerly unsuspected teratogen is inherently more important than one that fails to find a relationship between a drug and birth defects. This is because a finding that a drug causes birth defects may affect treatment decisions, while a negative finding as to an agent not previously thought to be teratogenic will not. Perhaps more important, a negative finding proves only that one particular research design, as applied to one group of subjects, failed to yield a statistically significant result. It does not prove the safety of the drug being tested, but only that the procedure failed to detect an association. It is only when the additional logical link is present—that the design and execution of a given research project would have disclosed a relationship if one

154. Id. at 139 (Table 2).
155. Id. at 141.
156. Id.
157. The eminent philosopher of science, Sir Karl Popper, explained the theoretical value of a negative finding in scientific research with his frequently-cited example of the hypothesis that no swans are black. One must examine every swan in the world to prove this hypothesis, and that is impossible. Moreover, proof of the existence of one black swan will show the hypothesis false. Thus, the hypothesis that no swans are black (or, by analogy, that a certain drug cannot cause a birth defect) can never be proven, and is subject to disproof by a single contrary example. K. POPPER, THE LOGIC OF SCIENTIFIC DISCOVERY 101 n.1 (Harper Torchbook trans. 1968).
It is natural that the first study to be published will be one purporting to find proof of a teratogenic effect.\footnote{See, e.g., Bracken, \textit{Spermicidal Contraceptives and Poor Reproductive Outcomes: The Epidemiologic Evidence Against an Association}, 151 Am. J. Obstetrics and Gynecology 552, 555 (1985) (negative data on relation between spermicide and malformations were not reported until publication of reports suggesting a positive correlation).} It is quite common in epidemiology for the first published studies of an association to suggest a positive association, with subsequent reports being negative; \ldots The reason for this is fairly obvious. Investigators are more likely to write up positive findings, reviewers to consider them of interest, editors to publish them, and the press to publicize them. It is only after the initial observation is published that investigators who have negative data feel obliged to report them.\footnote{Supra note 134, at 3428.}

Indeed, the medical profession currently is concerned that the bias against publication of negative results may reduce the information available for use in reaching decisions about patient care.\footnote{Altman, \textit{Doctors Concerned About Unpublished Results}, N.Y. Times, May 16, 1989, at C5, col. 1.} Nonetheless, negative results remain largely unavailable to doctors faced with treatment decisions. Despite the justified caution with which a first study purporting to find teratogenicity is greeted, it nevertheless can be accurate, and once a study appears in print, the scientific community is on notice of the research conducted.\footnote{Years ago, researchers could publish findings about which they were uncertain in obscure journals that would not be read. In this way, they could protect their claims to discovery of some new phenomenon while risking little loss of prestige if their research was without merit. Today, however, computerized research makes it much less likely that a so-called “buried” publication will evade the notice of one researching a particular topic. Mills, supra note 134, at 3428.} If a single study suggests that a drug may be teratogenic and the drug is sold without a warning after the publication date, a lawyer whose client used the drug and gave birth to a damaged baby has the basic elements of a suit for failure to warn.\footnote{See generally supra note 126 and accompanying text.} Even if there is a strong reaction against the study and the scientific community considers it refuted by later research or criticism, the existence of the study could, depending upon the law’s view of when a duty to warn arises, cre-
ate an issue of fact regarding the reasonableness of selling a drug without a warning.

V. COURT-IMPOSED STANDARDS OF DRUG MANUFACTURERS’ DUTY TO Warn

As people are exposed to a newly released drug and reports of possible adverse reactions accumulate, a body of data develops that may allow epidemiologists and medical researchers to identify a drug’s hitherto unknown side effects. Courts have held that the dangers about which a manufacturer must warn may change as new information about side effects emerges.164

A drug manufacturer is held to the standard of an expert in the field of drug side effects.165 That is, the duty to warn extends beyond actual knowledge the manufacturer gains from research it performs to include knowledge available to an expert through the scientific literature.166 Because scientific literature is constantly growing, manufacturers are under a continuing duty to monitor scientific developments and update their warnings.167 Merely imposing an ongoing duty to monitor and warn, however, leaves unresolved the inevitable issue of how much and what kind of evidence must be amassed before a duty to warn obtains.

