Off-Label or out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs

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Off-Label or Out of Bounds?  
Prescriber and Marketer Liability for 
Unapproved Uses of FDA-Approved Drugs  

James O'Reilly¹ and Amy Dalal²

I. INTRODUCTION

The year 2003 marks four decades since Congress first required drug makers to prove the effectiveness of their pharmaceutical drugs prior to the marketing of those drugs. Over the forty years since its adoption, this statutory command has given Americans the world’s most protective regulatory system for drug consumers.³ This article discusses how, in the last five years, Congress and the Food and Drug Association have made changes to that protection, by lowering the regulatory barriers to “off-label” promotion of pharmaceuticals for unapproved uses.

The Food and Drug Administration ("FDA") has comprehensively examined the proof underlying drug effectiveness claims for four decades. The Food and Drug Administration Modernization Act of 1997⁴ ("FDAMA") has been recognized by the FDA as “one of the most demanding challenges faced by the agency in its 92-year history.”⁵ The FDAMA has reaffirmed the FDA’s role as protector of the public health, but has also imposed significant new obligations on the agency; thereby limiting its control on governing pharmaceutical marketing practices.

One major aspect of FDAMA is section 401,⁶ which imposes a limitation

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of the FDA’s previously absolute authority\(^7\) to prohibit the dissemination of off-label information by drug manufacturers.\(^8\) The FDA reviews and approves the marketer’s claims of drug benefit when it approves the new drug’s label.\(^9\) The advertising and promotion of the claims can begin once the FDA approval of the product label containing that specific use claim is received.\(^10\) By contrast, an “off-label” claim is one that has not undergone the FDA scrutiny and approval.\(^11\) To say that a claim is off-label signifies that government scientists have not yet approved that claim based on scientific studies; it does not necessarily mean that the drug does not have the effect that it is claimed to have.

Traditionally, the FDA has generally recognized a physician’s right to prescribe the best medicine for treatment.\(^12\) This tolerance, however, has had an uneasy linkage to the FDA obligation to assure that manufacturers comply with the law’s requirement for pre-marketing approval of claims for all new drugs.\(^13\) This led to pressure from various interest groups to enforce some amount of regulation on the off-label use of drugs, while drug marketers pressed to be freed from FDA control of all claims of product effectiveness. The result has been a congressional grant of authority, codified in section 401 of FDAMA,\(^14\) to the FDA to regulate the distribution of information by drug manufacturers. Section 401 is aimed at ensuring that only truthful, non-misleading information concerning prescription drugs and devices is distributed to the medical community, including, but not limited, to physicians.

Off-label promotion of prescription drugs has always been a troublesome area for the FDA enforcement staff.\(^15\) This article describes and critiques the various approaches in dealing with off-label use, assesses the passage of FDAMA, highlights the litigation under FDAMA relating to promotion of off-label use information, and analyzes the present FDA policies and initiatives. This article will then examine the litigation issues and the

pressures of new communication methods, such as Internet websites, upon the FDA's ability to control the flow of promotional information about prescription drugs. Lastly, this article will evaluate the long-term effects of FDAMA's section 401 and offer predictions and recommendations for the future of off-label use.

II. SECTION 401 AND ITS ROOTS

The Food Drug & Cosmetic Act, prior to its 1997 amendments, expressly forbade the sale of a drug whose labeling or advertising claims of effectiveness had not yet received approval from the FDA.\textsuperscript{16} FDA policy held that “pharmaceutical manufacturers cannot proactively discuss off-label uses, nor may they distribute written materials (promotional pieces, reprints of articles, etc.) that mention off-label uses.”\textsuperscript{17} The 1997 Amendments resulted from a major effort of lobbyists for the pharmaceutical industry. Specifically, section 401 of FDAMA enables drug manufacturers to distribute information regarding the off-label use, provided that the manufacturer complies with the following requirements:

1. submission of a supplemental new drug application (“NDA”) for the new use;
2. dissemination of information that is not abridged, false, misleading, or posing a significant health risk to the public;
3. all clinical research found in the disseminated materials is the work of the manufacturer;
4. submit a copy of the materials to the FDA at least sixty days prior to dissemination; and
5. include in all disseminated materials prominent disclaimers clarifying that the information disclosed concerns a drug that has not been approved by the FDA for that particular use.\textsuperscript{18}

Manufacturers have a continuing obligation to provide the FDA with any new information that arises concerning their product. As section 401 was written, prior to its FDA reinterpretation, if a manufacturer failed to comply with the requirements, the FDA could order the termination of the distribution of information until corrective action was taken by the manufacturer.\textsuperscript{19}

\textsuperscript{17} Janet Woodcock, M.D., Lecture to Drug Information Association, \textit{A Shift in the Regulatory Approach} (June 23, 1997), at http://www.fda.gov/cder/present/diamontreal/regappr/sld001.htm.
III. OFF-LABEL PRESCRIPTION OF DRUGS

Off-label prescribing is common in almost every field of medicine. In 1995, the American Medical Association estimated that in the United States 40-60% of prescriptions were written for off-label uses. Currently, off-label use is especially common in the areas of oncology, rare diseases, AIDS treatment, and pediatrics. For example, it is approximated that 50% of cancer treatment drugs, 80-90% of drugs used to treat rare diseases, and 80% of drugs used in the pediatric field are prescribed off-label to patients. The situation has existed for many years, especially in the treatment of cancer. Though a product’s label may list one or two diseases for which the approved drug is indicated, physicians often opt to prescribe that drug for an “off-label” use of the approved drug. The use is characterized as a new use, because it has not yet been accepted by the FDA, and accordingly, the manufacturer is required to demonstrate full clinical research results showing its effectiveness for that specific medical problem or disease.

One of the most prominent examples of off-label use is the celebrated drug Viagra, for erectile dysfunction. Viagra was originally approved by the FDA to treat chest pain caused by heart disease. Now, Viagra is hailed as one of the most successful impotency drugs for adult males. Similarly, aspirin was prescribed by physicians off-label for many years to reduce the risk of heart attacks. It was not until 1998 that the FDA finally approved such use. Off-label activities are defined as “use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling.” These activities can take three basic forms: off-label use, off-label prescription, and off-label marketing and promotion. All of these activities deal with the use of drugs in ways not included in the labeling of the drugs, and thus, in ways not approved by the FDA.

The FDA has historically sought to avoid conflict with any individual physician’s decision to prescribe a drug to an individual patient for an off-label purpose, stating that “once a [drug] product has been approved for

marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling."27 This official agency policy, known as the "practice of medicine exemption," reflects the history of the 1938 Act, which was sponsored by physician-Senator Royal Copeland.28 Copeland wanted to assure his medical constituents that the new requirement for government approval of new drugs would not adversely impact their ability to prescribe drugs for their patients.29 Accordingly, the 1938 Act is silent about the prescriber's responsibility, and the matter is left to state licensing agencies and the tort system by default. Additionally, a specific protection for prescriber choice was built into the medical device statutes, using the same "practice of medicine" approach.30

Congress has chosen to remain silent regarding the constraints upon the FDA's powers to protect this potent constituency.31 This instance of statutory inaction permits a medical practitioner to lawfully prescribe an FDA approved drug for an unapproved use, provided that there is a benefit to the patient, the patient is completely aware of the nature of his treatment, and the patient has consented to the use of such treatment.32 Although physicians are not required to disclose to their patients that a drug is being used off-label, it is generally considered good practice to do so.

