

The risky business of off-label use

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Off-label use of drugs and devices is an accepted part of modern medical practice. When harm results, lawyers must navigate the maze of regulatory and case law to hold drug companies accountable.

Because the FDA requires that prescription drugs and medical devices undergo lengthy, costly review and testing before their approval and marketing, American consumers trust the agency to ensure that these products are safe and effective. But most people do not realize that many drugs and medical devices are prescribed for uses that the manufacturer did not intend and that have not been tested for safety and efficacy.

Indeed, doctors are free to prescribe FDA-approved medications and devices in any way they deem medically appropriate, without regulatory oversight.¹ At least one court has acknowledged that off-label use is “subject to asymmetrical—if not necessarily inconsistent—regulatory treatment.”²

Lawsuits brought by patients injured as a result of off-label use have raised complex issues that the courts are

working to resolve. Recent changes in statutes governing the FDA and an ever-growing body of federal and state case law make representing injured clients challenging. But the effort is worthwhile: Litigation over off-label use has the potential to improve drug safety for all health care consumers.

Off-label use is a key component of mainstream medical practice and a recognized exception to FDA oversight.³ Many off-label uses are recommended by research institutions, professional organizations, and standard pharmaceutical reference books. They are especially common in treating AIDS, cancer, and rare diseases. The Supreme Court has said that off-label use “is an accepted and necessary corollary of the FDA’s mission to regulate [drugs and medical devices] in this area without directly interfering with the practice of medicine.”⁴

FDA policy states that “once a [pharmaceutical] 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.”⁵ This policy, known as the practice-of-medicine exemption, reflects the history of the 1938 Food, Drug, and Cosmetic Act (FDCA).⁶ The FDCA was intended to regulate the manufacture of pharmaceutical products, rather than the conduct of doctors in prescribing them. Similarly, the 1997 Food and Drug Administration Modernization Act (FDAMA), amending the FDCA, includes specific protection for prescriber choice.⁷

At the same time, the FDCA prohibits drug and device manufacturers from marketing or promoting a product for a use that the FDA has not approved.⁸ If its labeling includes information about unapproved uses, the drug has been “misbranded.”⁹

The FDAMA says that if a manufacturer intends to promote a drug for new uses, it must resubmit the drug for FDA testing and approval.¹⁰ However, the act’s so-called Mack-Frist provision, §401, allows manufacturers or their sales representatives to provide physicians with peer-reviewed articles from scientific or medical journals or reference books and information about clinical trials of off-label uses of the product.¹¹ Before the FDAMA, companies collected such

references and occasionally provided them in response to physician inquiries. However, §401 appears to permit companies to proactively disseminate this type of information, contrary to the FDA’s prior blanket prohibition of promoting off-label uses.

Specifically, §401 allows distribution of information regarding off-label use if the manufacturer

- submits to the FDA a supplemental new-drug application for the new use
- disseminates information that is not abridged, false, or misleading and does not pose a significant health risk to the public
- ensures that all clinical research described in the information is the manufacturer’s work
- submits a copy of the information to the FDA at least 60 days before disseminating it to doctors
- includes prominent disclaimers clarifying that the drug has not been approved by the FDA for that particular off-label use.¹²

Ironically, the FDAMA was enacted only two months after the popular diet drugs fenfluramine and dexfenfluramine were withdrawn from the market because of adverse events linked to their off-label use. These drugs, marketed by American Home Products Co. (AHP, now Wyeth), were FDA-approved for short-term use as stand-alone therapies. Beginning in 1992, medical articles in peer-reviewed journals sug-

gested that fenfluramine could be taken for longer periods if combined with phentermine, another diet drug.¹³ AHP did not sponsor these studies but responded to physician inquiries by providing copies of the articles, which implicitly promoted the off-label, long-term use of fenfluramine together with phentermine.