A. Warn Upon a Hint of a Possibility of Danger

_Wells v. Ortho Pharmaceutical Corp._,168 illustrates one possible standard of how much evidence will result in a court finding a duty to warn: a hint of a possibility of a side effect requires a warning. In _Wells_, the parents of a child born with multiple congenital anomalies sued Ortho, the manufacturer of a spermicide cream that the child’s mother used for contraception. The District

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164. See Basko v. Sterling Drug, Inc., 416 F.2d 417, 426 (2d Cir. 1969) (defendant manufacturer of drug chloroquine had duty to warn when previously unknown danger became apparent); Davis v. Wyeth Laboratories, Inc, 399 F.2d 121, 129 (9th Cir. 1968) (duty to warn attached when danger from taking polio vaccine became apparent.)


166. Id.

167. Schenebeck v. Sterling Drug, Inc., 423 F.2d 919, 922 (8th Cir. 1970) (drug manufacturer has a continuous duty to keep abreast of scientific knowledge concerning the side effects of its drugs).

Court in *Wells* imposed a duty to warn on the drug manufacturer "as soon as there was a 'hint' of a possibility that the Product causes birth defects." A "'hint' of a possibility" is any amount of scientific evidence. If held to this warning requirement, drug companies would have to issue warnings whenever any research of any kind could be read to suggest a teratogenic effect. Thus, whether the underlying research were epidemiological, animal-based, or *in vitro*, and regardless of its reliability, the company is bound under *Wells* to issue a warning based upon a "'hint' of a possibility." Moreover, when considered in light of the tendency for the first published study concerning teratogenicity to report a positive result, and with Karnofsky's Law guaranteeing that at some dosage any drug will cause birth defects in some species, it would appear this standard threatens to impose liability for failure to warn upon evidence that a significant majority of experts in the field would consider grossly insufficient.

Among the medical authorities cited in *Wells* by the plaintiffs' expert and the judge, who sat as the trier of fact, was a study published in the *Journal of the American Medical Association* in 1981. The 1981 study suggested that the question of whether...

169. *Id.* at 294.
170. *See id.*
171. In the years since *Wells* was decided, no court has either adopted or rejected this standard with a citation to *Wells*. Although a similar standard is stated in *Lindsay v. Ortho Pharmaceutical Corp.*, 637 F.2d 87, 91 (2d Cir. 1980) (holding that New York law requires manufacturers to "warn of all potential dangers which it knew, or in the exercise of reasonable care should have known, to exist.") (citations omitted), the court in *Lindsay* cited only one New York decision on this point, *Baker v. St. Agnes Hospital*, 70 A.D.2d 400, 421 N.Y.S.2d 81 (N.Y. App. Div. 1979). *Baker* in no way supports the proposition that New York requires drug manufacturers to warn of "all potential dangers." Instead, the *Baker* court held that a "manufacturer is under a duty to warn the medical profession of dangers inherent in its biological drugs which, in the exercise of reasonable care, it knew or should have known to exist." *Id.* at 405, 421 N.Y.S.2d at 85. Unfortunately, one New York court appears to have adopted the error in *Lindsay*, albeit in dicta. *See Ullman v. Grant*, 114 Misc. 2d 220, 220, 450 N.Y.S.2d 955, 956 (N.Y. Sup. Ct. 1981) (The court found that the plaintiff did "not state a cause of action for breach of warranty since it is not the duty of the pharmacist to warn of possible side effects in the use of a drug but rather the duty of the drug manufacturer and prescribing physician to warn of any possible adverse reaction . . . .").