The long life of the practice of medicine exemption stems from the FDA's recognition of limits on its ability to oversee the actual use of drugs, and the recognition that physicians should be given a great deal of autonomy in their prescribing practices. In 1997, the FDA's chief drug official stated, "the FDA recognizes that off-label use by prescribers is often appropriate and may represent the standard of practice."33 However, this freedom accorded to physicians does not go unsupervised, because the fear of tort liability and medical malpractice claims serves as a check on the prescribing practices of physicians.34

This off-label use is a critical economic issue for drug manufacturers' profitability. When a drug is prescribed for an unapproved use, for which the marketer believes the drug to be effective, its sales may increase

28. "(T)his bill makes certain that the medical practitioner shall not be interfered with in his practice" 78 CONG. REC. 3, 2728-9 (1934) (statement of Sen. Copeland).
29. Id. at 2728.
33. Woodcock, supra note 17.
34. David J. Goldberg, Off-Label Prescribing is Common and Accepted in Mainstream, DERMATOLOGY TIMES (Oct. 2000).
dramatically, causing the company’s profit potential to skyrocket. A fairly recent example of this potential is the diet drugs debacle. Sales of two individual drugs, Fenfluramine and Phentermine, in their FDA-approved form, were modestly successful. However when combined together as a diet drug, Fen-Phen, sales skyrocketed as physicians began prescribing the combination for weight loss purposes. Unlike the majority of drugs prescribed for unapproved uses, or in unapproved forms, Fen-Phen caused a number of serious problems in its users, including valvular heart disease, and even death. The Fen-Phen controversy demonstrated that greater control of promotional communication about unapproved uses is needed to assure the safety and efficacy of new drugs.

IV. FDA ENFORCEMENT AND THE PROMOTION OF OFF-LABEL USES

An important distinction must be drawn whenever off-label uses are discussed. The prescribing physician is given freedom to prescribe for off-label uses because the incentives to aid individual patients are socially desired. Conversely, the pharmaceutical company’s incentives are purely financial and more likely to consider the corporate profitability potential over the risks or benefits for individual patients. The FDA rarely challenges individual physicians, but continually challenges the promotional claims of major pharmaceutical marketers. In the FDA’s view, permitting drug companies to promote off-label use would “diminish or eliminate” incentives to obtain definitive clinical study data. The end result would erode the statutory standard of proof of drug efficacy, diminish the use of evidence-based medicine, and “could result in harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective.”

The FDA made extensive efforts from 1962 to 1997 to force all claims of new drug effectiveness to undergo rigorous evaluation of clinical data prior to the advertisement or oral claim being made to prescribing physicians. Through warning letters and other punitive and precautionary statements, the FDA sought to aggressively control the issuance of pharmaceutical product benefit claims that had not yet been reviewed, accepted, and incorporated into the FDA-approved labels for a drug. Even when the warning letters did not lead to litigation, the negative publicity about regulatory displeasure sometimes harmed the targeted companies’ stock

35. Rheingold, supra note 32, at 53.
38. Woodcock, supra note 17.
market perception. Any new drug sponsor who needs additional regulatory approvals in the future would have a strong incentive to stop making a claim for an existing drug once the FDA questioned its claim. The FDA had the statutory authority, the judicial encouragement, 39 and the practical power to resist excessive claims.

Lacking any express authority to regulate physicians' prescription of drugs for off-label indications, the FDA focused its resources on curtailing drug manufacturers' promotional and marketing activities. 40 In the era before Internet search engines and mass media coverage of new pharmaceutical developments, physicians learned of new uses primarily from manufacturer sales representatives. Thus, the FDA became accustomed to the use of its controls against drug manufacturers, as the optimal means to restrain claims of a drug's effectiveness that had not yet received the FDA's approval.

Prior to the 1997 FDAMA, drug manufacturers were explicitly prohibited from promoting their drugs for any unapproved use. Unapproved use would render the drug "misbranded" in violation of the Food, Drug and Cosmetic Act. 41 The FDA imposed such strict rules on drug manufacturers for two reasons. First, allowing the free dissemination of information regarding off-label use would act as a disincentive for drug companies to perform the requisite clinical studies, to prove that the drug is safe and effective for the unapproved use. 42 Bypassing these studies enabled the drug companies to save an enormous amount of time and money. Second, because drug manufacturers have a direct financial stake in the success of their products, information being disseminated by such manufacturers have a greater chance of being biased, and thus a greater chance of misleading the health care professional. 43 These two reasons supported the FDA's policy towards off-label use and drug manufacturers

39. Weinberger v. Hynson Westcott & Dunning, 412 U.S. 609, 622 (1973) (noting how the Supreme Court granted the extraordinary authority for an administrative body, the FDA, to determine the scope of its own jurisdiction, through a conscious deference to the FDA on definitions of new drug status. For a further discussion on this topic, see James O'Reilly, 1 FOOD & DRUG ADMIN. § 13.04 (1993)).

"[T]he physician may, as a part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration." Id.; see also David Kessler, Regulating the Prescribing of Human Drugs for Nonapproved Uses Under the Food, Drug and Cosmetic Act, 15 HARV. J. LEGIS. 693, 698 (1978).


42. For a discussion on the incentives, see Sidney A. Shapiro, Limiting Physician Freedom to Prescribe a Drug for Any Purpose: The Need for FDA Regulation, 73 NW. U. L. REV. 801, 863 (1978).

43. Bradshaw, supra note 12, at 2.
until November 1997, when FDAMA was adopted.

V. POLICIES UNDERLYING ADOPTION OF FDAMA SECTION 401

Under FDAMA's section 401, for the first time in FDA history, drug manufacturers were given the right to advertise off-label uses of their products, provided that they complied with a set of requirements prior to using the marketing claim. This was a historic retreat from the 1962 statutory policy, which required specific proof and approval of each claim. The retreat widened later, as a result of the litigation discussed later in this article.

Section 401 is construed by the FDA as a “safe harbor” for drug manufacturers. Under this “safe harbor,” if a manufacturer complied with the statutory requirements, the FDA could not prosecute a company for the off-label promotion of its product. If the safe harbor is not satisfied, and a claim is made that was not approved on the FDA-approved product label, then a violation has occurred, and the FDA may still resort to traditional misbranding or unapproved new drug charges against a drug marketer.

Congress wanted to strike a sound balance between protecting the public's safety from unscrupulous drug manufacturers, and patients' access to the best treatment possible. Section 401 was crafted by Republican Senators William Frist and Connie Mack, and endorsed by several key Democrats. The compromise language allowed a balance to be struck between these two interests.

VI. ARGUMENTS FAVORING THE OFF-LABEL PROMOTION

The passage of FDAMA and especially section 401 was the culmination of a long-standing debate between two divergent views of the role of drug

44. 76 Stat. 784 § 104 (1962).
45. The “most notable” aspect of the 1962 legislation was its requirement “that before a drug could enter the market it must be shown to be ‘effective’ for its intended use – the use recommended in its FDA-authorized labeling.” Alan Kaplan, Fifty Years of Drug Amendments Revisited: In Easy-to-Swallow Capsule Form, 50 FOOD & DRUG L.J. 179, 182 (1995).
46. The FDA conceded in a later appellate argument that section 401 would be a safe harbor, not an affirmative imposition by FDA upon each claim. See Washington Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000). This reflects a substantial retreat from the 1960’s command that every new drug claim be specifically approved or be deemed in violation of the statute. 21 U.S.C. § 355 (2000 & West. Supp. 2000).
approval: those who believed that promotion of drugs for off-label use would allow the public access to potentially life-saving treatments versus those who believed that off-label use of drugs posed a real threat to the health and well-being of the American public. It is important to understand the arguments asserted by each of these camps and to evaluate how their views have played a role in the passage of FDAMA.

