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# “OFF-LABEL” SPEECH: UNCERTAINTY REIGNS FOR DEVICE AND DRUG MAKERS

By

Professor Ralph F. Hall

For more than a decade, the pharmaceutical industry, the Food and Drug Administration (“FDA”) and the courts have struggled to integrate FDA’s regulation of off-label promotion of drugs<sup>1</sup> with the First Amendment’s protection of free speech. After a decade of sporadic litigation, limited legislative action, periodic enforcement actions and numerous continuing legal education programs, the issue remains undecided. Five years ago, Judge Royce Lamberth expressed his frustration with this state of affairs by noting “after six years worth of briefs, motions, opinions, congressional acts, and more opinions, the issue remains 100% unresolved.” *Washington Legal Foundation v. Henney*, 128 F. Supp. 2d 11, 15 (D.D.C. 2000) (“*WLF V*”).

The core question is whether a manufacturer can be prohibited from discussing or promoting drugs that are being legally prescribed in an “off-label” manner by physicians. FDA currently prohibits a manufacturer from promoting a drug with an FDA-approved use for an unapproved (i.e. “off-label”) use. However, the physician is free to use and promote the drug for that off-label use.

The issue came to the forefront in Washington Legal Foundation’s (WLF) challenge to FDA’s restrictions on the manufacturer’s dissemination of off-label, peer-reviewed scientific articles and on support for continuing medical education (CME). The district court issued an injunction limiting certain aspects of FDA’s restrictions on off-label speech and finding certain provisions of the Food Drug and Cosmetic Act (“FDCA”) as amended by the FDA Modernization Act (FDAMA) unconstitutional. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998) (“*WLF II*”) and *Washington Legal Foundation v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999) (“*WLF III*”). However, the U.S. Court of Appeals for the District of Columbia Circuit found the case moot after FDA argued that the FDAMA provisions regarding off-label promotion operate only as a “safe harbor” and do not create any new or independent enforcement rights. *Washington Legal Foundation v. Henney*, 202 F. 3d 331 (D.C. Cir. 2000) (“*WLF IV*”). Given that decision, Judge Lamberth in *WLF V* found his injunction to have been “wholly vacated by the Court of Appeals.”

While the *WLF* cases dealt with peer-reviewed scientific articles and CME programs, off-label speech is

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<sup>1</sup>Device promotion poses many of the same questions.

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**Ralph F. Hall** serves as Visiting Associate Professor of Law at the University of Minnesota Law School and as Counsel to the law firm Baker & Daniels, Indianapolis, Indiana, and Washington D.C.

actually much broader. Off-label speech involves any discussion about a product's uses, safety, or efficacy that is outside of the FDA-approved labeling. As such, off-label promotion includes not only a discussion about an unapproved indication, but also a discussion of unapproved "claims" regarding approved uses. Off-label promotion can include scientific information presented in non-peer reviewed sources or in a company's marketing material. Such speech could equally be directed to physicians or patients.<sup>2</sup>

Recently, the 1<sup>st</sup> Amendment issues have gained renewed attention. The pace of FDA enforcement against drug promotion seems to have increased.<sup>3</sup> WLF itself has created a "DDMAC Watch" program and is communicating to FDA its concerns that there is no constitutional basis for these enforcement actions. These issues are not unique to drugs; for example, there have also been 1<sup>st</sup> Amendment challenges in the dietary supplement/health claim area.<sup>4</sup>

Thus the matter stands today – an open and unresolved question of what constitutional limitations FDA can place on off-label promotion.

**Overview.** The 1<sup>st</sup> Amendment issues arise from several competing interests. First, FDA is charged with approving new drugs and new or expanded indications for already approved drugs. FDA generally prohibits the promotion of off-label uses.<sup>5</sup> Violation of these provisions exposes an individual or corporation to civil or potentially, criminal, liability.

FDA worries that unfettered off-label promotion will eviscerate both its pre-market approval process and its promotion and advertising controls. FDA is concerned that companies won't spend the time and money seeking an approval if they can freely promote that use without FDA approval. As such, FDA will not have the opportunity to review and approve safety and efficacy claims and, FDA fears, the public health will suffer.

Despite FDA's prohibitions on manufacturers, a physician can freely promote or use a drug for an off-label purpose. More patients are insisting upon access to even unproven therapies in critical situations. Some estimate that 30-70% of drugs used in cancer treatment are off-label. Many physicians and patients want access to information about all available therapies, particularly when the older, approved therapies are not viewed as effective or optimal. Industry wants the freedom to disseminate off-label information. While this has potential for commercial benefit, it provides valuable, perhaps life-saving, information to physicians and patients. Finally, as discussed below, the 1<sup>st</sup> Amendment allows only limited restrictions on commercial speech, and then only to support a compelling governmental interest and in the least restrictive manner possible.