The Second Circuit Court of Appeals has stated a less rigorous standard when it applied Connecticut law. For a discussion of that standard, see *Basko v. Sterling Drug, Inc.*, 416 F.2d 417 (2d Cir. 1969); *infra* notes 194, 202-06 and accompanying text.
172. *See supra* text accompanying notes 159-61.
173. *See supra* text accompanying notes 150-52.
the spermicide was a teratogen deserved further study and pru-
dently identified its conclusions as "tentative until confirmed by
other data."\textsuperscript{176} The authors' "comment" section discussed the fact
that the children born of mothers who used the spermicide, but
nonetheless became pregnant, bore children with no one set of
deformities.\textsuperscript{176} The article acknowledged that "[t]he absence of a
single, well-defined syndrome among the infants whose mothers
used spermicides raises doubt about a causal connection between
these agents and the disorders noted."\textsuperscript{177}

In fact, subsequent research failed to confirm the findings of
the study.\textsuperscript{178} One of the investigators who worked on the original
1981 study, Dr. Richard N. Watkins, wrote to the \textit{Journal of the
American Medical Association}, the periodical that published the
original study, and recanted the study's tentative conclusion.\textsuperscript{179}
Dr. Watkins attributed the inaccuracy of the study to its assump-
tion that any woman who had a prescription for spermicides
within approximately eleven months of conception had actually
been using the drug.\textsuperscript{180} Dr. Watkins also reported that an expert
FDA panel considered the study and concluded in 1983 that it
was "unpersuasive because of poor design and unsupported by
well-designed studies."\textsuperscript{181} Despite the weakness of the study and
its expressed reservations and its disclaimer of a positive conclu-
sion, the plaintiffs were allowed to call a physician to testify that
the study raised a serious question about the safety of the spermi-
cide.\textsuperscript{182} While the Watkins letter itself was not written until after
the \textit{Wells} case was decided, it demonstrates that as early as 1983,
the study had fallen into disrepute in the scientific community and
was little more than a hint of a possibility that the spermicide
could have caused the plaintiff's birth defect.

Application of the hint of a possibility standard stated in
\textit{Wells} mocks the purpose of warnings. First, Karnofsky's Law in-
sures that a hint of a possibility of teratogenicity will be found for

\begin{itemize}
\item \textsuperscript{175} Jick, \textit{supra} note 174, at 1332.
\item \textsuperscript{176} \textit{Id.} at 1331-32.
\item \textsuperscript{177} \textit{Id.} at 1332.
\item \textsuperscript{178} Bracken, \textit{supra} note 160, at 554.
\item \textsuperscript{179} Watkins, \textit{Vaginal Spermicides and Congenital Disorders: The Validity of a
\item \textsuperscript{180} \textit{Id.}
\item \textsuperscript{181} \textit{Id.}
\item \textsuperscript{182} \textit{Wells}, 615 F. Supp. at 272.
\end{itemize}
almost every drug in use. Moreover, long after the medical and scientific communities have determined that a given agent does not cause birth defects in humans, the research hinting at the opposite conclusion will still exist, and will still raise the possibility of a teratogenic effect. An equivalent to Shepard's Citations for medical literature, which would enable doctors and scientists to know readily which articles have been superseded, contradicted, or disproved, does not exist. Thus, for example, if the warning requirement of Wells were adopted, aspirin would require a warning about birth defects, since it is a teratogen in some animals. Aspirin’s known teratogenicity in animals has never been shown in humans and the drug is regarded as safe for use during pregnancy; nonetheless, evidence of an association in animal studies undoubtedly rises to the level of a hint of a possibility.

Issuing warnings on such flimsy evidence would create several problems. First, women who have taken the drug and are pregnant when the warning is issued may choose to abort the fetus based on a mere hint of a possibility. Women who are more cautious may have a sonogram performed to ascertain whether the fetus is deformed. Sonography is not currently believed to pose a threat to the fetus, but research indicates that there is at least a hint of a possibility that fetuses may suffer neurological damage from sonograms. Second, valuable therapeutic agents might be made unavailable to pregnant women. If the warning is made directly to

