Promotion of Off-Label Uses of Prescription Medical Products: FDA’s Proposed New Guidance

By Bruce Patsner, M.D., J.D.

Prescription medical products approved by the U.S. Food and Drug Administration (FDA) can be promoted to healthcare consumers (direct to consumer advertising, DTCA) or to physicians. Advertising and promotion to consumers can only be for the indications FDA approved the product for, and FDA has issued several final guidance documents for manufacturers concerning risk information which must appear in consumer-directed print advertisements and in broadcast advertising such as television. By contrast, most promotion to physicians is via distribution of reprints of articles in medical journals, and although promotion to physicians can be for either on-label or off-label uses, off-label promotion is only permissible if done by physicians, not the manufacturer. Promotion of off-label uses to physicians in any fashion has always been controversial, and the regulatory playing field has been lately been complicated by the recent “sun-setting” of the current FDA regulatory framework; several high-profile cases by state and federal prosecutors against companies such as Johnson and Johnson and Pfizer for “repeated and persistent fraud by misrepresenting, concealing, and otherwise failing to disclose to physicians” important drug and device safety and efficacy information for promoted off-label uses; and FDA-related commercial speech case law which appears to be at odds with FDA policy.

In an effort to provide much-needed regulatory guidance to manufacturers, FDA recently proposed new guidelines for allowing manufacturers to promote off-label uses of devices and drugs by dissemination of journal article reprints. This proposed guidance was

---

6 Daren Fonda and Barbara Kiviat, Curbing the Drug Marketer: How a clampdown on pitching drugs for unapproved uses is changing the way Big Pharma operates, TIME, July 5, 2004, p.31.
outlined in a draft guidance issued February 15, 2008\textsuperscript{10} and accessible via the internet.\textsuperscript{11} The 60 day notice and comment period for this proposed new rule expired on April 21, 2008. The final version of the guidelines has yet to appear, but even a cursory perusal of comments reveals that response to the proposed rule was strong and swift.\textsuperscript{12}

Off-Label Use: General Considerations

The 1938 Federal Food, Drug and Cosmetic Act\textsuperscript{13} requires that the new drug demonstrate substantial evidence of efficacy and safety in adequate and well-controlled clinical trials for the indications which will appear in the label before it can be approved for marketing (sale) in the United States. The label for a prescription medical product approved by FDA\textsuperscript{14} is intended to provide all of the information judged to be necessary for the drug, device, or biologic to be used safely and effectively for the product’s indicated\textsuperscript{15} patient population or disease.

An off-label use by definition is one for which safety and efficacy data was not submitted to FDA for approval. Once a drug or medical device is approved its use by a licensed physician is not limited to the indications in the label but rather only by the individual physician’s judgment as to what is best for the individual patient. In some clinical settings off-label use is of great value in patient care: it’s common in treatment of adult cancer patients, and ubiquitous in the pediatric patient population because testing of new drugs still relatively uncommon in children. The FDA does not regulate the practice of medicine,\textsuperscript{16} and thus does not regulate off-label \textit{use} of prescription devices or drugs by physicians. However, FDA does regulate the manufacturing, labeling, and \textit{promotion} of these items, and it is the latter – promotion – which is the rub. FDA is legitimately concerned that promotion of an approved drug or device for an untested, off-label use might lead to unreasonable consumer expectations about the safety or effectiveness of the product.


\textsuperscript{11}The FDA’s proposed new rules for off-label promotion of medical products through distribution of medical literature are available at http://www.fda.gov/oc/op/goodreprint.html.


\textsuperscript{13}FEDERAL FOOD, DRUG AND COSMETIC ACT, 21 U.S.C. § 396 (1938) [hereafter FDCA].

\textsuperscript{14}Id.

\textsuperscript{15}UNITED STATES FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH (CDER), CDER HANDBOOK.

\textsuperscript{16}Statement of Janet Woodcock, Director of the Center for Drug Evaluation and Research, Before the House Subcommittee on Oversight & Investigations, 106th Cong. (1999), “FDA does not generally regulate the practice of pharmacy or the practice of medicine – the States traditionally have regulated both the prescribing and dispensing of drugs.” See also Peter Barton Hutt, \textit{Regulation of the Practice of Medicine Under the Pure Food and Drug Laws}, 33 J. A. FOOD AND DRUG OFFICIALS 3 (1969).
Industry Promotion of FDA Approved Medical Products