Proponents argue that the key benefit to off-label use is that it allows more data to be readily available to prescribers. The main thrust of the proponents' arguments revolves around the theory that for the benefit of patients, it is essential to allow drug manufacturers to market the off-label uses of their products in medical literature and events frequented by medical practitioners. By doing so, physicians and other medical personnel are able to make more informed decisions for their patients' treatment. Leaders of the American Medical Association ("AMA") have commented that section 401 is a "meticulously crafted, bipartisan provision [that] sets out both a suitable mechanism and pertinent safeguards that assure that the information manufacturers disseminate is both appropriate and credible." 51

Proponents of the free dissemination of information regarding off-label use believe that because off-label use is so widespread, it is imperative for medical practitioners to have access to the most up-to-date information in order to formulate the most informed decision when treating their patients. Because physicians receive a large amount of information from the pharmaceutical companies, placing restrictions on the dissemination of such information can potentially lead to patients receiving sub-optimal treatments. 52

According to proponents, prescribing physicians could benefit from the additional data about drugs. It is nearly impossible for a physician to read all of the medical journals and compendia available, especially given the proliferation of medical reading materials, both hard copy and on the internet, in the last decade alone. As Senator Bill Frist, one of the authors of section 401, stated in his congressional testimony, "If a conscientious doctor were to read two medical articles before retiring every night, he would have fallen 550 years behind in his reading at the end of the first year." 53 There is a high potential risk of a physician missing an important study that may have a significant impact on his or her treatment decisions. It is therefore asserted that if a drug marketer is given the freedom to advertise the drug for unapproved uses, then the potential for a physician to

receive incomplete or inaccurate information is significantly decreased.

Another reason in favor of free dissemination of off-label information was the delay and cost of the FDA's drug approval process. The FDA approval process is complex and detailed, and its timing cannot keep up with the fast pace of medical discovery about pharmaceutical benefits. Even with the advent of the accelerated "fast-track" approval process, the process for drug approval is one that is still lengthy and time-consuming. In 2000, the process for approval was estimated to take between seven to ten years. The practical effect of the process is that it is hard to for regulators to keep up with the pace of medical technology and research. Additionally, the FDA drug approval process imposes high costs. The average cost to get a drug on the market was estimated to be $880 million per drug over fifteen years. Permitting off-label advertising for a drug allows the drug manufacturer to postpone committing to the approval process and thus keep research and development costs down, while still gaining the revenue from off-label sales. The cost benefits to the FDA from permitting off-label advertisement are also apparent. Former House Commerce Committee counsel, Alan Slobodin, commented that the FDA was unnecessarily expending resources monitoring off-label uses. If the agency was to permit such off-label uses, resources could be used for other more pressing purposes, such as the evaluation of new drugs.

A further advantage of a liberal off-label use policy cited by the proponents is the benefit such advertisements will have on the twenty million Americans who are suffering from orphan diseases. Federal law defines orphan diseases, such as Lou Gehrig's disease and cystic fibrosis, as those diseases that afflict fewer than 200,000 Americans. Because orphan diseases affect a small minority of the American public, it is not economically reasonable for a drug manufacturer to conduct expensive clinical studies into a new use for a drug that will benefit only a small number of people. Thus, those who are afflicted with orphan diseases are typically treated with medications that are used off-label. With the free

55. Goldberg, supra note 34, at 1.
56. Bradshaw, supra note 12, at 6.
59. Id. at 195.
60. Id.
62. Id. at 15.
63. Id.
dissemination of off-label information those medical practitioners who treat orphan disease will be privy to more information regarding the treatment options available for their patients afflicted with these rare diseases.  

In some circumstances, the manufacturer may go further and adopt the orphan, receiving federal research grant funds and obtaining exclusive marketing rights for the sponsor whose orphan drug is approved for a rare disease.

Some commentators assert that off-label announcements will help to expedite the development and accessibility of new treatments. By reducing the time and money needed to pass the rigorous FDA approval process prior to a new claim, it is argued, the manufacturers can redirect these resources towards the development of new uses for their FDA approved products.

Although these benefits all seem persuasive, opponents to the dissemination of information for unapproved indications also have a number of valid arguments that have influenced many of the restrictions found in section 401.

VII. ARGUMENTS OPPOSING EASIER OFF-LABEL PROMOTION

The arguments opposing a liberal off-label policy of promoting unapproved pharmaceuticals are compelling. Before FDAMA was adopted, the FDA asserted that permitting drug companies to promote off-label use would remove incentives to obtain definitive clinical study data, weaken the goal of evidence-based medicine, erode the drug efficacy requirements, and harm patients by unstudied uses that “actually lead to bad results, or that are merely ineffective.”

After FDAMA section 401 was adopted, the amendment drew harsh criticism from consumer groups who asserted that section 401 provides “dangerously inadequate protection for the American public from the substantial risks of unknowingly being prescribed drugs for off-label uses.” In a congressional submission, Public Citizen, a “consumer watchdog group,” asserted that section 401 did not do enough to protect consumers. The group asserted that in FDAMA, Congress “shamelessly” ignored the deaths resulting from the “fen-phen” disaster, and argued that additional “objective comparative drug information” should be written specifically to consumers disclosing all the risks and

64. Id.
66. See Salbu, supra note 58, at 193.
67. Woodcock, supra note 17.
benefits associated with the prescription drugs and their off-label uses. Public Citizen also expressed discontent towards the Congressional oversight committee for not inviting representatives of consumer and patient groups, such as Public Citizen, to testify on the impact of FDAMA, but allowing to representatives of the regulated industries to make presentations. Public Citizen wrote:

“This special interest law places the economic well-being of multinational pharmaceutical manufacturers above the health and safety of the American public and marks a low point in U.S. drug regulatory history by weakening law meant to protect the public from needless drug-induced injury. Congress, by continually adding new responsibilities to an overburdened FDA, while keeping the Agency’s budget constant, in effect ties the hands of the FDA and deregulates the pharmaceutical industry at the expense of public safety.”

The lower proof prerequisites required had the effect of altering the historical basis for having a proof of drug efficacy in the first place. Forty years of experience with the effectiveness requirement showed that it made a difference in the validity of drug product claims. Because a promotional effort supporting a drug’s unapproved use, by encouraging off-label use among physicians, lacks the public health protection that comes with having the FDA screen the validity of the claim, opponents argue that using a drug in an unapproved fashion poses a serious threat to consumer safety. This argument has history behind it. To pass the agency’s rigid drug approval scrutiny, sponsors have known since the early 1960’s that they must generate strong evidence of the safety and efficacy of the drug. No such comprehensive showing is required before commencing the promotion of the drug for an off-label use.