Many who used fen-phen suffered severe and sometimes fatal side effects, including both primary pulmonary hypertension and valvular heart disease. Peer-reviewed literature showed that the longer fen-phen was used, the greater the frequency of both conditions.¹⁴ Most of the injuries and deaths, along with most of AHP’s estimated \$16 billion liability to date, probably resulted from the off-label use of fen-phen, since the scientific literature shows that few injuries occurred among short-term users.¹⁵

It is uncertain whether these adverse effects would have been detected in clinical trials if long-term use of fen-phen had been submitted for FDA approval. What is clear is that they could not have been detected in the small-population studies AHP used to promote fen-phen. The fen-phen fiasco demonstrates the risk inherent in promoting off-label uses without the full panoply of testing and review that new drug uses must undergo to gain approval.

Federal preemption

Defendants in state lawsuits involving harm from off-label

uses often argue that federal law preempts such claims. In *Buckman Co. v. Plaintiffs' Legal Committee*, a case involving the promotion and speedy approval of an off-label use of a medical device, the Supreme Court endorsed the defense of federal preemption in pharmaceutical and medical device cases, holding that "fraud on the FDA" claims were impliedly preempted by the FDCA as amended by the FDAMA.¹⁶

The plaintiffs were patients who claimed to have suffered injuries resulting from bone screws that had been implanted in their spines. They sued the manufacturer and the consulting company that assisted the screw manufacturer in obtaining FDA approval of the devices. They claimed that both "made fraudulent representations to the FDA as to the intended use of the screws and that, as a result, the devices were improperly given market clearance and were subsequently used to the patients' detriment."¹⁷

The Court reasoned that such claims encroach on the inherently federal relationship between the FDA and the entities it regulates because the relationship is governed by federal law. The majority opinion discussed at length the FDA's practice-of-medicine exemption, including off-label drug and device use, and acknowledged the agency's recognition that off-label prescription can have value. The Court suggested that "fraud on the FDA" claims

would discourage manufacturers from seeking approval for devices with potentially beneficial off-label uses.¹⁸

Despite its endorsement of off-label use and the FDA's policy supporting it, the *Buckman* majority did not hold that all state law claims relating to off-label uses are preempted. Instead, the

Contrary to the FDA's prior blanket prohibition, a 1997 revision in the law appears to permit companies to proactively disseminate peer-reviewed articles and clinical trial information about off-label uses of a drug or medical device.

Court noted that its holding of implied preemption was based on the fact that "the fraud claims exist solely by virtue of the FDCA disclosure requirements."¹⁹ Therefore, other state law claims concerning the promotion and marketing of off-label uses that parallel federal safety requirements are still viable.²⁰

In fact, the Court in *Buckman* made clear that claims based on traditional state tort law that had predated the federal enactments in the FDCA, such as those at issue in an earlier case, *Medtronic, Inc. v. Lohr*, were still viable.²¹ The *Lohr* claims included a state law defective-drug claim and claims based on allegedly defective labeling and marketing.²²

Both *Buckman* and *Lohr* left several questions unresolved. One is how far the

lower courts will extend the *Buckman* holding to preclude claims that are not entirely based on a violation of a federal statute but involve evidence of fraud on the FDA.²³

Lohr also left open the question of whether the premarket approval process imposes specific federal requirements

on a medical device maker so as to trigger preemption under the Medical Device Amendments. Several federal and state courts have concluded that it does.²⁴

Other questions concerning the interplay of federal and state jurisdiction over lawsuits involving off-label use are unsettled. In *Rubel v. Pfizer, Inc.*, an Illinois case involving the drug *Neurontin*, the drug company removed the case to federal court, claiming preemption.²⁵

The plaintiffs sought relief under the Illinois Consumer Fraud and Deceptive Business Practices Act, claiming that Pfizer had illegally marketed *Neurontin* for off-label use. Although the complaint alleged that the company's conduct had violated federal statutes and regulations, it carefully limited the causes of action to a single state-law

claim.

The district court held that despite the “plaintiff’s myriad references to federal law,” no federal question existed.²⁶ Because the plaintiffs made no federal claim for relief, and because the FDCA lacks private enforcement provisions that would encompass the plaintiffs’ claims, the court remanded the matter to state court.

Several types of claims concerning promotion of off-label use of drugs are still viable.