FDA attempts to regulate the promotion of off-label use of prescription drugs and devices have been successfully challenged in federal court.\textsuperscript{17} The Supreme Court considers promotion of drugs and devices to be a form of commercial speech. In \textit{Washington Legal Foundation v. Friedman}\textsuperscript{18} the court determined that the commercial speech doctrine and the \textit{Central Hudson} test\textsuperscript{19} apply to FDA efforts to regulate advertising and promotion of the medical products it approves. FDA efforts to restrict off-label promotion in the past decade have generally been found too broad to survive challenge under \textit{Central Hudson} and thus have been ruled an unconstitutional abridgment of First Amendment rights.\textsuperscript{20} The Supreme Court has even been willing to allow drug and device promotion which might be misleading provided there is a sufficient disclaimer about the medical information.\textsuperscript{21} On the other hand, the more recent \textit{Caputo} decision\textsuperscript{22} did uphold the ability of FDA to restrict off-label promotion of a medical device when there was no satisfactory, less restrictive way to do so. In other words, although manufacturers are proscribed from off-label promotion by statute, federal court decisions suggest otherwise. New guidance from FDA could serve to help calm the waters.

A Proposed New Guidance for Manufacturers

In September 2006 the provisions of the 1997 Food and Drug Administration Modernization Act (FDAMA)\textsuperscript{23} that governed the promotion of off-label indications for drugs and devices expired. Under FDAMA, a safe harbor was created for manufacturers permitting them to promote off-label uses of their products.\textsuperscript{24} Sponsors could disseminate peer-reviewed studies from scientific literature about off-label uses provided these studies had been or would be part of a supplementary New Drug Application (sNDA).\textsuperscript{25} When this provision of FDAMA “sun-setted,” the regulatory framework reverted back to that prior to 1997 which prohibited any promotion of a prescription drug for unapproved uses, a regulatory approach already rejected by the Supreme Court in the \textit{Washington Legal Foundation v. Friedman}, 13 F. Supp. 2d 51 (D.D.C. 1998). Much of the controversy started in 1994, when the Washington Legal Foundation sued FDA, hoping to overturn FDA’s policies on limiting drug and device manufacturers from distributing what it viewed as truthful information on off-label uses of their products.\textsuperscript{18}

\footnotesize
\begin{itemize}
  \item \textsuperscript{17} A. Elizabeth Blackwell and James M. Beck, \textit{Drug Manufacturers’ First Amendment Rights to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory}, 58 FOOD AND DRUG L.J. 439 (2003).
  \item \textsuperscript{19} \textit{Central Hudson Gas & Elec. Corp. v. Public Service Commission}, 447 U.S. 557 (1980).
  \item \textsuperscript{20} \textit{Western States Medical Center v. Shalala}, 238 F.3d 1090 (9th Cir. 2001), affirmed 535 U.S. 357 (2002), “if the government can achieve its interests in a manner that does not restrict speech, or that restricts less speech, the government must do so.” This case involved efforts to restrict pharmacies’ promotion of specific prescription drugs they were compounding.
  \item \textsuperscript{21} A. Elizabeth Blackwell and James M Beck, \textit{Drug Manufacturers’ First Amendment Rights to Advertise and Promote Their Products for Off-Label Use: Avoiding a Pyrrhic Victory}, 598 FOOD AND DRUG L. J. 439 (2003).
  \item \textsuperscript{22} \textit{United States v. Caputo}, 288 F. Supp. 2d 912 (N.D. Ill. 2003). \textit{Caputo} was a criminal, not a civil case, and one of the allegations concerned whether the medical device in question had been approved by FDA for any use.
  \item \textsuperscript{24} \textit{Id.}
  \item \textsuperscript{25} \textit{Id.}
\end{itemize}
Foundation cases, in which the Supreme Court ruled that the off-label promotion of drugs and devices is a form of commercial speech and therefore subject to First Amendment protection.

The Proposed New Rules for Promotion of Off-Label Uses of Medical Products

The proposed new rules no longer require sponsors to submit a supplement New Drug Application (sNDA) and do not compel manufacturers to immediately update the labels for their products as soon as they become aware of potentially important new safety information. Rather, a company will only need to revise its label after it has established “sufficient evidence of a causal association” between its product and the reported adverse event(s).

The Draft Guidance proposals do impose significant constraints on the dissemination of medical journal articles about off-label uses though. These restrictions state (1) the medical or scientific article must be published by an organization with an independent editorial board; (2) the journal article must be peer-reviewed; (3) the information in the article should address “adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate safety and effectiveness”; (4) the article must not be false or misleading; (5) the use discussed in the article must not pose a significant risk to public health; (6) financial interest disclosures accompanying the article must be prominently displayed; (7) the article should be disseminated along with the product’s approved label; and (8) sales people distributing the material should not discuss the article.