The FDA takes a similar position against the promotion of off-label use. The agency believes permitting off-label promotion undermines its authority by allowing drug manufacturers to bypass its strict review and approval process. Additionally, the lack of resources available limits the agency’s ability to effectively regulate such off-label promotion to assure manufacturers are complying with the statutory requirements. However, the agency, realizing that off-label use is becoming increasingly popular in modern medical practice, is constantly looking for ways to increase its


70. See PUBLIC CITIZEN, supra note 68.

71. Salbu, supra note 58, at 202.
involvement in this area.\textsuperscript{72} The next issue deals with the disincentives created by a strict off-label use policy. Opponents claim that relaxing the legal standards for promotion of an off-label use removes any incentive for drug manufacturers to spend the time and money needed to perform clinical studies to prove the safety and efficacy of their product. In fact, if a manufacturer does conduct such clinical studies he may learn that off-label use is in fact ineffective and/or harmful, and thus be banned from further sale of the product.\textsuperscript{73} Opponents cite the Fen-Phen debacle as evidence of the consequences that can occur when drugs are used in an unapproved form for an unapproved purpose without conducting more research into their safety.\textsuperscript{74} The incentive that justified expenditures for testing was the ability to later advertise this drug for this purpose. The post-FDAMA ability to promote the off-label use of their product causes drug manufacturers to be unmotivated to conduct clinical research into the safety and efficacy of their product. Competing drug manufacturers are also discouraged from conducting such research studies for comparative and competitive entries into that market, and the market for drug clinical studies is this reduced. If one manufacturer is able to advertise their product’s off-label use and gain the sales from such advertisements, competing manufacturers will not spend the time and money conducting clinical trials to prove the safety of their product for the same use, particularly when such research will amount to lost sales from such delay.\textsuperscript{75} Perhaps the most telling argument against the free promotion of off-label use by drug manufacturers is that allowing such promotion will encourage manufacturers to “game the system,” to seek FDA approval only for the narrowest and easiest to establish uses for their products. If the manufacturer knows that it can advertise the product for a variety of uses once initial approval of a use is granted, the drug firm will be unlikely to make its initial application to the FDA broader than necessary. Under this concept, a drug manufacturer will conduct only the minimum required number of clinical trials needed to gain initial approval for one basic use. The many other disease indications for which the drug will be actively marketed will not have been proven safe or effective.\textsuperscript{76} Dr. Sidney Wolfe of Public Citizen commented: “In a sense, huge numbers of people are going to be made guinea pigs for unapproved uses of drugs.”\textsuperscript{77}

\textsuperscript{72} Ascroft, \textit{supra} note 52, at 101.
\textsuperscript{73} Bradshaw, \textit{supra} note 12, at 18.
\textsuperscript{74} \textit{Id.} at 16.
\textsuperscript{75} \textit{Id.} at 18.
\textsuperscript{76} \textit{Id.} at 19.
\textsuperscript{77} Schiavone, \textit{supra} note 24, at 1.
These opponent concerns are directly addressed in FDAMA with the requirement that the drug manufacturer wishing to make the claim is required to certify to the FDA that it will file a new drug application ("NDA") for the off-label use, or submit to the FDA a protocol and schedule for conducting the requisite clinical studies and filing a supplemental application.\textsuperscript{78}

Another consideration focusing on the patient's interest is the issue of insurance coverage. As recently as ten years ago most insurance companies, HMOs, and governmental plans, including Medicaid, refused to cover the cost of off-label medications.\textsuperscript{79} Insurance companies typically considered such uses to be experimental and refused to reimburse patients for the costs of such treatments.\textsuperscript{80} Some insurance companies, including Kaiser Permanente, have conceded to cover uses listed in major compendia, but many off-label uses for drugs are still not included in these compilations.\textsuperscript{81} Patients, therefore, are often left to pay out-of-pocket for such off-label drugs and devices, costs of which are anything but minimal.\textsuperscript{82} Most states, however, have since passed legislation prohibiting insurance companies from excluding coverage for the off-label use of a drug in the treatment of certain ailments.\textsuperscript{83} States vary on the limitations included in their individual legislations. Maine, for example, limits coverage to just the treatment of cancer, HIV, or AIDS,\textsuperscript{84} whereas California takes a broader view covering the use of a drug in the treatment of any "chronic and seriously debilitating condition."\textsuperscript{85}

Insurance carriers are under pressure to cover all off-label uses. The AMA's official policy encourages such coverage, stating, "[w]hen the prescription of a drug or use of a device represents safe and effective therapy, third party payers should consider the intervention as reasonable and necessary medical care, irrespective of labeling, and should fulfill their

\begin{itemize}
\item \textsuperscript{78} 21 U.S.C. § 360(a) (2000).
\item \textsuperscript{79} This remains an active area of conflict regarding denials of coverage; see, \textit{e.g.}, Coram Healthcare Corp. v. Wal-Mart Stores, Inc., 2002 WL 31599577 (S.D.N.Y. 2002) (finding that the FDA does not approve drugs generally, but for use with specific illnesses).
\item \textsuperscript{80} Alexander T. Tabarrok, \textit{Assessing the FDA via the Anomaly of Off-Label Drug Prescribing}, \textit{5 INDEP. REV.} 25, 35 (Oct. 2000).
\item \textsuperscript{81} Telephone Interview with Patricia Van Patten, Pharmacy Business Support Specialist, Kaiser Permanente (Nov. 26, 2002).
\item \textsuperscript{82} Bradshaw, \textit{supra} note 12, at 20.
\item \textsuperscript{83} Tabarrok, \textit{supra} note 80, at 35.
\item \textsuperscript{84} 24 ME. REV. STAT. ANN. § 2320-G (West 2002).
\item \textsuperscript{85} \textit{CAL. HEALTH & SAFETY CODE} § 1342.7 (West 2000).
\end{itemize}
obligation to their beneficiaries by covering such therapy." With such strong support, and with the increasing popularity of off-label use, there may very well be significant changes made in the carriers' policies in the future.

Opponents argue that physicians both have access to all medical journals and are able to place special requests with drug manufacturers for any information that may be unavailable through traditional sources. These opponents presuppose that the physician is aware of the off-label use and has the time to make such requests. Typically, a physician has to make quick treatment decisions for his patient. If he has to wait for a response from a drug manufacturer, the patient may unnecessarily suffer from such delay.

In summary, the opponents' arguments appear to have more validity. Without a sufficient regulatory control, market forces alone give inadequate incentives to protect the drug consumer. Some drug manufacturers may abuse the process by not investing in proof of the safety and efficacy of their product and by skewing the promotion of their product to their financial benefit. The safety of the American consumer was the reason why efficacy proof was required in new drugs after 1962, and it remains a societal imperative. These concerns have influenced Congress's passage of FDAMA and its requirements, but the resistance by drug marketers has called into question the degree to which the FDA could protect consumers from ineffective drugs.

VIII. IMPACTS OF RECENT FIRST AMENDMENT LITIGATION

The manufacturers of pharmaceuticals have been aided in their arguments by a Washington-based advocacy organization that supports the business community's efforts to reduce federal regulatory power. Eight years of litigation against the FDA by a group advocating for less FDA regulation resulted in a historic retreat by the FDA from an aggressive view of its post-FDAMA power to regulate product claims.

In 1993, the Washington Legal Foundation ("WLF") filed a citizen's petition with the FDA claiming that the agency's restrictions on the distribution of off-label information at continuing medical education ("CME") programs violated drug manufacturers' First Amendment rights.


When the FDA denied the petition, WLF filed a lawsuit in the District Court for the District of Columbia ("WLF I"), claiming that the FDA's off-label policies infringed on the First Amendment rights of WLF members. The FDA responded by attempting to get the case dismissed on various grounds, including arguing that WLF lacked standing to bring the suit because statements of policy are not final and should not be subjected to judicial review. The judge, however, rejected the FDA's arguments and the case proceeded to the discovery phase.

In the discovery phase, WLF was allowed the rare freedom to depose top-ranking FDA officials, including the Associate Commissioner for Policy Coordination, the Director of the Office of Compliance, Center for Devices and Radiological Health, and even the Commissioner. Following discovery and other pre-trial preparations, both the FDA and WLF filed motions for summary judgment with the court.