183. *See supra* note 151 and accompanying text.
185. *Id.*
187. Sonography at higher intensity than is used for fetal examinations has caused neurological damage in experimental animals. Kohorn, Pritchard & Hobbins, *The Safety of Clinical Ultrasonic Examination*, 29 Obstetrics & Gynecology 272, 273 (1967). Current research overwhelmingly supports the safety of fetal ultrasound examination. See, e.g., Stark, *et al.*, *Short- and Long-Term Risks After Exposure to Diagnostic Ultrasound in Utero*, 63 Obstetrics & Gynecology 194, 194 (1984) (study found no biologically significant differences between children exposed to diagnostic ultrasound in utero and unexposed children); *id.* (citing studies therein). However, it may still be possible to find a physician who would write a letter to the editor of a respected journal asserting that the research does not demonstrate the safety of fetal ultrasound examination. See, e.g., Reitz, *Risks After Exposure to Diagnostic Ultrasound in Utero*, 67 Obstetrics & Gynecology 752, 752 (1986). This evidence, which the majority of scientific and medical experts apparently do not consider an adequate basis for belief in a danger of ultrasound examination, might well be held sufficient to require a warning under the hint of a possibility standard.
the consumer, some consumers might choose to forego the beneficial effects of a drug because of a warning based on scientifically inadequate or even discredited evidence. If the warning were given only to the medical profession, it is possible that doctors would not prescribe the drug for pregnant women, fearing both the adverse side effect and the possibility of litigation.

Ironically, there would be almost no safe avenue by which the drug manufacturer could distinguish in its warnings between a drug known to be a teratogen and one about which there is only a discredited hint. Drug warnings must warn and not reassure. That is, purported warnings that call into question the evidence underlying them do not protect the manufacturer from liability. And while there may be articles in the literature concluding that a drug is not a teratogen, a warning in the Physicians’ Desk Reference, ("PDR"), a standard reference for drug contraindications, duplicates the manufacturer’s warning. Therefore, a doctor who goes no further than the PDR may not prescribe a useful drug based on a scientifically unsupported warning under the hint standard. Even if the medical literature reported overwhelmingly that a drug is safe, a warning in the PDR may constitute the basis of a suit against the prescribing doctor, and the threat of litigation could discourage use of the drug.

Perhaps the most dangerous result of requiring warnings on a hint of a possibility is that those warnings may numb the attention doctors and consumers pay to drug side-effect warnings in general. Warning labels are an increasingly prevalent response to real or imagined dangers of consumer products. The volume of warn-
ings issued about a vast range of products threatens their effectiveness. If a general awareness develops that drug warnings are founded on dubious evidence as a matter of course, the effect of all warnings will lessen further.

Requiring warnings based on a mere hint of a possibility of a teratogenic side effect has the potential of generating needless panic, thereby denying the therapeutic benefits of drugs to patients who could benefit from its use without facing what medical science would deem an appreciable risk. At the same time, the variety of products believed safe for which such warnings would have to be issued might dull the effect of warnings for drugs with proven, dangerous side effects. Both effects combine to reduce the value of drug warnings to society. As a matter of good social policy, failure to warn upon a hint of a possibility should not be a basis for liability.

B. A Duty to Warn of “Apparent” Dangers

Some courts have held that a drug manufacturer must issue a warning when the danger of a side effect is “apparent.” The decisions do not state explicitly to whom the danger must be apparent, but the likely intent is that it must be apparent to reasonable drug manufacturers, who are deemed experts in the field of drug side effects. A corollary to the “apparent” standard is that a drug company, although an expert in the field, cannot rely on that expertise simply to disagree with existing scientific evidence of a side effect, and thereby avoid the duty to warn. Beyond the bare use of the word “apparent” and its corollary, courts have not attempted to explain how to recognize when a suspected terato-
genic effect becomes "apparent." The word itself suggests a high degree of proof. Dictionary definitions of the word include, "readily understood . . .; evident; obvious," and "capable of being easily perceived or understood; plain or clear." 

