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A Low Dose Prescription: Criminal Prosecution of Off-Label Drug Promotion



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Overview

Drug company scientists discover that a rare debilitating disease may be treated with a drug licensed to treat an unrelated ailment. The Food and Drug Administration (“FDA”) has not approved the drug for the rare disease. While the company begins time consuming and expensive clinical trials to test this discovery, patients with the rare disease ask their doctor for the drug. Doctors seek as much information as possible on this “off-label” use. The drug company wants to get the word out quickly about the new use.

- Should a drug company be permitted to promote the drug for the new use before FDA approval, and if so, what can the company say?
- Should doctors be permitted to prescribe a drug for an unapproved use, and if so, under what conditions?
- If doctors can prescribe the drug, how do they obtain information on the correct dosage and adverse side effects?
- Under what circumstances can a company provide “off-label” information to doctors?

The answers are unclear. Permitting a drug company to promote off-label uses results in faster and more efficient dissemination of information to doctors that in turn may save the lives of patients with certain terminal diseases¹ and in relief for patients with rare diseases who often must rely upon off-label uses to treat their disease. Prohibiting off-label promotion encourages drug companies to conduct appropriate studies before promoting a drug.

Faced with these issues, the government has essentially opposed drug company promotion of off-label uses. While doctors are allowed to prescribe drugs for off-label uses, drug companies are prohibited from promoting drugs for such uses in most circumstances.² The rationale is to protect the public from drug use that does not meet FDA standards, while protecting doctors’ medical discretion to treat patients. An inherent inconsistency exists. While doctors are most knowledgeable in diagnosing their patients, drug companies are most knowledgeable about their drugs. Accordingly, the party most knowledgeable about the drug cannot explain to doctors the drug’s treatment qualities, dosing regimen and adverse effects.

Nonetheless, off-label drug use is widespread. A 2004 study involving 355,409 hospitalized patients 18 years or younger showed that doctors treated almost 80% of them with at least one

off-label drug. *Off-Label Drug Use in Hospitalized Children*, Archives of Pediatrics & Adolescent Medicine, Vol. 161, No. 3 (March 2007).³ During 1997 hearings, Senator Frist testified that off-label uses constituted 40-60% of all drug prescriptions, over 70% of all pediatric drug prescriptions, and as much as 90% of all oncology prescriptions. 143 CONG. REC. S8162-02 (daily ed. July 28, 1997). Government programs often reimburse such uses. Medicare covers off-label uses of cancer drugs if included in certain medical compendia. 42 U.S.C. § 1395x(t) (2).

Off-label drug prescriptions have spawned criminal charges of off-label promotion by drug companies and their agents, malpractice claims against doctors who prescribed drugs for off-label uses, insurance coverage disputes for off-label drug treatments, and class action litigation by off-label drug users alleging injury. This article focuses solely upon criminal charges.

Criminal Prosecution of Off-Label Drug Promotion

Drug promotion takes many forms: sponsored educational seminars on drug uses, distribution of journal articles and reference texts discussing drug uses, and sales representative discussions with medical professionals on drug uses. Off-label drug promotion comes into play when a drug company includes off-label uses in its promotional activities.

No statute explicitly criminalizes off-label drug promotion. Prosecutors, however, have charged off-label drug promotion under statutes prohibiting the promotion of “misbranded” and “new unapproved” drugs.

The Food Drug and Cosmetic Act (“FDCA”) prohibits the introduction of a misbranded drug into interstate commerce. 21 U.S.C. § 331 (a). A drug is misbranded if its labeling is “false or misleading,” 21 U.S.C. § 352 (a), or if its labeling does not contain “adequate directions for use,” 21 U.S.C. § 352 (f) (1). The government has charged that off-label drug promotion furthers the introduction of a drug label that “misleadingly” fails to address or provide directions for the off-label use.

The FDCA also prohibits the introduction of an unapproved new drug into interstate commerce. 21 U.S.C. § 331(d) and 355(a). The government has charged that off-label drug promotion causes the introduction of an “unapproved new drug,” i.e., a drug marketed for an unapproved new use.

