

# THE FDA'S GUIDANCE ON OFF-LABEL REPRINTS: WHAT'S OLD IS NEW AGAIN

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On January 13, 2009, the Food and Drug Administration (FDA) issued its long-awaited final guidance titled “Good Reprint Practice for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drug and Approved or Cleared Medical Devices” (the Guidance), which governs the conditions under which pharmaceutical and medical device manufacturers may distribute articles, publications, and other information to physicians describing non-FDA-approved uses for drugs or devices.<sup>1</sup>

The question of whether and under what circumstances drug and device companies can distribute reprints of articles on off-label uses of their drugs and devices has been the topic of much debate over the last decade. While having a defined set of guidelines governing this practice should be seen as a positive development for both manufacturers and government, not everyone has viewed it as such. Issuance of the Guidance has led many to worry that the FDA has shifted its policy and opened the door for industry to promote its drugs and devices for off-label uses through the dissemination of reprints. To better understand whether these concerns are justified, this article reviews the

controversy over the dissemination of off-label reprints and seeks to place the Guidance in the context of this long-running debate.

## The Controversy over Distribution of Off-label Reprints

Federal statutes and FDA regulations prohibit manufacturers from promoting approved drugs or devices for unapproved uses, also known as “off-label” uses.<sup>2</sup> In the past five years, federal prosecutors and healthcare regulators have stepped up enforcement against manufacturers that engage in prohibited off-label promotion. Investigations in this area often focus on certain marketing practices that are more susceptible to illegal activity. Some of these practices clearly cross the line into off-label promotion by the manufacturers. For example, sales representatives clearly are not permitted to offer unsolicited suggestions to physicians to use their company’s drug or device off-label. Similarly, manufacturers’ printed marketing materials may not advise readers of the efficacy of their drug or device for off-label uses.

Other practices, however, fall into a gray area. For example, industry sponsorship of continuing medical education programs on off-label uses may be viewed as an attempt by

a manufacturer to convince physicians to use their drug or device for unapproved purposes. It may also be viewed, however, simply as an effort to share data with physicians on novel treatments that may not have undergone the rigorous testing required for FDA approval.

Distribution of article reprints addressing an off-label use also falls into this gray area. While no government investigation has been based exclusively on a company's distribution of off-label reprints, at least one civil lawsuit under the False Claims Act has cited variations of the practice as evidence of a company's intent to promote a drug for an off-label use.<sup>3</sup>

Over the last decade, there has been vigorous debate over whether the practice should be permitted. Proponents argue that so long as the data presented in an article is truthful and non-misleading, physicians should be afforded the opportunity to receive as many articles as possible on a given treatment and decide for themselves whether it is appropriate for their patients. They argue that any efforts to stymie this process of information sharing works to the detriment of patient care. Opponents view the distribution of off-label reprints simply as another method by which pharmaceutical and medical device companies can promote one of their products for off-label uses. They fear that the data presented in an article may be biased or that the company may only distribute articles discussing favorable studies. They also fear that by allowing such distribution, manufacturers have less incentive to seek approval from the FDA for new uses.

The effort to balance these interests has led to a variety of statutory, regulatory and judicial solutions.

### **Prior Efforts to Resolve the Controversy**

The controversy over distribution of off-label reprints first came to a head in 1998 when the Washington Legal Foundation (a nonprofit public interest group) challenged the FDA's enforcement of a policy restricting the dissemination of "enduring materials," such as article reprints, describing off-label uses. In a July 1998 decision, the court held that the FDA's restrictions were more extensive than necessary to serve the asserted government interest and consequently violated the First Amendment.<sup>4</sup> The court issued an injunction to stop the FDA from prohibiting, restricting, sanctioning, or otherwise seeking to limit any pharmaceutical or medical device manufacturer or any other person from "disseminating or redistributing to physicians or other medical professionals any article concerning prescription drugs or medical devices previously published in a bona fide peer-reviewed professional journal. . . ."<sup>5</sup>

On November 20, 1998, the FDA published certain implementing regulations relating to Section 401 of the FDA Modernization Act of 1997 (FDAMA). These included a provision allowing for dissemination of off-label reprints only if the manufacturer met certain criteria such as registering with the FDA for approval of the new uses within a certain timeframe and submitting the subject articles for FDA review at least 60 days prior to disseminating them. In a July 1998 decision,

Judge Royce Lamberth of the U.S. District Court for the District of Columbia, who issued the injunction in 1998, confirmed that his injunction applied not only to the guidance documents in effect in 1998, but also to the implementing regulations of FDAMA.<sup>6</sup>

Judge Lamberth's injunction was later vacated in 2000 when the FDA argued on appeal that the FDAMA provision restricting dissemination of off-label reprints was merely a safe harbor and did not create any new or independent enforcement rights.<sup>7</sup> The FDA then issued a Notice confirming this position.