In Davis v. Wyeth Laboratories, Inc., the Ninth Circuit Court of Appeals held that a drug company had a duty to warn of the possibility of contracting polio from a vaccine at the time the plaintiff received the drug. The court noted that the danger of contracting the disease was not a known or foreseeable risk of taking the vaccine early in the use of the vaccine, but the court held that the duty to warn began when the danger became "apparent." The court then noted that a Surgeon General's report, issued before the plaintiff was given the drug, made the dangers apparent, imposing a duty to warn.

The standard of apparent danger was adopted by the Second Circuit Court of Appeals in Basko v. Sterling Drug, Inc., with explicit reliance on Davis. The plaintiff in Basko suffered from progressive blindness that she claimed was caused by chloroquine, a drug she received from 1953 to 1961 for treatment of a skin condition. The first scientific study that considered the question of whether chloroquine causes loss of vision was published in 1957, and concluded that the research subjects' eye problems were not caused by the drug. Research reported in October of 1959, however, reached the opposite conclusion. The defendant used the 1959 report as authority for its request to the FDA in the Summer of 1960 to include specific warnings about eye damage in the drug packaging materials. Under these facts, the court refused to grant summary judgment for the defendant, holding that it was for the jury to find whether the warning of possible permanent eye damage, given in 1960, was timely and adequate.

The "apparent" standard may be particularly well-suited to

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199. 399 F.2d 121, 130-31 (9th Cir. 1968).
200. Id.
201. Id. at 129.
202. 416 F.2d 417, 426 (2d Cir. 1969) (citing Davis).
203. Id. at 419.
204. Id. at 426.
205. Id. at 422.
206. Id. at 422, 426.
combat the problem of dubious scientific evidence when the plaintiff's case depends upon proof of implied knowledge of the dangers of a drug. Courts generally seem unwilling to block expert testimony regarding causation except in extreme cases,\(^{207}\) and reversals on appeal are rare.\(^{208}\) Thus, the apparent standard opens an additional area of expert testimony: whether the causation about which plaintiffs' experts will testify was sufficiently obvious at the time the drug was administered or prescribed to be "apparent."

A scientist's own, unpublished investigations can be used to prove causation. Currently, a single article, unsupported or refuted by later research, which states even a tentative conclusion, might support a jury verdict regarding causality and serve as a first hint requiring a warning.\(^{209}\) Indeed, even an article concluding that no danger of side effects exists might be used to argue the contrary, based on an expert's reclassification of the data presented. However, where a plaintiff must show that the danger of a side effect was apparent to experts in the field, the proof depends on the state of the scientific literature on a given date. The expert would have to identify the publications upon which the conclusion that dangers were apparent rests.

To the extent that scientists insert findings of even minimal value into the scientific literature, a complete lack of articles concluding that a drug has a certain side effect is a very powerful indictment of a plaintiff's case. When no literature is found, judges should have little difficulty ruling as a matter of law that no danger was apparent. While it may be an acceptable practice for scientists to "reclassify" data from others' research or to reorganize it to arrive at a conclusion different from that of the original study,\(^{210}\) and while such testimony might be allowable to show causation, it cannot prove that a danger was apparent. The court should presume that, if the danger were truly apparent, the authors of the original study or some later article in a professional journal would have so stated. Thus, if the only support in a plaintiff's case consists of published articles failing to conclude that substantial evidence of teratogenicity exists, it may still be possible to decide liability as a matter of law.

Similarly, if the particular drug has been explored by numer-

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207. See supra notes 69-81 and accompanying text.
209. See supra notes 168-82 and accompanying text.
ous reliable investigators and the overwhelming weight of scientific evidence has refuted earlier suspicions, the danger cannot be apparent and liability should not flow from a failure to warn. While lawyers may convince a jury of causation by relying upon "hired gun" experts whose testimony is facially unreliable to the scientific community, the need to present a triable issue as to whether the danger was apparent requires that the plaintiffs show more reputable proof. The Eleventh Circuit Court of Appeals recognized the value of scientific peer review when it noted that "the examination of a scientific study by a cadre of lawyers is not the same as its examination by others trained in the field of science or medicine."211 The peer review controls of science, essential to the reliability of scientific testimony, would thus be brought into the courtroom under the apparent standard, since liability would flow not only from what experts are willing to say in court, but also from what they are willing to commit themselves to in writing before their peers.212