Most people do not realize that doctors are free to prescribe FDA-approved medications and devices in any way they deem medically appropriate, without regulatory oversight.

For example, in *Tardy v. Eli Lilly & Co.*, the court permitted the plaintiffs to proceed with claims for fraudulent misrepresentation and concealment related to off-label promotion of Zyprexa, an antipsychotic drug. It dismissed other claims on the basis of the learned intermediary defense.²⁷

In *United States ex rel. Franklin v. Parke-Davis*, a federal qui tam action was filed and successfully settled against the drug company. The complaint alleged that Parke-Davis had engaged in an extensive and far-reaching campaign to use false statements to promote increased prescriptions of Neurontin for off-label uses, which caused the filing of false claims for reimbursement by the federal government.

The court denied Parke-Davis’s motion to dismiss for the most part and held that the False Claims Act could be used to create liability where failure to abide by FDCA rules and regulations amounts to a material misrepresentation made to obtain a government benefit.²⁸

Learned intermediary doctrine

According to the learned intermediary doctrine, a drug or device manufacturer is protected from liability for injury if it has provided a

sufficient warning to the prescribing physician. This issue is more complex when a case involves an off-label use.

The manufacturer’s warnings describe effects that can occur when the drug is used as directed, and they list precautions and contraindicated uses. Risks associated with off-label uses are not included in the labeling, so one must look elsewhere to determine whether the manufacturer warned physicians sufficiently to invoke this defense.

For example, if research articles discussing off-label uses were provided to doctors, it would be important to know whether the risks of such use were disclosed at the same time. A search of the literature could also show what was known by the relevant

medical community.

In *Proctor v. Davis*, an Illinois appellate court upheld a jury verdict against Upjohn Co. for a plaintiff who suffered eye injuries because of the off-label, intraocular injection of Depo-Medrol, a corticosteroid. The court found that Upjohn had promoted this use even though the company had known about possible severe adverse effects for over 20 years. In particular,

Upjohn encouraged and participated in disseminating misleading information concerning the use of its drug to the “learned intermediaries,” through financial support, technical assistance, and abundant supplies of the drug during the period when Upjohn was receiving adverse information concerning the use of this drug. Ironically, some of these very reports became part of the literature which was supposed to inform the “learned intermediaries” about application of the drug intraocularly. . . . Doctors who have not been sufficiently warned of the harmful effects of a drug cannot be considered “learned intermediaries,” and the adequacy of warnings is a question of fact, not law, for the jury to determine, as it did in the instant case.²⁹

The court held that Upjohn promoted the off-label use of the drug without attempting to communicate the risks. It found the company’s sponsorship of flawed literature particularly egregious because Upjohn used it to “plant the seed” of misinformation

that resulted in harmful use of the drug.³⁰

Although Proctor was decided a few months before the FDAMA took effect, the act probably would not protect a manufacturer under similar circumstances. Section 401 permits manufacturers to disseminate peer-reviewed literature promoting off-label use only when the information is not false or misleading and does not create a risk to public health. When the manufacturer promotes off-label use without informing physicians of known risks, neither the learned intermediary doctrine nor the FDAMA should provide a shield against liability.

Counsel investigating adverse events resulting from off-label use should consider the potential for liability based on the manufacturer's withholding information about risk from doctors and patients. Sources of risk information beyond the label must be investigated.

Off-label use of drugs and medical devices will continue to be a significant part of medical practice. Although it may provide benefits to patients, its risks are potentially greater, exacerbated by manufacturers' sponsorship of studies to support off-label use, biased reporting of data, and publication of only favorable studies.³¹ Patients injured by off-label drug use have the right to hold manufacturers responsible when they fail to adequately warn of the risks. ■