FDA’s arguments favoring a new rule for regulating the dissemination of off-label uses of approved drugs and devices are correct, up to a point. Doctors do need to obtain information about potential new uses of drugs and devices in a timely manner, and manufacturers actively engaged in direct clinical research can be invaluable sources of such information. Sometimes the off-label use is the standard of medical care even if the off-label indication is not in the drug or device label. However, the larger issue is whether it is necessary for companies to promote off-label uses at all, since this information does appear in the medical literature and doctors are more than capable of searching the medical literature on their own. More worrisome is that the few reviews on the published peer review literature being distributed by manufacturers shows bias in the

---

29 Draft Guidance, supra note 10.
selection of studies,\textsuperscript{31} manipulation of the literature, and “no evidence that the published peer-review literature accurately represents the state of knowledge about sponsors’ products.”\textsuperscript{32} Recent controversies over drug manufacturer clinical trials published in prestigious medical journals have raised legitimate concerns that the integrity of both industry and academia have been compromised,\textsuperscript{33} with the result that it is more difficult to claim that scientific articles used in promotion of off-label uses are truly objective.

Some in Congress\textsuperscript{34} and academic medicine have suggested that the proposed new rule is little more than a perfunctory attempt at regulation of unbridled industry marketing activity that will “encourage an explosion” of off-label use.\textsuperscript{35} There is no data to support this contention, and off-label drug use is already commonplace in all areas of medicine. But the proposed new rule is not without serious problems. At the very least the new evidentiary requirement for making changes to the label should be eliminated, for several reasons:\textsuperscript{36} (1) it could take years to acquire this data and thus lessen FDA’s power to require companies to warn doctors and patients about possible drug-related injuries at the earliest possible time; (2) the new requirement seems to make it more difficult to sue manufacturers in court for failure to warn claims concerning the label; and (3) the new rule appears inconsistent with Congressional intent expressed in the Food and Drug Administration Amendments Act of 2007\textsuperscript{37} that drug companies should update labels once they become aware of any new safety information.

Where This Is Headed

Although some critics have strongly suggested that FDA’s new guidance for off-label dissemination of journal article reprints discussing non-approved uses of medical devices and prescription drugs allows marketing disguised as science,\textsuperscript{38} the real problem is that it is both marketing and science. Any new rules will have to address this inherent tension. The concern about how to view scientific literature disseminated by manufacturers with a marketing agenda is a legitimate one and will likely not go away given all of the bad

\begin{itemize}
  \item See Congressman Waxman’s letter to FDA Commissioner von Eschenbach, which suggested that the proposed rule was part of a concerted effort by the Bush administration to allow massive promotion of off-label uses of drugs and devices by manufacturers, \textit{available at} http://oversight.house.gov/story.asp?ID=1641 (last accessed November 30, 2007).
  \item Food and Drug Administration Amendments Act of 2007.
\end{itemize}
press this year about drug maker deceit, ghostwriting of articles, celebrity physicians on television, and concerns over transparency and selection of data. Moreover, there is little doubt that because industry is required by law to present the bad aspects of their products along with the good, there is the potential that the writing in commissioned or sponsored medical journal articles may be biased to downplay risks just as occurs in television ads.

It is unclear how much more FDA can do. Some of the conduct in question concerns that of physician investigators and their relationships with manufacturers during the course of their medical practice as well as how prestigious medical journals police their own conduct as scientific reviewers. This is more a matter of regulation of the medical profession than regulation of food and drug law. This situation might be helped by full transparency and full disclosure of all financial and advisory board relationships between investigators and manufacturers for all medical publications regardless of their origin. Sworn statements by authors of medical literature noting whether writing was done by others or whether any data were omitted at the request or insistence of the manufacturer could also help.

Given the Supreme Court’s commitment to protection of commercial speech even when it may not be completely truthful and the essentially unregulated manner in which the practice of medicine oversees off-label prescription of drugs and devices by physicians, FDA’s new rule may be the best we can hope for. Even the most reasonable FDA guidance on promotion of off-label will not, and should not, protect manufacturers from federal and state prosecution when their promotional activities are fraudulent; neither will the First Amendment under those circumstances. But manufacturers’ full compliance with new FDA guidelines might provide much-needed consumer protection and a measure of balance to how off-label uses are presented to physicians, while at the same time acknowledging that off-label promotion will likely never go away.

*Health Law Perspectives* (June 2008), available at:
http://www.law.uh.edu/healthlaw/perspectives/homepage.asp

41 Hackster, M.D., *Using celebrities to sell drugs isn’t good enough anymore. You need a celebrity with a professional degree*, FORBES November 27, 2006 at 52.
42 *Id.*