Even if a plaintiff can point to an article or two that purport to identify a side effect, under the apparent standard, the court should not automatically hold that the plaintiff's case is sufficient. Scientific editors strive to give scientists open access to the journals that are the mainstay of scientific communication, even if those individuals hold extreme minority views. An article may be published because it posits an interesting possibility rather than because it makes a convincing proof of its thesis.213 Indeed, if a scientist goes "gently round the bend" and "expound[s] some incoherent irrational theory" he may still be published by editors committed to open communication in science.214 For this reason, a beneficial rule would be that the danger is not apparent unless there is at least a respectable scientific minority supporting the existence of the dangerous side effect.

Courts already decide when a scientific view rises to the level of a respectable minority. For example, medical malpractice claims can be taken away from the jury if the defendant doctor followed a course of action that a "respectable minority" of doctors in the appropriate field would have taken.215 In the context of

211. Perry v. United States, 755 F.2d 888, 892 (11th Cir. 1985).
212. See supra text accompanying notes 127-45.
213. J. ZIMAN, supra note 128, at 131.
214. Id. at 144.
litigation against a drug manufacturer, the court in *Chambers v. G. D. Searle & Co.*\textsuperscript{216} held that the opinion of a single expert, the only dissenting doctor on an FDA panel drafting drug warnings, was insufficient to let the plaintiff's claim of insufficient warnings go to the jury.\textsuperscript{217} The court recognized that the plaintiff might have prevailed if the issue were whether the dissenter was actually correct or incorrect. However, the issue was whether or not the manufacturer exercised ordinary and reasonable care in issuing its warnings. The court concluded that the manufacturer's use of warnings approved by the FDA panel, despite the dissenter's view, was not a breach of the manufacturer's duty of care as a matter of law.\textsuperscript{218}

Thus, excluding scientific evidence not supported by a respectable minority of scientists within the relevant discipline is another way that courts can use scientific opinion to prevent cases from being decided on the basis of generally unacceptable scientific evidence.

**C. A Duty to Warn When a Danger is Knowable by Ordinary Care**

The general rule to avoid tort liability for harms resulting from use of a product is that the manufacturer or seller must warn of a danger if it knows or should know of the danger through the exercise of ordinary care.\textsuperscript{219} Ordinary care includes a reasonable inquiry into the state of the relevant literature.\textsuperscript{220} Although this standard gives no direction to the trier of fact regarding how much certainty is required before a warning should be given, it appears to be used frequently in drug product liability suits. For instance, the standard treatise on jury instructions, *Federal Jury Practice and Instructions*, cites the decision in *Basko v. Sterling Drug, Inc.*, which applied the "apparent" standard.\textsuperscript{221}

\textsuperscript{217} Id. at 383-84.
\textsuperscript{218} Id.
\textsuperscript{220} Id.
\textsuperscript{221} 3 E. DEVITT, C. BLACKMAR & M. WOLFF, FEDERAL JURY PRACTICE AND INSTRUCTIONS, CIVIL § 82.09 (1987) (citing Basko v. Sterling, Inc., 416 F.2d 417 (2d. Cir.}
The court in *Basko* noted that a defendant drug manufacturer cannot be expected to warn against unknown dangers from the outset, but offered no guidance for an instruction regarding how certain a harm must be for omission of a warning to be tortious. Indeed, even a popular handbook on drug litigation, which includes suggested plaintiffs' and defendants' requests to charge the jury in a hypothetical oral contraceptive case, provides no discussion of the amount of knowledge necessary to trigger a warning. Rather, the suggested requests to charge mention only that there is a duty to warn "based upon what the manufacturer knew, or, with the exercise of reasonable care should have known."