In 1997, in a historic move by Judge Royce C. Lamberth, the court denied the FDA's motion and granted WLF's motion for summary judgment. In his opinion, Judge Lamberth acknowledged off-label use as an "established aspect of the modern practice of medicine" whereby open dissemination of scientific information regarding such uses are "of great import" to the medical community. The threshold issue in WLF I was the determination of whether the FDA's policies were regulating speech or regulating conduct. Because conduct was afforded less constitutional protection than speech, this threshold issue was critical to the outcome reached in the case. The court, rejecting the FDA's argument that the policies involved conduct, stated that "[t]his court is hard pressed to believe that the agency is seriously contending that 'promotion' of an activity is conduct and not speech, or that 'promotion' is not entitled to First Amendment protection."

Next, the court addressed how to classify the "speech." Rejecting the FDA's argument that the "speech" falls outside of First Amendment protection because of the government's broad powers to regulate industry,
the court found that the agency did not have an unrestricted power to limit speech. The court stated that although scientific and academic speech "reside at the core of the First Amendment" and require the highest degree of constitutional protection, such information should be classified as commercial in nature because manufacturers have a direct financial interest in the promotion of off-label information. Unlike pure speech, commercial speech is subjected to more relaxed judicial standards. Once the court determined that "speech" was commercial, it then applied the four-pronged Central Hudson test, which is used to review the constitutionality of restrictions on commercial speech.

In applying the Central Hudson test, the court initially found that health claims made in off-label promotional material were neither unlawful nor inherently misleading. In his opinion, Judge Lamberth criticized the FDA's characterization of the off-label "speech" as inherently misleading: "In asserting that any and all scientific claims about the safety, effectiveness, contraindication, side effects, and the like regarding prescription drugs are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them, [the] FDA exaggerates its overall place in the universe." Judge Lamberth further noted that the FDA has a number of internal controls in place that assure the off-label "speech" being disseminated is reliable and truthful. However, Judge Lamberth placed a caveat on his ruling, stating that his decision in no way hinders the FDA from restricting claims that are actually false and misleading.

Next, the court evaluated the remaining three Central Hudson prongs. The court found that the government has a substantial governmental interest in regulating off-label speech in order to protect the health and safety of the American public. Within this general protection of health and safety, the government stated that curtailing off-label promotion furthers two specific interests: 1) ensuring that unbiased and accurate information is disseminated to medical practitioners, and 2) providing manufacturers with

97.  Id. at 62-64.
98.  Id. at 59.
99.  Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n of N.Y., 447 U.S. 557, 566 (1980). In commercial speech cases, a court must first determine whether the expression is protected by the First Amendment. To satisfy the first prong, the expression must concern a lawful activity and not be misleading. Second, a court must determine whether the asserted governmental interest is substantial. If both inquiries are answered in the affirmative, the court must then determine whether the regulation directly advances the asserted governmental interest, and finally, whether it is not more extensive than is necessary to serve that interest. Id.
100.  Friedman, 13 F. Supp. 2d at 67.
101.  Id. at 68.
102.  Id.
the incentive to receive FDA approval for their product's previously unapproved uses. Finding only the latter interest legitimate, the court held that the government could not regulate off-label "speech" out of fear of misuse by physicians. The court stated, "a physician's livelihood depends upon the ability to make accurate, life-and-death decisions based upon the scientific evidence before them," and thus, it can be assumed that a physician will have the sophistication and knowledge to critically evaluate any information concerning off-label use that is presented to them.

Additionally, the court found that because the FDA does not pass judgment on a physician's ability when an off-label use article is presented in sources or contexts unrelated to drug manufacturers, the agency's assertion of its power to limit claims for the "good of the recipient" was "wholly and completely unsupportable." It questioned as unclear "why the ability of a doctor to critically evaluate scientific findings depends upon how the article got into the physician's hands, or whether a manufacturer suggests speakers or content for a CME seminar." \(^{104}\)

Deferring to the judgment of Congress, the court held that the government does have a substantial public safety interest in compelling manufacturers to get approval of off-label claims. The third prong of the Central Hudson test states that a restriction on commercial speech must advance a governmental interest in a direct and material way. By proscribing a manufacturer's ability to market their product for an off-label use, there is a strong financial incentive for the manufacturer to file a supplemental application for the new use with the FDA. The court found these restrictions to directly advance the government's substantial interest. \(^{105}\)

Despite being successful on the first three prongs of the Central Hudson test, the FDA failed to convince the court on the fourth prong, i.e., that the restrictions were no more extensive than necessary. The court noted there were a number of less restrictive alternatives were available to the government that similarly encourage drug companies to seek FDA approval for their products' off-label uses. For the court, the most apparent alternative was full disclosure of the risks and benefits of the product by the manufacturer. \(^{106}\) Although the court believed this alternative to be less burdensome and still effective in satisfying the needs of the FDA and Congress, it found that given the nature of drug manufacturers, the ideal of full disclosure may be too much to expect. Thus, finding the restrictions on

\(^{103}\) Id.
\(^{104}\) Id.
\(^{105}\) Id. at 72.
\(^{106}\) Id. at 73.
off-label speech overly broad, the court granted WLF’s summary judgment motion, ruling that the FDA could not constitutionally restrict drug manufacturers from promoting the off-label uses of their products to the medical profession.\textsuperscript{107}

In the midst of the WLF I case, Congress passed FDAMA. As discussed previously, FDAMA’s section 401 permitted manufacturers to disseminate off-label information in specific medical literature, provided the manufacturer complies with a number of onerous statutory conditions. These conditions conflicted with the WLF I ruling, so WLF sued again (“WLF II”). In 1999, the same district court held that the injunction imposed in WLF I applied to section 401 of FDAMA.\textsuperscript{108} The ruling in WLF II delivered a major defeat for the FDA by striking down portions of FDAMA for violation of the First Amendment. In his ruling, Judge Lamberth described the government’s arguments supporting FDAMA as “preposterous.”\textsuperscript{109} Affirming its prior decision declaring the speech at issue commercial, the court applied the \textit{Central Hudson} test to the restrictions found in FDAMA. As it did in the WLF I decision, the district court held that section 401 was overly extensive in scope. The court found that the requirements, particularly the requirement that drug manufacturers file a supplemental application for the new use with the FDA, constituted a type of “constitutional blackmail” on manufacturers to conduct clinical studies.\textsuperscript{110} Additionally, the court found that adequate incentives were already in place to encourage drug manufacturers’ to seek additional FDA approval, such as the ability to market approved products to a wider market, a greater confidence on the part of doctors to prescribe drugs for such approved uses, and protection from future tort claims against the manufacturer.\textsuperscript{111} The court noted that manufacturers are acutely aware that as the market for prescription drugs becomes more competitive, the guarantee of safety and reliability that comes with an FDA approval will become more important as a deciding factor for health care providers. It is this market pressure that will motivate the manufacturer to seek FDA approval for their off-label use. Given these pre-existing incentives and the availability of less-burdensome alternatives, the court held that FDAMA unduly burdens commercial speech in violation of the First Amendment. Amending the WLF I order \textit{sua sponte}, the court declared these conditions as unconstitutional.

\begin{itemize}
\item \textsuperscript{107} \textit{Id.} at 73-74.
\item \textsuperscript{109} \textit{Id.} at 85.
\item \textsuperscript{110} \textit{Id.} at 87.
\end{itemize}
of section 401 of FDAMA unenforceable.\footnote{112}{Henney, 56 F. Supp. 2d at 87.}