As long as a manufacturer complied with the conditions of this "safe harbor," the distribution of off-label reprints would not be used as evidence of intent to market the product for an unapproved use. Following the second WLF decision, manufacturers relied upon this safe harbor to legally distribute articles and other materials discussing off-label uses. In 2006, however, Section 401 of FDAMA, which was the focus of the later WLF litigation, expired. Until 2009, manufacturers had no guidance from any governmental or regulatory body on how to distribute off-label reprints without running afoul of the law. The Guidance, though presented only as recommendations, was intended to fill that gap.

### **FDA Guidance**

The Guidance is premised on the fact that "the public health may be advanced by healthcare professional's receipt of medical journal articles and medical or scientific reference publications on unapproved

new uses of approved or cleared medical products that are truthful and not misleading.”<sup>8</sup> Therefore, unlike FDAMA, which many viewed as too restrictive to be of any practical use, the Guidance supports the dissemination of off-label articles, though subject to certain conditions. For example, scientific or medical journal articles disseminated pursuant to the Guidance should be:

- Published by an organization with an editorial board that uses experts who have demonstrated expertise in the subject of the article and who are independent of the organization to review and objectively select, reject or provide comments about proposed articles, and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- Peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- Not in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article.<sup>9</sup>

Information included in these articles should address “adequate and well-controlled” clinical investigations that are considered “scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device.”<sup>10</sup>

The information disseminated must not be false or misleading, or pose a significant risk to the public health. In addition, a disseminated publication: (1) should not be primarily distributed by the drug or device manufacturer; (2) should not be written, edited, excerpted or published specifically for, or at the request of, a drug or device manufacturer; and (3) should not be edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

The Guidance also retains some of FDAMA's previous recommendations relating to the manner in which scientific and medical information should be disseminated to healthcare professionals. For example, the information that is distributed:

- should be in an unabridged format and cannot be marked, highlighted, summarized, or characterized by the manufacturer in any way;
- should be accompanied by the approved labeling for the drug or medical device;
- should be accompanied by a comprehensive bibliography when such information exists;
- where an article's conclusion has been disputed by another, a representative sample of the articles discussing contrary results should also be disseminated; and
- should be distributed separately from promotional materials.<sup>11</sup>

Finally, any reprint of a journal or reference publication should be accompanied by a prominently

displayed and permanently fixed disclosure from the manufacturer stating: (1) the described uses have not been approved by the FDA; (2) any author known to the manufacturer having a financial interest in the product or manufacturer or who is receiving compensation from the manufacturer; (3) any person who provided funding for the study; and (4) all significant risks or safety concerns known to the manufacturer concerning the unapproved use.<sup>12</sup>

### The Guidance in Context

When a draft version of the Guidance was issued in February 2008, critics warned that it signaled a shift in FDA policy toward allowing off-label promotion through the dissemination of reprints. Issuance of the final version of the Guidance did little to quell that criticism. Such criticism, however, may have been misplaced for a few reasons.

First, though there is limited case law in this area, the court that examined this issue the closest—Judge Lamberth in the WLF decisions—held that manufacturers have a first amendment right to distribute off-label reprints, albeit with certain restrictions. The FDA likely understood that it needed to begin with the premise that a blanket prohibition on disseminating off-label reprints was not a viable option. The only question, then, was whether the proposed restrictions advanced the government's interests in the least restrictive manner.<sup>13</sup>

Second, permitting dissemination of off-label reprints was not a new concept to the FDA. As discussed above, the practice was permitted

under FDAMA under certain restrictions. The Guidance is less restrictive than FDAMA in some ways, but more restrictive in others. For example, the Guidance does not require that the manufacturer apply, or intend to apply, to the FDA for an indication in the new use that is the subject of the article, nor does it require that the manufacturer submit the article to the FDA for review 60 days prior to dissemination, both of which were required under FDAMA. However, the Guidance imposes several new restrictions, including a prohibition on disseminating letters to the editor, abstracts and study reports, and a requirement that a representative article reaching a contrary conclusion must accompany any article to be disseminated.

