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The Washington Legal Foundation Litigation and Its Aftermath

Introduction

The lawsuit brought by the Washington Legal Foundation (WLF) against the Food and Drug Administration began in 1994 and recently was put to rest, at least temporarily. Amazingly, despite six years of fierce legal combat, two decisions by a district court, an act of Congress, and a ruling by a court of appeals, the core issue remains essentially unresolved.

That issue is whether FDA violates the First Amendment of the US Constitution when it restricts the involvement of device and drug manufacturers in disseminating truthful scientific information about off-label uses of their products. Such information may appear in enduring materials (reference textbooks and peer-reviewed published articles) or discussed at company-sponsored continuing medical education (CME) and scientific symposia. FDA has acknowledged that third party discussion of off-label uses in enduring materials and CME programs is legitimate, constitutionally protected speech. However, FDA believes it has the right to limit the involvement of drug and device manufacturers in sponsoring and disseminating such speech.

This article discusses the key developments in the WLF lawsuit against FDA and addresses where things stand at present now that the WLF litigation has come to rest. May manufacturers disseminate truthful and non-misleading off-label information? If so, what restrictions apply? What are the regulatory risks?

Intended Use

Under the Federal Food, Drug, and Cosmetic Act of 1938, as amended, a drug or medical device generally may only be sold for intended uses that FDA has approved.[1] The intended uses of a drug or device may be set forth in labeling, advertising, promotional material, or oral statements by the manufacturer or its representatives.[2] In practical terms, evidence of "intended use" may be found in a company's Web sites, promotional brochures, journal and radio advertising, sales talks, office visits, training materials, samples, demonstrations and trade show displays.

Off-Label Promotion

A manufacturer wishing to label or advertise its already approved medical product for a new indicated use generally must submit a supplemental marketing application to FDA for approval. However, after FDA has approved a product for any single labeled use, a physician may use or prescribe it for other unlabeled uses as part of the unregulated practice of medicine. This regulatory paradox creates an incentive for the manufacturer to avoid a new marketing application by spreading the word to physicians about such "off-label" new uses. If physicians use or prescribe products for off-label uses, manufacturers may enjoy increased sales without the expense and uncertainty of conducting additional clinical studies, preparing new marketing applications, or undergoing FDA's detailed review processes.

To address this issue, FDA always has prohibited companies from producing their own marketing material discussing off-label uses or approaching physicians (or consumers) to discuss such uses. When a manufacturer violates this prohibition, FDA reserves the right to bring an "intended use" enforcement action, in which the product is deemed adulterated and/or misbranded under the Act, because the manufacturer's dissemination of off-label information has allegedly created an unapproved new intended use.[3]

FDA Responds To New Industry Tactics

In the early 1990s, FDA became concerned that some manufacturers were using indirect tactics to disseminate information about unapproved new uses. Companies were sponsoring CME programs featuring discussions about unapproved new uses for their products. Companies also were providing healthcare professionals with enduring materials mentioning such uses. These tactics did not involve company-generated information about off-label uses, but allowed a company to simply disseminate medical and scientific information arising from third parties.

The FDA countered these new tactics with

enforcement policies embodied in three guidance documents. Two of the guidance documents limited the circumstances under which companies could permissibly distribute enduring materials. These guidances were published as Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data and Guidance for Industry Funded Dissemination of Reference Texts.[4]

A third guidance document concerning manufacturer involvement in CME programs was published as the Final Guidance on Industry-Supported Scientific and Educational Activities.[5] This guidance set forth 12 factors that FDA will consider, as a matter of enforcement discretion, in determining whether an industry-sponsored CME program is truly independent and non-promotional. Among the most important factors is the degree to which a company maintains control over the content of the program and selection of speakers and moderators. Other factors include meaningful disclosure (of company funding and significant relationships between the program provider, presenters or moderators, and the supporting company and whether unapproved uses of products will be discussed); the focus of the program (single product versus all available treatment options); and audience selection (e.g., whether invitations or mailing lists are generated by the sales department of the supporting company).

WLF Lawsuit

It was FDA's attempt to impose restrictions on the dissemination of enduring materials and sponsorship of CME programs that was the basis for the WLF's lawsuit. The WLF asserted that the three guidance documents violated the First Amendment right of physicians to receive information about off-label uses from manufacturers.

The district court found that the activities in question were commercial speech that enjoyed limited First Amendment protection in accordance with the test set forth by the US Supreme Court in *Central Hudson Gas and Electric Corp. v. Public Service Comm'n of New York,* 447 US 557 (1980). Under Central Hudson, commercial speech is analyzed under a four-part test: (1) is the speech neither unlawful nor inherently misleading; (2) does the government have a substantial interest in regulating the speech; (3) do the restrictions directly advance the government's interest; and (4) is the government's policy more restrictive than necessary?