Response to the ruling in WLF II was immediate. Shawn Gunnarson of the WLF described Judge Lamberth's ruling in WLF II as "mak[ing] it very clear that the First Amendment is alive and well."\footnote{113}{Judge Overturns Law That Limits Release of Drug-Use Info., N.Y. TIMES, July 29, 1999, at A18.} WLF's attorneys called their cases "the pivotal cases influencing the evolution of FDA's approach to marketing."\footnote{114}{John Kamp et al., FDA Marketing v. First Amendment: Washington Legal Foundation Legal Challenges to Off-Label Policies May Force Unprecedented Changes at FDA, 54 FOOD & DRUG L.J. 555, 555 (1999).} The FDA position was recognized by most experts as having been adversely affected by the WLF II case.\footnote{115}{Cooper, supra note 47.} The District of Columbia Circuit issued its opinion in February 2000, dismissing the appeal and vacating the lower court's injunction.\footnote{116}{Washington Legal Found. v. Henney, 202 F.3d 331, 337 (D.C. Cir. 2000).} The Court of Appeals decision was based primarily on the FDA's oral argument at the hearing, which made the very critical concession that its interpretation of FDAMA is limited to the establishment of a "safe harbor" under which manufacturers would be protected from misbranding or "intended use" enforcement actions if they comply with certain statutory requirements.\footnote{117}{Id. at 335.}

In light of the agency's restated policy position, the WLF dropped its constitutional objections to FDAMA. Nevertheless, the court issued its mandate vacating the WLF II district court injunction and stating that "[t]he government has announced here nothing less than an official interpretation of the FDAMA which the agency may not change unless it provides a reasoned explanation for doing so."\footnote{118}{Id. at 336-337.} The result of the years of litigation was that the manufacturers prevailed, but the rules for future conduct remained cloudy.\footnote{119}{Cooper, supra note 47.}

The outcome of the WLF litigation was worth the drug industry investment in support of the efforts.\footnote{120}{The pharmaceutical industry's amicus brief supported WLF. Henney, 202 F.3d at 332.} FDA is now constrained in its use of section 401, and drug claims will undergo 401 scrutiny only when the marketer seeks a safe harbor for those claims. In order to comply with the First Amendment and the rulings in the WLF cases, the FDA had to accept a more limited role under FDAMA; section 401 is not the mandatory screening tool for all claims that had been its 1997 intention. The future enforcement attitude of the FDA may be more restrained; coincidentally, in
2001, Daniel Troy, the successful litigation advocate for WLF, became Chief Counsel of the FDA.\textsuperscript{121}

\section*{IX. LIABILITY RESULTING FROM OFF-LABEL USES}

When a patient is injured by the off-label use of a product, he or she will typically file a products liability claim against the manufacturer and a malpractice claim against the doctor. These dual claims often lead to the battle of the defendants at trial, where each side blames the other for the resulting injury. The manufacturer claims the doctor's use was unforeseeable, while the doctor claims that such use was one commonly engaged in by the profession and sanctioned by the manufacturer.\textsuperscript{122} The informational material, or lack thereof, circulated to medical community concerning such off-label use, is strong evidence either for or against the manufacturer's knowledge about the foreseeability of such off-label usage. The jury will ultimately determine who should be held liable to the patient for the failure to warn, if such a failure is a remedy in tort.

\subsection*{A. Manufacturer Liability}

Regulatory inaction against a drug marketer's off-label promotion does not mean the drug marketer is free of adverse consequences. If drug manufacturers promote their products for off-label uses, potential tort liability may increase. The manufacturer has a duty to warn about the risks involved with its product. Most pharmaceutical product liability cases arise under a claim of failure to warn.\textsuperscript{123} Plaintiffs assert the off-label use of the drug that caused the harm should have been the subject of a warning; in their defense, manufacturers argue that there was no way that they could have foreseen their products being used in such an unapproved manner, and therefore the drug marketer should not be held liable for the injury resulting from such unapproved use. The defendant marketer is considered an expert and is rarely successful with such a defense.\textsuperscript{124}

Since the passage of FDAMA, it will be even harder for a manufacturer to prove that it was unaware that its product was being used for such unapproved purposes. The manufacturer is obligated to include certain disclosures (e.g. that the drug has not been approved by the FDA) in its labeling and other marketing materials for the product's off-label uses.\textsuperscript{125} A plaintiff's search of the electronic databases retained by the manufacturer

\begin{flushleft}
121. See www.fda.gov for a listing of the FDA board members.
122. Rheingold, \textit{supra} note 32, at 55.
123. Ascroft, \textit{supra} note 52, at 108.
124. Rheingold, \textit{supra} note 32, at 55.
\end{flushleft}
will show that others asked about the same type of use for this drug.

Tort liability for the drug manufacturer can also stem from incomplete product testing,\textsuperscript{126} or the negligent transmission to the FDA of incomplete or inaccurate clinical data to support such use.\textsuperscript{127} But failure to warn litigation is the most likely liability risk for manufacturers. Both litigation expenses and damage awards can cause a significant cost burden to the manufacturer, which will be passed along to drug purchasers.\textsuperscript{128}

Pharmaceutical marketers asserted that Congress should pass preemptive legislation that exonerates drug companies from liability for any label statement that had received FDA approval.\textsuperscript{129} They claim that through the approval process, the FDA is asked to make significant judgments on the risk, safety, and reliability of new drugs and new indications, and these judgments should receive deference in the form of preclusion of jury verdicts about unreasonable risks from an FDA-reviewed product.\textsuperscript{130} The drug industry asserts that federal preemption of state law would lead to a greater number of tort outcomes consistent with the regulatory reviews of those products. The present lack of consistency in state jury outcomes has proven very challenging for pharmaceutical manufacturers, who market and sell their products across many jurisdictions with a single U.S. label.\textsuperscript{131}

\textbf{B. Physician Liability}

Drug marketers have no common law or statutory duty to directly warn patients of the risks involved with prescription drugs. Manufacturers, however, fulfill their legal duty by providing adequate warnings to physicians, under the Learned Intermediary Doctrine,\textsuperscript{132} by which manufacturers are obligated to adequately disclose to physicians all known risks and contraindications for their products.\textsuperscript{133} Additionally, manufacturers must continually monitor the product's use and is held accountable to respond to any new risks that may occur. Once a

\textsuperscript{126} Strict liability for inadequate warning arises when an adverse effect of a drug is "known or reasonably scientifically knowable", under some states' jurisprudence. See, e.g., Carlin v. Superior Court, 920 P.2d 1347, 1349 (Cal. 1996).

\textsuperscript{127} Negligence claims may survive but a direct claim of fraud upon the FDA would probably be rejected under the Supreme Court's approach in the comparable claim of medical device fraud, Buckman v. Plaintiff's Legal Committee, 531 U.S. 341 (2001).


\textsuperscript{129} Ascroft, \textit{supra} note 52, at 109.

\textsuperscript{130} \textit{Id.}

\textsuperscript{131} \textit{Id.} at 109-10.