Notes

1. The American Medical Association adds a caveat: if such use is based on scientific evidence and sound medical opinion. Policies of the AMA's House of Delegates, Patient Access to Treatments Prescribed by Their Physicians, H-120.988(1)(a)(2004), available at www.ama-assn.org/apps/pf_new/pf_online (click on "Health Policies of the HOD," then H-120.000, "Drugs: Prescribing and Dispensing," then H-120.988)(last visited Feb 1, 2005).
2. See, e.g., *Wash. Legal Found. v. Henney*, 202 F.3d 331, 332 (D.C. Cir. 2000).
3. James M. Beck & Elizabeth D. Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 FOOD & DRUG L.J. 71, 79-80 (1998).
4. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 350 (2001).
5. Citizen Petition Regarding the FDA's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59820, 59821 (Nov. 18, 1994) (citing Policy Statement, Uses of Approved Drugs for Unlabeled Indications, 12 FDA DRUG BULL. 4-5 (1982)). For a discussion of the FDA's policies, see generally James O'Reilly & Amy Dalal, Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs, 12 ANNALS HEALTH L. 295 (2003).
6. 21 U.S.C. §§301-99 (2000); see 78 CONG. REC. 3, 2728-29 (1934) (statement of Sen. Copeland).
7. 21 U.S.C. §396 (2000).
8. See *id.* §331(a) and §331(d).
9. *Wash. Legal Found.*, 202 F.3d 331, 332-33 (citing 21 U.S.C. §331(a)).
10. 21 U.S.C. §§360aaa(b)(1)(a), 360aaa-3 (2000).
11. *Id.* §301. See also The FDA Modernization Act of 1997, FDA Backgrounder (Nov. 21, 1997), available at www.fda.gov/opacom/backgrounders/modact.htm (last visited Feb 1, 2005).
12. 21 U.S.C. §360aaa(b) (2000).
13. See, e.g., Michael Weintraub, Long-Term Weight Control Study: Conclusions, 51 CLINICAL PHARMACOLOGY & THERAPEUTICS 642 (1992).
14. See, e.g., James G. Jollis et al., Fenfluramine and Phentermine and Cardiovascular Findings: Effect of Treatment Duration on Prevalence of Valve Abnormalities, 101 CIRCULATION 2071 (2000); Stuart Rich et al., Anorexigens and Pulmonary Hypertension in the United States: Results from the Surveillance of North America Pulmonary Hypertension, 117 CHEST 870 (2000).
15. See *Merck Pulls Vioxx off the Market*, Investor Guide Daily (Oct. 1, 2004) (stating Wyeth has reserved \$16 billion to \$17 billion for fenfluramine liability and has paid more than \$13 billion to date), available at www.investorguide.com/cgi-bin/dailyarchives.cgi?date=100104 (last visited Feb. 1, 2005).
16. *Buckman*, 531 U.S. 341, 343.
17. *Id.* at 347.
18. *Id.* at 350-51.
19. *Id.* at 353.
20. See, e.g., *Proctor v. Davis*, 682 N.E.2d 1203, 1214-15 (Ill. App. Ct. 1997).
21. *Buckman*, 531 U.S. 341, 352-53 (citing *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996)).
22. The Lohr Court found that the state laws were not expressly preempted under the Medical Device Amendments. The issue in *Buckman* was implied preemption. See *Buckman*, 531 U.S. 341, 352.
23. See, e.g., *Davenport v. Medtronic, Inc.*, 302 F. Supp. 2d 419 (E.D. Pa. 2004); *Dusek v. Pfizer, Inc.*, No. Civ. A. H-02-3559, 2004 WL 2191804 (S.D. Tex. Feb. 20, 2004).
24. See cases cited in *Davenport*, 302 F. Supp. 2d 419, 431.
25. 276 F. Supp. 2d 904 (N.D. Ill. 2003), appeal dismissed, 361 F.3d 1016 (7th Cir. 2004).
26. *Id.* at 907.
27. No. CV-03-538, 2004 WL 1925536, at *4-5 (Me. Super. Ct. Aug. 3, 2004).
28. 147 F. Supp. 2d 39, 51-52 (D. Mass. 2001).
29. *Proctor*, 682 N.E.2d 1203, 1214-15.
30. *Id.* at 1215.
31. See Barry Meier, *Contracts Keep Drug Research Out of Reach*, N.Y. TIMES, Nov. 29, 2004, at A1.

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