**Key First Amendment Requirements.** *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, 447 U.S. 557 (1980) sets forth the current U.S. Supreme Court test for the validity of government restrictions on commercial speech as opposed to "pure" or political speech. First, both the speaker (i.e., manufacturer) and the recipient (i.e., the physician or patient) have certain 1<sup>st</sup> Amendment rights. *Central Hudson* sets forth the four factors courts use to determine the validity of commercial speech restrictions: (1) The speech must involve a lawful activity and not be inherently misleading<sup>6</sup>; (2) The restriction must involve a substantial government interest; (3) The restriction in question must directly advance the asserted interest; and (4) The restriction must be no more extensive than that required to advance the asserted interest.

The Supreme Court applied this test to FDA-regulated speech in *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002). In this case, the Supreme Court invalidated FDA prohibitions on advertising pharmacy compounding services. The Court applied the *Central Hudson* test, and found that the government had

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<sup>2</sup>The current "safe harbors" for off-label promotion are generally found in 21 CFR Part 99 (2005), the (now vacated) WLF district court injunction, industry codes of conduct and in a review of enforcement actions. These specific provisions are outlined in many other places and are not the subject of this paper.

<sup>3</sup>The percentage of all CDER enforcement letters that are issued from the Division of Drug Marketing, Advertising, and Communication ("DDMAC") and thus raise some promotional issues is about 25-30% higher for the January to July 2005 period than for the 2002-2004 time period.

<sup>4</sup>See, for example *Pearson v. Shalala*, 164 F. 3d 650 (D.C. Cir. 1999).

<sup>5</sup>See 21 U.S.C. §§ 331 and 352.

<sup>6</sup>In the FDA world, labeling can be misleading even if technically or literally true. *U.S. v. 95 Barrels of Apple Cider Vinegar*, 265 U.S. 438 (1924).

an interest in regulating pharmacy compounding, but rejected the prohibition on advertising because it was not the least restrictive means to achieve the government's interests.

The district court in *WLF II* and *III* applied the *Central Hudson* factors to off-label drug promotion involving peer-reviewed scientific articles and industry sponsored education programs. While these decisions were essentially vacated by *WLF IV* on mootness grounds, the district court findings are instructive:

1. Off-label promotion involves a legal activity and is not, de facto, misleading.
2. The government has a substantial interest in encouraging manufacturers to submit for pre-market approval. (Interestingly, the articulated governmental interest was not the protection of public health.)
3. Certain of the off-label restrictions related to peer-reviewed scientific articles and CME events did advance the governmental interests, but others did not.
4. Certain of the restrictions were too extensive to pass constitutional muster.

The argument that the government interest in question is not protecting public health but rather encouraging submissions has received less attention than it deserves. If correct, that holding should shift the debate from the restrictions appropriate to protecting public health to those restrictions necessary to enforce a bureaucratic requirement to file for an approval. Interestingly, the court in *WLF* did not explore in depth the purpose for the pre-market approval requirement, namely to ensure that only safe and effective drugs are marketed in order to protect public health.<sup>7</sup> If the end (i.e., protection of public health) is not the government's interest, how can the means to achieve that end (i.e., the pre-market approval) be a protectable interest? Other cases such as *Thompson v. Whitaker*, 248 F. Supp. 2nd 1 (D.D.C. 2002) (dealing with dietary supplement promotion) do view protection of public health as the government interest at issue.

While future 1<sup>st</sup> Amendment cases may or may not address the first *Central Hudson* factors, they will assuredly debate with great vigor whether off-label restrictions actually advance the government's interest (whatever it might be) in the least restrictive manner. In this context, the government, not industry, has the burden to establish that less restrictive approaches do not exist. Courts in cases such as *Western States* have been unwilling to simply defer to FDA's conclusions. *Whitaker* went so far as to review the scientific basis for FDA's substantive positions and refused to simply accept FDA's argument that disclaimers are not adequate protection.<sup>8</sup>

FDA's challenge is to: 1) articulate a compelling governmental interest that justifies gagging one speaker (the manufacturer) while allowing another (a physician) to say the identical thing, and 2) justify the absence of less burdensome restrictions. To do so, FDA has to justify restricting speech based upon the identity or employment status of the speaker.

**Current Status.** While these issues percolate, FDA continues to bring enforcement actions against off-label promotion of drugs outside of the safe harbors of FDAMA, 21 CFR Part 99 (2005),<sup>9</sup> and the (vacated) *WLF II* and *III* injunctions. FDA's general pattern has been to include in any enforcement action an assertion that the material is, in some way, misleading. Under the first prong of *Central Hudson*, "inherently misleading," commercial speech can be prohibited or regulated, while "potentially misleading" speech is more protected. Whether a court would agree that these particular promotional activities are actually misleading is undecided.