\textsuperscript{132} \textbf{RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY} § 6, cmt. e (1998).

manufacturer satisfies its duty to warn the learned intermediary, it generally wins tort cases alleging a failure to warn.\textsuperscript{134}

Placing the ultimate duty to warn patients in the hands of the physician is essential to preserving the doctor-patient relationship. Because physicians make the individualized decisions on the treatment of their patients, they are in the best position to convey the risks and benefits of such treatment to their patients. Treatment decisions are based on the circumstances surrounding the individual’s ailment, and the treating physician should be the most familiar with these circumstances. Assuming that the physician is fully informed by the manufacturer of the drug’s risks and benefits,\textsuperscript{135} the physician is then under a duty to disclose these risks and to gain the patient’s informed consent to treatment. Physicians do not routinely obtain the signed informed consent of patients when prescribing a particular drug, and such a requirement would probably be awkward if it existed.\textsuperscript{136}

If the patient claims malpractice from the prescription of inappropriate medications, commentators have suggested that the causes of action could include failure to obtain informed consent, ordinary negligence, or strict liability arising out of failure to adhere to the statements about the drug in the Physician Desk Reference ("PDR") or package insert.\textsuperscript{137} The exposure to potential liability increases as the doctor diverges from customary medical standards of care. In the fen-phen litigation, doctors prescribed diet drugs for periods of time longer than the brief use approved by the FDA on the drug’s labeling, and prescribed it for some patients who should not have qualified for its use.\textsuperscript{138} In the bone (pedicle) screw cases, orthopedists used screws designed for long bones, like the femur, during more delicate back surgery.\textsuperscript{139} As one court held, "[p]hysicians may be found negligent if their decision to use a drug off-label is sufficiently careless, imprudent or unprofessional."\textsuperscript{140}

In \textit{Richardson v. Miller}, the plaintiff brought a medical malpractice and products liability action against her attending physician claiming negligence and violation of the standard of due care for the use of terbutaline during her labor. Although terbutaline was approved by the FDA only for the treatment of bronchial asthma, it was commonly used by physicians to help

\textsuperscript{134} Nicole Endejann, \textit{Is the FDA’s Nose Growing?: The FDA Does Not "Exaggerate" its Overall Place in the Universe When Regulating Speech Incidental to "Off-Label" Prescription Drug Labeling and Advertising}, 35 AKRON L. REV. 491, 524-26 (2002).

\textsuperscript{135} RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6 (d)(1) (1998).

\textsuperscript{136} Endejann, supra note 134, at 526.

\textsuperscript{137} Rheingold, supra note 32, at 54-55.

\textsuperscript{138} \textit{In re} Diet Drugs Prods. Liab. Litig., 282 F.3d 220 (3d Cir. 2002).

\textsuperscript{139} Rheingold, supra note 32, at 52.

\textsuperscript{140} Richardson v. Miller, 44 S. W. 3d 1, 20 (Tenn. Ct. App. 2000).
retard the progression of labor in mothers by relaxing the uterine muscles. Terbutaline may be taken orally or in a pump designed to subcutaneously inject small amounts of the drug into the patient’s body in timed intervals. Despite having little experience with the terbutaline pump, the defendant physician arranged for an infusion pump to be attached to the plaintiff. Plaintiff alleges that as a result of the administration of terbutaline during her labor, she suffered a major heart attack resulting in permanent heart damage. At trial, the court granted defendant’s motion to exclude all references made to the off-label use of terbutaline, including the drug’s listing in the PDR and its package insert. On appeal, the Tennessee Court of Appeals found that the trial court had committed reversible error by excluding this evidence. The court found that information regarding the off-label nature of a drug is essential in helping to establish the standard of care against which the defendant should be judged. The defendant failed to abide by the warnings issued by the FDA which cautioned against the use of a terbutaline infusion pump in the treatment of pre-term labor. Thus, the appeals court found that the lower court’s decision to exclude such evidence on the dangers of off-label use of terbutaline “materially hampered” the plaintiff’s ability to prove her medical malpractice claims against the defendant. The court vacated the lower court verdict and remanded the case for a new trial.

Under a claim of pure negligence, a plaintiff must prove the physician’s conduct was a significant departure from the standard of care of a reasonable physician under similar circumstances. Typically, a physician’s standard of care is established by evaluating how physicians in similar situations acted on prior occasions in treating their respective patients. Standards of care for medical practitioners vary among different communities and expert witnesses are required to know the community standards of the place where the injury occurred. At trial, the burden of proof rests with the prescribing physician to justify a deviation from the

141. Id. at 5.
142. Id. at 7.
143. Id. at 8.
144. Id. at 9.
145. Id.
146. Id. at 15.
147. Id. at 23.
standard of care. Negligence claims often result in a battle of experts—the plaintiff's experts try to characterize the physician's conduct as a gross departure from the standard of care while the defendant's experts try to establish that the physician's conduct was in fact in accordance with ordinary protocol.

Another cause of action against a physician is a claim of strict liability. A plaintiff may use FDA-approved labeling, the Physician's Desk Reference listing, and the package insert, to establish a prima facie standard of care in the use of a particular medication. The burden of proof then lies with the defendant physician to explain the off-label use of the product in accordance with the standard. The vast majority of cases, including the Tennessee Court of Appeals in Richardson, have held that the PDR listing is admissible at trial in establishing a standard of care, but only if expert testimony regarding standard of care is introduced during trial.

Besides tort claims, an injured patient may bring a malpractice cause of action against his or her physician for the off-label use or, even, for failure to use the drug in an off-label way if it would have been the best treatment option for the patient. Medical malpractice claims regarding prescribing practices have increased in recent years. As Dr. Michael Fetters, assistant professor of family medicine at the University of Michigan stated, "I think physicians are always practicing with some unconscious fear of being sued because it is very prevalent." Medical malpractice laws vary from state to state.

Medical malpractice insurance and defense is a significant cost for physicians, and medical literature cautions that physicians who prescribe medications for off-label use has resulted in potentially greater malpractice risk. To reduce risk, physicians are urged to remain informed on the latest news for the medication and its uses, maintain a file separate from the patients' files on the literature dealing with the off-label use of the medication, emphasize to the patient that the proposed treatment involves the off-label use of the medication, and document the continuous informed consent by the patient to such treatment.

152. Rheingold, supra note 32, at 55.
153. Richardson, 44 S. W. 3d at 20.
154. Stoffelmayr, supra note 128 at 281.
placed on continuous communication between the manufacturer and the physician, the physician and the patients, and the physician and the medical community. Ultimately, it will be the physicians, keeping in mind the potential liability, who will decide the best treatment options for their patients.

X. POTENTIAL FOR FUTURE CHANGES IMPACTING LIABILITY FOR OFF-LABEL USES

Product liability law is a branch of common law torts that has traditionally varied among the states. For example, no national products liability law covers all pharmaceutical "failure to warn" claims. The Restatement (Third) of Products Liability was recommended to the states by the American Law Institute in 1997. However, its provisions show a heavy influence by the drug industry and the defense bar, so it remains controversial when considered by state courts. This inconsistency poses a number of difficulties for both the pharmaceutical marketer, whose promotional activities span many jurisdictions, and the physician, who must weigh the potential malpractice liability risks against the benefits of the treatment options for his or her patient.

The drug industry has sought to preempt state tort law governing off-label use of prescription drugs, by proposals for a federal statute that includes a defense that FDA approval of a drug would bar any products liability claims against the manufacturer. In 1995, the House of Representatives passed a products liability bill that would preclude the award of punitive damages if the marketer satisfies the FDA's requirements for safety and efficacy for their product and its use. This would serve as a strong economic incentive for pharmaceutical companies to seek FDA approval for all uses. Additionally, the rejection of punitive damages would create more certainty for manufacturers because it would negate the current confusing distinctions across jurisdictions. Although this bill served as an indication of potential reforms, the industry failure to persuade Congress to adopt the change will be revisited in the 108th Congress.

The changing environment of the pharmaceutical marketplace is affecting the actions of manufacturers. As the risk of malpractice liability increases, physicians may be more cautious about prescribing a medication to their patient for an off-label use. Thus, as the availability of competing drugs increases, physicians may prefer treatment options that are approved by the FDA for that particular use. Specific FDA approval is a signal to the physician that the product has met safety and efficacy standards. There will

158. Id.
be a competitive advantage to having the ability to broadly publicize a
drug's approval for this use, including the consumer television advertising
claims that a drug is "now the first drug approved for use against X." With
this increased competition among drug therapies comes an increased
number of sales messages; the sales representative and the advertisements
seek to convince physicians to prescribe the product, and "now FDA
approved for X use" aids in the promotion.