The district court concluded that the speech was neither unlawful nor inherently misleading and that the government had a substantial interest in encouraging manufacturers to seek FDA approval of off-label uses that were directly advanced by the restrictions. However, the court also held that the guidances restricted speech more than was necessary to achieve the government's legitimate objective. Thus, the district court held that the guidances were unconstitutional on their face.[6] On this basis, the district court issued an injunction preventing FDA from restricting or prohibiting any manufacturer from: disseminating enduring materials regardless of whether they discussed off-label uses, and suggesting content or speakers to independent program providers in connection with CME programs regardless of whether off-label uses were to be discussed.

As the WLF lawsuit proceeded in district court, Congress enacted the Food and Drug Administration Modernization Act of 1997 (FDAMA).[7] Section 401 of FDAMA superseded the enduring materials guidances by authorizing manufacturers to disseminate enduring materials containing off-label information, subject to important restrictions. In brief, those restrictions include requirements that the enduring materials be: about a drug or device that is legally marketed; disseminated only to permitted audiences (i.e., healthcare practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and federal and state agencies); peer-reviewed and disseminated only in the form of an unabridged reprint or copy; submitted to FDA 60 days prior to dissemination along with any other clinical trial information the manufacturer has relating to the safety or effectiveness of the new use. Furthermore, the enduring materials must carry a disclosure that they pertain to an unapproved use and, if FDA requires, must carry additional information necessary to provide objectivity and balance. Also, the manufacturer must certify that it has completed the necessary clinical studies and will submit a supplemental application within six months to bring the new use on label. Alternatively, if the necessary studies have not been completed, the manufacturer must submit for FDA approval a protocol and proposed schedule and must certify that the studies will be completed and the supplemental application submitted within 36 months.

Section 401 became effective several months after the district court issued its injunction in the WLF

lawsuit. This development was a partial victory for FDA, because Section 401 was not subject to the district court's injunction. While FDA was still restrained from enforcing the CME guidance, Section 401 now allowed FDA to impose significant restrictions on the dissemination of enduring materials without interference.

FDA's partial victory was short-lived. WLF returned to district court and obtained a ruling that Section 401 and the implementing regulations were unconstitutional on their face and that the injunction applied to them as well.[8]

All parties expected that the United States Court of Appeals for the District of Columbia would provide a resolution to the constitutional questions raised by the WLF litigation. However, at oral argument, FDA "clarified" its position on the legal significance of Section 401 and the CME guidance, advising the Court of Appeals that these are merely "safe harbors" that assure manufacturers who follow the requirements that the dissemination of off-label information cannot be used against them. FDA indicated that these provisions do not provide any independent basis for an enforcement action. WLF agreed that if FDA's position was as indicated, WLF no longer had a constitutional objection to Section 401 or the CME guidance.

This development led the Court of Appeals to find that there was no longer a constitutional dispute. On this basis, the Court of Appeals vacated the district court's injunction and dismissed FDA's appeal.[9] In a puzzling footnote, the Court of Appeals said that part of the injunction still stood, but it did not say which part.

FDA's "Notice"

In March 2000, FDA published a notice explaining how it interprets the Court of Appeal's decision.[10] FDA believes that Section 401 is a safe harbor for manufacturers and that the CME guidance document merely gives notice of how FDA will exercise its enforcement discretion. If a manufacturer disseminates off-label enduring materials or sponsors CME programs without following the restrictions, FDA is free to proceed with an intended use enforcement action. The statutory basis for such an action would be FDA's long-established authority to prosecute manufacturers for misbranding and/or adulteration, and the action would not draw any independent support from the manufacturer's failure to comply with Section 401 or the CME guidance document. FDA recognizes that, under the WLF rulings, the manufacturer could potentially raise a First Amendment defense.

WLF brought a motion in district court attacking FDA's notice, arguing that it would have a chilling effect on industry and that it violated the part of the injunction the Court of Appeals left standing. On November 30, 2000, the district court interpreted the Court of Appeals' opinion to have vacated the entire injunction (despite the puzzling footnote suggesting that part of the injunction survived). Because the injunction no longer exists, the district court concluded that FDA's notice logically could not have violated it.

So What Are The Rules?