On the CME front, the FDA approach is to disassociate the manufacturer from all substantive involvement in the CME program except for unrestricted funding. As such, the manufacturer has no control over speaker selection or content. The manufacturer's free speech rights are being "protected" by forcing the manufacturer to be disassociated from the speech. Industry has acquiesced to many of these CME rules in trade association codes of conduct.<sup>10</sup> The inclusion of these requirements in these codes is not mere window dressing.

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<sup>7</sup>See 21 U.S.C. § 355.

<sup>8</sup>The standard to be used by the courts in assessing such substantive decisions appears open. A *Chevron* approach as applied in *Young v. Community Nutrition Institute*, 476 U.S. 974 (1986) is certainly a possible approach. However, 1<sup>st</sup> Amendment cases such as *Whitaker* and *Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir. 1999) seem to defer much less to FDA's interpretations or decisions.

<sup>9</sup>Whether the lengthy prior approval requirements of 21 CFR Part 99 (2005) could withstand a 1<sup>st</sup> Amendment challenge as anything other than a safe harbor provision is an open question.

<sup>10</sup>Both PhRMA (a major drug industry trade association) and AdvaMed (a key device industry trade associate) have adopted codes of conduct that include many restrictions on CME participation.

In an enforcement situation, the failure to comply with an industry code can have significant ramifications. The U.S. Sentencing Guidelines Manual § 8B2.1 Commentary 2 (B) (2004) states that the failure to follow an industry code “weighs against” a finding that the company has an effective compliance and ethics program.

The government has also now linked off-label promotion to False Claims Act liability. It argues that the off-label speech induces the physician to submit claims to Medicare/Medicaid, and that seeking reimbursement for off-label use is a false claim. The government has advanced this theory against involving Park Davis and TAP Pharmaceuticals. In these cases, the speech issues are almost always linked with other, more odious, conduct.

Few cases deal with the connection between truthful off-label promotion and false claims liability. In *United States ex rel Franklin v. Park Davis*, 2003 WL 220048255 (D. Mass.) the district court refused to grant the defendant’s motion for summary judgment against the False Claims Act count. Linking off-label promotion to False Claims Act liability opens a potentially significant second line of attack on off-label promotion that is separate and apart from the FDA promotional restrictions. If this argument is correct, industry faces treble damage claims (and *qui tam* plaintiffs) rather than enforcement letters from DDMAC.<sup>11</sup>

**Conclusion.** The issues surrounding off-label drug promotion will continue to garner great attention. Several issues reinforce the need for a prompt resolution. First, there is no end in sight to off-label uses and the need for information about them. The pressure on industry to discuss off-label uses will continue given the willingness of patients and physicians to use products off-label and the time and expense required to obtain an FDA approval.

The second trend is the increasing role of the patient in health care decisions. Until recently, physicians were often the real decision maker on health care issues. Now, the patient is playing a greater role in health care decisions and is insisting upon more information on both on- and off-label uses.

Third, product indications often differ between countries. What is on-label in Europe may be off-label in the U.S. Efforts to limit access to European promotional materials, particularly Internet material, are probably ineffective. Modern information technology makes it almost impossible to restrict communications by geography, training, or position.

Judicial review is needed and almost inevitable. The courts must address a number of key questions:

- What is the government’s interest in controlling off-label speech?
  - o Is it public health, compliance with the approval process, or something else?
- Does restricting off-label speech actually advance that interest?
- Are there less burdensome alternatives?
  - o Are disclaimers alone adequate?
- Is off-label speech “inherently misleading”?
- Are different rules applicable to different types of material, sources of information or audiences?

So, where does this leave us today? Most of industry will wait for someone else to challenge these restrictions. When that happens (and it will), the protection given to commercial speech will be balanced against demonstrable government needs. FDA will need to establish that off-label promotion will gut the product approval process, pose some real risk to patients, or is “inherently misleading” if it expects courts to uphold off-label restrictions. In addition, FDA has the burden and will need a record to establish that a less restrictive approach such as disclaimers is not reasonably effective in advancing the government’s interests. Given the fact-intensive analysis used in cases such as *Western States* and *Whitaker*, the courts may well craft different rules for different types of speech (e.g., scientific articles versus promotional brochures) and different audiences (e.g., physicians versus patients).

Until such resolution there will be an uneasy truce as everyone awaits the next round.

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<sup>11</sup>A detailed analysis of this potentially very significant development is beyond the scope of this paper.