The outcome of the WLF litigation fits into the puzzle here: a "safe
harbor" is quite useful if the FDA does, in fact, take enforcement cases
against drug marketers who make excessive or false claims, and the FDA
enforcement cases inevitably result in negative publicity for the
manufacturer.¹⁵⁹ Therefore, it is in the best interest for the manufacturer to
be cautious in following the 401-submission requirement, before making
claims about the off-label use of its product. This caution should induce
manufacturers to use the FDA's section 401 procedures, and at best, should
convince them to seek FDA new drug approval in order to support the
claims made about the product and its particular use.

XI. INTERNET COMMUNICATIONS CHANGE PARADIGMS

Not only is the pharmaceutical marketplace becoming more competitive,
but with the advent of the Internet, manufacturers are also finding new
methods for the dissemination of information regarding the off-label use of
their product.¹⁶⁰ This poses significant policy problems for the FDA.¹⁶¹
Most manufacturers operate websites offering information about their
products and their uses, information that may be accessed by both
consumers and medical professionals. The quality of medical information
on the Internet varies widely, as medical experts have warned physicians.¹⁶²
The Internet and its implications for off-label use were not debated when
FDAMA was adopted. But the FDA has long treated all forms of
promotional media under the same rules.¹⁶³

A commentator observed that because the terms of section 401 do not
mesh well with internet delivery of information, the website dissemination
of data on a drug's off-label use cannot qualify for the "safe harbor"

¹⁵⁹. Id. at 115.
¹⁶¹. Id. at 600; for an excellent review of these issues see Nancy K. Plant, Prescription Drug Promotion on the Internet: Tool for the Inquisitive or Trap for the Unwary?, 42 St. Louis U. L.J. 89 (1998).
¹⁶². William M. Silberg et al., Assessing, Controlling and Assuring the Quality of Medical Information on the Internet, 277 JAMA 1244 (Apr. 16, 1997).
protection under section 401. As a result, it is actually subjected to a greater degree of regulation as a result. The reader will note with interest how FDA deals with the enforcement of 401 in the coming years; the commentator may be correct in anticipating that FDA will challenge Internet abuses.

The Internet offers many advantages, including ease of access and variety of forms of data delivery, for both the drug manufacturer and the prescribing physicians. Its use as a website dissemination medium would also allow patients to have greater access to information regarding their treatment options. The website operated by the manufacturer might limit what it reveals, to avoid regulatory problems; but the off-label use data might be prominently circulated by private websites which are free to offer advice and information so long as they do not act as agents of the drug maker. Further, Internet vendors of drugs are so heedless of regulatory controls that FDA Commissioner Jane Henney warned in a 2000 speech: "Unfortunately, the Internet purchase can bypass all of the public health safeguards."

The Internet's ease of access to information regarding the off-label use increases the potential liability of manufacturers and physicians. If there is a negative consequence from the use of such treatment, it will be harder to prove that such a consequence was unforeseeable, especially given the accessibility of the risk information from Internet websites easily located via search engines. Some commentators argue that the information disseminated over the Internet should be accorded the same First Amendment protection as information disseminated via other media. The many capabilities of the Internet, proponents argue, would allow manufacturers to tailor their "speech" to comply with the statutory requirements of FDAMA. Since FDAMA, this issue has been debated but not resolved, and some form of statutory resolution of the conflict is inevitable in the future.

XII. OTHER PRESSURES IMPACTING PROMOTIONAL CONTROLS

Harmonization of drug approval across national boundaries is an active

165. Dr. Jane Henney, Address to Mid-America Coalition on Health Care (March 27, 2000).
167. Id. at 218-19.
and growing field,\textsuperscript{169} and the approval of drug effectiveness claims prior to marketing is likely to be a tenet of global drug authorities. The bargain that industry achieved with the U.S. Congress in 1997 to loosen controls on claims under section 401 may not hold up when other nations ask why unapproved uses can be widely promoted here. This may be a pressure to change back toward the 1962 policy of pre-marketing efficacy proofs.

Expanded patient information access may doom the paternalistic approach to pre-market approval of new uses. A regulatory system that builds a delay into the passage of data, awaiting scientific verification and regulatory approval, will inevitably lag behind the speed of electronic transmission in today’s Internet environment. Science is not static and human clinical research studies are evolving along with pharmaceutical chemistry. The sick or dying patient is likely to welcome most off-label use, since the patient can have today’s latest therapies based on information with disclaimers or 1998’s therapies based on information with the stamp of federal approval. Consumers seem to be urging physicians to offer more choices based upon data that has not awaited federal blessings, and that is a major paradigm shift from the assumptions that underlie the drug efficacy statutes of the 1960’s.

Additionally, the volume of the activity may make it impossible to police with the FDA’s inadequate enforcement budget. Off-label use is now so widespread that it is virtually impossible for the regulatory process to keep up with the pace of innovation. In fact, in some cases the off-label use has become considered the standard of care, and failure to follow this standard may be grounds for malpractice claims.\textsuperscript{170} Drugs used in unapproved indications are commonplace in the treatment of cancer, AIDS, pediatric diseases, and rare diseases. Those suffering from these ailments have come to depend on off-label use in their treatment. However, opponents of the off-label use believe that expansion of such uses without FDA scrutiny poses a significant threat to the health and well-being of the American public. Strong voices in the debate surrounding off-label use will advocate for the two mutually exclusive policy positions.

XIII. CONCLUSION

Off-label use of drugs as a physician choice is a necessary and positive aspect of flexible treatment for patients. The risks that it carries should be borne by the physician. If the marketer of a drug wishes to profit from a drug’s sale based on claims of beneficial effects, without first obtaining


\textsuperscript{170} Stoffelmayr, \textit{supra} note 128, at 278.
FDA approval of the claims, the drug marketer now can use the FDAMA section 401 vehicle to begin promoting the off-label use, with some assurance that its claims are shielded by a "safe harbor."

There are societal costs to giving manufacturers this profitable option. With the passage of FDAMA section 401 and the government's litigation concession in the WLF case that limits its coverage to a passive "safe harbor" role, the promotion of off-label use is institutionally controlled rather than banned outright. The FDA could act against a drug marketer's website or oral or written claim, or the marketer can claim a "safe harbor" under section 401, provided that the manufacturer satisfies certain statutory requirements. The drug marketer chooses either to be safe or to risk an FDA challenge. Either way, the 1962-1997 regime of a ban on off-label promotion has come to an end "with a whimper."

However, the 1997 law required a study of the effects of section 401, and as the National Academy of Sciences examines the potential abuses that may arise in future off-label disseminations of claims, it is likely that Congress will revisit the FDAMA's provisions. When it does, changes in the pharmaceutical marketplace are likely to affect future legislation. As this article went to publication, the sponsor of section 401 was elected Senate Majority Leader, so his personal stake in preserving the compromise language of 401 will probably prevent substantial changes for the near future at least.

As potential liability increases, and global standards for drug claim support evolve, drug manufacturers may be significantly more motivated to seek FDA approval for the additional uses of their products. The off-label use of drugs and devices will remain part of the practice of medicine in the future. Our society's assignment to the FDA of the role of medication "gatekeeper" needs to be enhanced, not diminished, in future legislative negotiations.

172. Cooper, supra note 47.