Third, the Guidance imposes many restrictions designed to allow dissemination but ensure against promotion. By restrictions such as limiting the involvement of drug and device manufacturers in the drafting and editing of the article, requiring that the article address well-controlled (though not randomized or double-blind) studies and requiring that the approved label accompany the article, the Guidance makes earnest attempts to limit the ability of a manufacturer to disseminate biased content or skew data to favor its product. It provides bright-line principles designed to ensure that all disseminated information is truthful and not misleading, which should be the primary objective of any such guidelines.

Fourth, some of the arguments for prohibiting dissemination of off-label reprints are based more on systemic issues than manufacturers' motives. For example, some critics worry that manufacturers will only disseminate articles demonstrating the efficacy of their drug or device for off-label uses, but not those showing that the drug is not efficacious for those uses.

As stated above, to the extent articles reaching contrary or different conclusions have been published, the Guidance requires that the manufacturer disseminate a representative sample of such articles along with the one showing the drug's efficacy.<sup>14</sup> Whether such contrary articles are available for dissemination, however, is another issue. In many cases, studies showing that a drug is not efficacious for a given use are not accepted to peer-reviewed journals for publication, though the existence of all clinical studies should be available on the website [clinicaltrials.gov](http://clinicaltrials.gov). The Guidance conforms to the belief that physicians should be critical readers of journal articles and that the benefits of widespread dissemination of peer-reviewed data outweigh the risks that a physician might not learn about an unpublished study reaching different or contrary conclusions.

The Guidance was issued at the end of the Bush administration and it is possible that the Obama administration may modify or rescind it. Indeed, Rep. Henry Waxman (D-Calif.), an early critic of the draft

version of the Guidance, has already requested that the Obama administration re-examine the final version. Unless it is rescinded, however, it will likely constitute "best practices" in the life sciences industry, and guide government investigations into these practices, for the foreseeable future.

For the most part, the Guidance should be welcomed by industry and government alike as relatively straightforward and clear guidelines in an area that has, for some time, lacked such clarity. In issuing this Guidance, the FDA understood that by ensuring that the articles present truthful and non-misleading data, physicians will be in a better position to analyze the information and make more informed choices in patient care.

Further, knowing that any reprints that are disseminated by manufacturers must comply with the requirements set forth in the Guidance, physicians may feel more comfortable relying on the information contained in the articles. Time will tell whether the Guidance will achieve its goal of allowing the dissemination of information on off-label uses while preventing manufacturers from using reprints unlawfully to promote their products for those uses.

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**End Notes**

- <sup>1</sup> See *FDA, Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (2009), available at <http://www.fda.gov/oc/op/goodreprint.html>.
- <sup>2</sup> See *Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 331*. The statutes and regulations do not prohibit healthcare professionals from using or prescribing drugs and devices off-label.
- <sup>3</sup> See *United States ex rel. Franklin v. Parke-Davis, 147 F.Supp.2d 39* (D. Mass. 2001).
- <sup>4</sup> *Washington Legal Foundation v. Friedman 13 F.Supp. 2d 51* (D.D.C.1998).
- <sup>5</sup> *Id.* at 74.
- <sup>6</sup> *Washington Legal Foundation v. Henney, 56 F.Supp. 2d 81* (D.D.C. 1999).
- <sup>7</sup> *Washington Legal Foundation v. Henney, (D.C. Cir. 2000). 202 F.3d 331*.
- <sup>8</sup> FDA Guidance at 3.
- <sup>9</sup> *Id.* at 4.
- <sup>10</sup> *Id.*
- <sup>11</sup> *Id.* at 5.
- <sup>12</sup> *Id.* at 5-6.
- <sup>13</sup> *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York, (1980). 447 U.S. 557.*
- <sup>14</sup> This provision in the final Guidance is broader than the equivalent provision in the draft Guidance. The provision in the draft Guidance only applied when another article or text specifically called into question the conclusions of the distributed publication. The provision in the final Guidance applies any time another article or text reaches "different or contrary" conclusions, even if it does not specifically call into question the conclusions of the distributed text.