This general tort standard gives the trier of fact the widest possible latitude in deciding which failures to warn are tortious. If the trier believes that reasonable care requires the manufacturer to issue warnings on a mere hint of a possibility of danger, the plaintiffs can prevail upon evidence that experts in the field would disregard as unreliable. If, however, the trier believes that reasonable care requires the manufacturer to be absolutely certain that the drug can cause a harm, then plaintiffs cannot prevail unless no doubt exists as to a drug's side effects. Thus, the general tort standard of care gives juries and, hence, drug manufacturers, no guidance in determining when enough evidence exists to require a warning. Over-warning or unwillingness to sell beneficial drugs are the likely results of giving the trier of fact such unrestrained discretion.

Leaving ambiguous the certainty required to trigger the duty to warn does not restrain the natural sympathy that the sight of a damaged youngster will arouse. By failing to define a minimum of certainty beneath which no warning is required, courts give free reign to sympathy and disguise verdicts based on emotion as determinations of the level of care required. Since courts are reluctant to overturn a jury's determination of what constitutes ordinary care, and since some plausible evidence that a manufacturer should have known of a danger will almost always exist, ver-

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1969) and numerous other duty to warn circuit court cases).
222. 416 F.2d at 426.
224. *Id.* at 794.
225. See supra text accompanying notes 168-82.
226. See supra text accompanying notes 186-193.
227. See supra text accompanying notes 96-97.
228. See supra text accompanying notes 146-52.
dicts based on sympathy may occur, and they will very rarely be reversible on appeal.\textsuperscript{229}

VI. CONCLUSION

Application of the "apparent" standard, combined with an understanding of the role of scientific literature in defining what side effects might be knowable by an expert in the field, would improve the quality of drug side-effect litigation. The need to show that the risk of a given side effect was "apparent" can force plaintiffs to produce evidence that at least a respectable minority of experts recognized the risk. This element will have to be proved through support of the relevant scientific literature and not by the testimony of an irresponsible expert, who might not be willing to give the same testimony before a group of scientific peers, nor by the testimony of an outlying expert, whose extreme view is contrary to the scientific consensus.

By requiring that the risk be proved apparent, courts would succeed in bringing the protections of scientific peer review into the courtroom. Summary judgment motions would protect defendants from the expense of unfounded trials because apparentness could be determined by a search of the relevant literature. Drug manufacturers would be assured that they would not be held liable for failing to issue a warning based on dubious scientific evidence, but manufacturers could still be sued if their warnings failed to reflect the current state of knowledge. At the same time, applying the "apparent" standard retains the incentives of the tort system to prevent manufacturers from ignoring scientifically plausible reports of side effects, thereby protecting the free flow of reli-

\textsuperscript{229} Courts generally treat a trier of fact's determination of whether a party exercised reasonable care or was negligent as a finding of fact. \textit{E.g.}, McCoy v. Raucci, 156 Conn. 115, 120, 239 A.2d 689, 692 (1968) ("Conclusions of negligence or freedom from it are ordinarily conclusions of fact"); Bussey v. Dawson, 224 Ga. 191, 193, 160 S.E.2d 834, 836 (1968) ("the well established rule \[is\] that questions of negligence . . . are peculiarly matters for the jury"). A finding of fact is generally upheld if it is not indisputably wrong and some evidence in the record supports it. \textit{E.g.}, Thomas E. Golden Realty Co. v. Echo Six, 9 Conn. App. 52, 56, 514 A.2d 390, 392 (1986) (stating that the function of the court is limited to determining if the decision of the trial court was clearly erroneous) (citing Damora v. Christ-Janer, 184 Conn. 109, 113, 441 A.2d 61, 64 (1981))); \textit{Bussey}, 224 Ga. 191, 193, 160 S.E.2d 834, 836 (1968) (holding that a court should not take the place of the jury in questions of fact except in "plain and undisputable cases"); Murphy v. Carron, 536 S.W.2d 30, 32 (Mo. 1976) (stating that the trial court's decision will be upheld unless there is no substantial evidence to support it).
able information vital to informed decisions about the use of therapeutic drugs.