Misdemeanor and felony charges and civil remedies are all available to the government. To bring misdemeanor charges, the government need only prove willfulness, while felony charges require proof of “intent to defraud or mislead.” 21 U.S.C. § 333(a) (1) and (2). While the meaning of “intent to defraud or mislead” under § 333 remains unsettled, caselaw suggests that, at a minimum, the government must introduce

evidence that the defendant “intentionally violated § 331 with the specific intent to defraud or mislead an identifiable government agency.” *United States v. Arlen*, 947 F.2d 139, 143 (5th Cir. 1991), *cert. denied*, 112 S. Ct. 1480 (1992); *United States v. Varela-Cruz*, 66 F. Supp.2d 274, 278 (D.P.R. 1999); *United States v. Bansal*, 2006 U.S. Dist. LEXIS 53475 *11 (D.Pa. Aug. 1, 2006).

First Amendment Implications

With few indictments charging the crime of off-label promotion, there has been little opportunity for the articulation of legal defenses. Of relevance is a lawsuit brought by the Washington Legal Foundation in opposition to the Food and Drug Administration Modernization Act’s (“FDAMA”) restriction of a drug company’s ability to distribute clinical reports on off-label drug uses. There, the court accepted the argument that the FDAMA impermissibly restricted commercial speech in violation of the First Amendment. *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998). This First Amendment argument is equally applicable to criminal prosecutions.

Off-label promotional activities may be considered commercial speech. The constitutional validity of restrictions on off-label promotion is analyzed using the four-pronged test established in *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, 447 U.S. 557 (1980). The first prong requires that the speech be neither unlawful nor inherently misleading. Truthful, off-label promotion passes this test because it concerns a lawful activity, i.e., the prescription of drugs. *Washington Legal Foundation*, 13 F. Supp. 2d at 66-69. The second prong requires that the government’s interest in the restriction be substantial while the third prong requires that the restriction directly advance that substantial interest. These tests are arguably satisfied as the government

has a substantial interest in encouraging drug companies to seek FDA-approval of off-label uses and restrictions on off-label promotion advance this interest. *Id.* at 71-72.

It is the final prong—requiring that the restriction be no more extensive than necessary to further the government interest—that the FDAMA failed to satisfy. The Supreme Court has stated “that if the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so.” *Thompson v. Western States Medical Center*, 535 U.S. 357, 371 (2002). In *Washington Legal Foundation*, the court found the FDAMA to be unconstitutional because the FDA could have required drug companies to provide complete and unambiguous disclosures that the “off-label” uses were not FDA-approved. *Washington Legal Foundation*, 13 F. Supp.2d at 73-74. This disclosure would provide an effective and less burdensome alternative to FDAMA restrictions. The court identified many benefits with this approach, including: (1) “[a] physician would be immediately alerted to the fact that the ‘substantial evidence standard’ [of FDA approved drugs] had not been satisfied, and would evaluate the communicated message accordingly;” (2) “permitting this limited form of manufacturer communication still leaves more than adequate incentives compelling drug manufacturers to get new uses approved by the FDA;” (3) “to the extent that physicians look to FDA approval as an important (or the exclusive) indication of safety and effectiveness, and either will not prescribe or are reluctant to prescribe absent such approval, manufacturers will seek to obtain FDA approval to make their products more appealing to the market;” and (4) “off-label prescriptions, presently legal, do constitute the most effective treatment available for some conditions. [and] the truthful [off-label] information may be life saving information, or information that makes a life with a debilitating condition more comfortable.” *Id.* at 73-74.⁴ The First Amendment equally bars off-label criminal prosecutions.

District of Massachusetts

The U.S. Attorney’s Office for the District of Massachusetts is a national powerhouse in the area of healthcare fraud prosecution.⁵ Yet, cases involving facts that arguably could support charges of off-label promotion have largely been resolved through civil dispositions, deferred prosecution agreements or guilty pleas to lesser criminal charges. Through such an approach, drug companies have not faced a bar from participating in government-funded programs.⁶

Bristol-Myers Squibb

In September 2007, Bristol-Myers Squibb Company (“BMS”) and its subsidiary Apothecon, Inc. (“Apothecon”) entered into a civil settlement agreement with the U.S. Attorney’s Office and Department of Health and Human Services, Office of the Inspector General (“OIG”) regarding the company’s sales and marketing practices including alleged violations of 21 U.S.C. §§ 331(a) and (d), through off-label promotion of the drug Abilify; two unrelated violations of the Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b)(2), through illegal remuneration to retail pharmacies, wholesalers and physicians; and three separate violations of the False Claims Act, 31 U.S.C. §§ 3729-33, through maintaining inflated prices for its drugs and misreporting its pricing of drugs. Under the agreement, BMS and Apothecon agreed to pay in excess of \$515 million. BMS also entered into a Corporate Integrity Agreement (“CIA”)⁷ with the OIG relating to off-label promotion. No criminal charges were filed.

