

Off-Label Promotion Of Drugs and Medical Devices

By Michael Kendall
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A spate of billion- and hundred-million-dollar settlements with the Department of Justice (DOJ) illustrates how the investigation of off-label promotions of drugs and devices has emerged as a predominant theory in pharmaceutical and medical-device prosecutions. Up to 60% of all prescription drug use in the United States is off-label, and the regulatory and medical issues are exceedingly complicated. The application of off-label regulations, therefore, has significant impact in these cases that generate enormous criminal and civil monetary penalties and can lead to misdemeanor convictions of corporate executives on a strict-liability theory.

Typically, prosecutors seek to punish off-label promotion with civil penalties under the False Claims Act predicated on billings to Medicare and Medicaid and criminal prosecution under the Food, Drug, and Cosmetic Act. Federal prosecutors have entered into criminal and civil settlements that included off-label allegations with Pfizer, Eli Lilly, Serono, Astra Zeneca, Cephalon,

Bristol-Myers Squibb, and Schering Plough, among others. Several device manufacturers have entered into off-label settlements too. The DOJ has made off-label investigations a continuing priority, which means off-label cases will be among the largest cases the Department prosecutes over the next several years.

The rules relating to the off-label marketing of drugs and devices are at times inconsistent. In order to sell a drug or medical device, the manufacturer must receive FDA approval, which means the FDA has determined the drug has efficacy (it works) and is safe enough for use. The FDA determines what illnesses the manufacturer can say the drug treats (“approved indications”) and how the drug should be administered (“on-label administration”). Federal law defines “off label” use of an approved drug as any use that is not included within the FDA-approved label. Manufacturers are prohibited from promoting drugs for such “unapproved uses.” See 21 U.S.C. §§ 355(a); 331(d). Notably however, although the FDA regulates the manufacture, labeling, and promotion of drugs, it does not regulate the practice of medicine. Once the FDA approves a drug for any use, physicians and other providers are free to prescribe it for off-label indications and administration. See 12 *FDA Drug Bulletin* 4 (April 1982). Providers may administer the drug or device off-label, alter dosing or means of administration (e.g., intravenous or subcutaneous), or use drugs and devices labeled for adults with children.

Medical research frequently documents efficacious off-label uses of medicine that are never presented to the FDA for inclusion on the label, or that the FDA takes years to approve. Practitioners incorporate successful off-label uses reported in medical journals into their practice without waiting for FDA approval, in order to provide the best care for their patients. Punishment of off-label promotion raises critical ethical issues as it pits concerns about providing the best patient care with the government’s desire to enforce the FDA’s regulatory scheme. If the government is too rigid or aggressive in its off-label enforcement, it may prevent desperately ill patients from receiving efficacious treatment.

There is substantial disagreement and litigation over the parameters of the FDA’s limitations on off-label marketing. On Jan. 13, 2009, the FDA issued a Notice designed to clarify the rules governing one aspect of the off-label marketing issue: distribution of “medical and scientific information” discussing off-label uses. This clarification can provide assistance to those defending off-label cases and force prosecutors to be more flexible when treading on patient care issues.

HISTORY OF THE FDA’S REGULATION OF OFF-LABEL USE

Originally, the FDA adopted the position that a manufacturer could not promote an off-label use of its product in any way. In 1997, Congress passed the Food and Drug Administration Modernization Act

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(FDAMA), Pub. L. 105-115, which relaxed these restrictions to allow manufacturers to distribute reports of clinical studies under limited circumstances. Though presumably still barred from general off-label advertising, under § 401 of the FDAMA, a sales rep could lawfully distribute materials regarding drugs' or devices' off-label uses if the manufacturer: 1) filed an application with the FDA to approve the indication; 2) sponsored the trials itself or had permission from a sponsor; 3) filed with the FDA all studies to be disseminated 60 days in advance of the intended dissemination; and 4) included a prominent disclaimer on the reports that the FDA has not approved the new use. 21 U.S.C. § 260aaa. This safe harbor allowed only two types of unabridged materials to be distributed: 1) peer-reviewed articles that have been published in a scientific or medical journal; and 2) scientifically sound reference publications. These prerequisites were so onerous that manufacturers did not utilize them for most off-label uses.

In 2000, after a lawsuit arguing that some provisions of FDAMA violated the First Amendment, *see Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Washington Legal Foundation v. Friedman*, 36 F. Supp. 2d 16 (D.D.C. 1999), the FDA revised its position, stating that it would not take regulatory action against any manufacturer that complied with § 401 of the FDAMA, nor would it regard the disseminated reports as evidence that the manufacturer violated the law. 65 Fed. Reg. 14286 (March 16, 2000).

THE FDA'S JAN. 14, 2009 GUIDELINES

The safe harbor in the FDAMA had a sunset provision that caused it to expire in 2006, and since that time DOJ off-label enforcement has grown. After nearly three years of studying the issues, on Jan. 14, 2009, the FDA issued a Notice authorizing sales reps to distribute certain medical articles discussing off-label uses. In particular, the

FDA recognized that "public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products." *See* FDA's "Guidance for Industry," January 2009, available at <http://www.fda.gov/oc/op/goodreprint.html>.

Some interest groups have argued that the Notice is too lenient and allows manufacturers to promote products that have not been adequately tested. There is little basis for such claims. The new guidelines do not give sales reps carte blanche to market off-label. To the contrary, the guidelines include limitations on what type of articles may be distributed as well as the manner of distribution. The new guidelines are somewhat similar to the old safe harbor: Sales reps may distribute only articles that come from peer-reviewed journals with editorial boards that satisfy certain criteria for independence and expertise. Manufacturers may not summarize, highlight, or alter the articles in any way, and the reprints must contain a "prominently displayed and permanently affixed statement" noting the uses discussed are not approved by the FDA.

With respect to distribution, the FDA mandates that any off-label articles distributed to doctors must be kept separate from promotional materials, and it prohibits sales reps from discussing off-label articles with doctors during sales calls. Furthermore, when publications exist that reach contrary or different conclusions, the manufacturer must disseminate representative contrary publications along with its off-label article. Recognizing that the line between marketing and educational programming is often blurred, the FDA also states that while reprints may be distributed at medical or scientific conferences "in settings appropriate for scientific exchange," off-label articles may not be shared "in promotional exhibit halls or during promotional speakers' programs."

Though the FDA's January 2009 Notice has clarified some rules regarding off-label marketing, it is not clear how the DOJ will enforce the guidelines. Indeed, even at first glance, a number of questions arise:

- How close in time may the promotional and information meetings be? The same day? The same week?
- Can sales reps attend informational meetings? Is a sales rep ever permitted to discuss an off-label article, even outside the context of a sales call? Footnote 7 of the Guidance for Industry implies that the sales reps would have to refer off-label questions to a separate department (manufacturers typically have a medical-affairs department with clinical expertise that can handle such inquires);
- May articles be distributed at medical or scientific conferences that are sponsored by a particular company?

CONCLUSION

In most off-label prosecutions, the government tries to portray the off-label use as detrimental to patient health, or claim there was not a truthful, complete disclosure of clinical data. The government tries to demonize the off-label promotion, as otherwise it is hard for the government to demand nine- or ten-figure settlements from companies that helped desperately ill patients. The recent FDA notice is a modest step toward ensuring appropriate communications on off-label uses.