In the aftermath of the WLF litigation, the status of a company's right to disseminate off-label information is cloudy. However, these observations may help:

1. The dissemination of company-generated labeling and advertising referring to off-label uses has always been subject to enforcement action under FDA's misbranding and adulteration authority. Some companies mistakenly concluded that the injunction originally issued in the WLF litigation allowed the dissemination of company-generated off-label information. In fact, this prohibition was not even challenged in the WLF litigation. Selective quotation from portions of a study or the company's summary of a study, generally are treated as company-generated material.
2. FDA allows companies to distribute enduring materials that discuss off-label use in response to truly unsolicited requests. This permission preceded the WLF litigation and remains in place today. It is a good idea to have clinical rather than marketing personnel fulfill these requests and to maintain a log documenting the request and response.
3. FDA has always prohibited the dissemination of promotional material that is false or misleading. Once again, this rule was not challenged in the WLF litigation. It is in full force and effect.
4. If a company disseminates peer-reviewed enduring materials (journal articles and reference texts) in compliance with the detailed requirements of Section 401 of FDAMA and the implementing regulations (21 CFR Part 99), such activity cannot be used as evidence of adulteration or misbranding in an enforcement action. Because the requirements of Section 401 and the implementing regu-

lation are onerous, this safe harbor is not likely to be used very often. Furthermore, it does not preclude FDA from bringing an enforcement action based upon other off-label information that a company disseminates.

5. If a company sponsors CME programs in compliance with the 12 factors in the CME guidance, FDA has said such activity will not be used as evidence of adulteration or misbranding in an enforcement action. Once again, the CME guidance is a safe harbor that does not immunize a company from an enforcement action based upon other off-label dissemination.
6. A company that fails to comply with FDAMA or the CME guidance risks a traditional intended use enforcement action for disseminating off-label information. The company may have a First Amendment defense. The question likely will be whether the company's activities are protected under the *Central Hudson* test applied in the WLF litigation. However, the application of the test in an enforcement action likely will depend upon the company's specific conduct and could be quite different than in the WLF litigation. As did WLF, the company will have the burden of showing that its speech was truthful and non-misleading and that the government's attempt to restrict it in the enforcement action does not directly advance a substantial governmental interest and / or is more burdensome than necessary. Although the WLF litigation suggests that a company's First Amendment defense will receive a respectful hearing in court, the outcome is far from certain.

As a practical matter, few companies will find the possibility of an untested First Amendment defense sufficiently attractive to run the risk of litigating an enforcement action. On the other hand, FDA would run a risk, too. If FDA loses an enforcement action on First Amendment grounds, the precedent potentially could jeopardize FDA's effort to restrict the dissemination of enduring materials and sponsorship of CME programs with off-label information.

This dynamic probably will lead FDA to be careful in choosing particularly egregious cases for its first few post-WLF enforcement actions. The strongest case for FDA would be one in which a company has engaged in an aggressive campaign to disseminate off-label information using both company-generated and enduring materials / CME programs, with no regard for the Section 401 and CME guidance safe harbors. Another strong case might involve a company that receives a warning letter with respect to off-label information in company-generated materials that then switches to enduring materials / CME programs as a means of disseminating the same off-label information and does not take advantage of the safe harbors in Section 401 and the CME guidance. A reasonably good case for FDA might involve a company that distributes a biased selection of off-label journal articles, providing only the favorable articles and omitting unfavorable ones. A weaker case for FDA might be a company that disseminates a fair and balanced selection of scientifically legitimate peer-reviewed enduring materials with appropriate disclaimers or a company that sponsors CME programs meeting all or most of the factors set forth in the CME guidance.

In sum, there will be a continuum of regulatory risk dependent upon each company's specific conduct. Although these off-label dissemination issues are not well settled at the moment, it would be unwise for companies to believe they have a license to freely distribute off-label information. Companies should proceed cautiously in order to avoid the unhappy fate of becoming post-WLF test cases. A prudent approach will help increase the odds that, if FDA disapproves of a company's activities, the agency will at least grant fair warning and an opportunity to cease and desist to avoid further enforcement action.

NOTES

1. For this purpose, a "drug" includes biologic products regulated under section 351(a) of the Public Health Service Act.
2. See 21 USC 321(m); 21 CFR §§ 201.128, 801.4; Action on Smoking and Health v. Harris, 655 F.2d 236, 239 (DC Cir. 1980).
3. See 21 USC §§ 331(a), (d), & (k), 351(f), 352(f), 352(o), 355(a).
4. Advertising and Promotion; Draft Guidances; Republication, 60 *Federal Register* 63,384; December 8, 1995.
5. 62 *Federal Register* 64,094; December 3, 1997. The draft guidance was set forth in Draft Policy Statement on Industry-Supported Scientific and Educational Activities, 57 *Federal Register* 56,412; November 27, 1992.
6. 13 F.Supp.2d 51 (DDC 1998).
7. Public Law No. 105-115, 111 Stat. 2296.
8. 56 F.Supp.2d 81 (DDC 1999); see also 36 F.Supp.2d 16 (DDC 1999) (denying FDA's motion to confine the injunction to the guidance documents).
9. 202 F.3d 331, 337 (DC Cir. 2000).
10. 65 *Federal Register* 14,286; March 16, 2000.

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