Pharmacia & Upjohn

In March 2007, the U.S. Attorney’s Office entered into a 36-month deferred prosecution agreement with Pharmacia & Upjohn Company LLC (“Pharmacia”), a subsidiary of Pfizer, Inc. (“Pfizer”), arising out of Pharmacia’s promotion of Genotropin for off-label uses. The Information charged Pharmacia with distribution of an unapproved new drug in violation of 21 U.S.C. §§ 331(d), 333(a)(2) and 355(a). Pharmacia agreed to pay \$15 million; if it violates any provision of that agreement, the U.S. Attorney’s Office may file the Information. Pfizer also entered into a five-year CIA which required that Pharmacia establish a “Specific Training” program on marketing and promotion of drugs and dissemination of information on off-label uses.

Schering Sales

In August 2006, Schering Sales Corporation (“Schering”) pled guilty to charges of conspiracy to make false statements to the FDA to avoid FDA scrutiny of Schering’s off-label promotion of Temodar and Intron A, in violation of 18 U.S.C. § 371. The Information alleged that Schering engaged in widespread marketing of drugs for unapproved uses. Yet, no criminal charges were filed under 21 U.S.C. §§ 331(d), 333(a)(2) and 355(a). Under the plea agreement, Schering paid a \$180 million fine and its preexisting CIA was expanded to incorporate off-label promotion.

Serono Laboratories

In October 2005, Serono Laboratories, Inc. (“Serono”) pled guilty to conspiring with a medical device manufacturer to market computer software devices for unapproved uses to increase the market for its drug, Serostim, as well as unrelated charges of offering illegal kickbacks. Serono paid \$704 million in criminal fines and civil payments. Although a civil settlement agreement alleged that Serono promoted the sale and use of Serostim for off-label uses, no criminal charges were filed. Serono entered into a five-year CIA that included obligations countering off-label promotion.

Warner-Lambert

In May 2004, Warner-Lambert pled guilty to charges of promoting Neurontin for unapproved uses in violation of 21 U.S.C. § 331(a), 331(d), 333(a), 352(f)(1) and 355. The Information alleged that Warner-Lambert promoted these uses despite the lack of clinically controlled data demonstrating Neurontin’s efficacy in treating these conditions and the FDA’s rejection of Warner-Lambert’s application for one indication. Warner-Lambert’s parent company, Pfizer, paid \$240 million in criminal fines and its existing CIA was expanded to include requirements relating to its marketing activities and dissemination of off-label information.

Conclusion

Strong arguments oppose criminal prosecution of off-label drug promotion. An open debate continues as to whether society’s interests are better served by permitting such promotion, rather than prosecuting it. The lack of a single statute directly criminalizing such conduct further weakens any criminal case. First Amendment barriers to such enforcement remain. Although the U.S. Attorney’s Office for the District of Massachusetts has extracted significant fines and stringent CIA requirements, it has demonstrated limited prosecutorial interest in seeking felony criminal charges for off-label drug promotion.”

Endnotes

¹The Boston Globe reported that “[f]rom 2002 to 2004, newly approved drugs took an average of 8.5 years to work their way through clinical trials to earn FDA approval.” Dietra Henderson, *FDA Rules Aim to Speed Drug Tests and Trim Costs*, Boston Globe, Jan. 13, 2006.

²The most notable exception permits the dissemination of off-label information in response to unsolicited requests for information from physicians. 21 U.S.C.A. § 360aaa-6; 21 C.F.R. § 99.1(b).

³A recent Boston Globe article reported: “Once the FDA approves a drug for adults, manufacturers seldom retest it in children. Physicians, however, frequently treat children with drugs approved for adults – a practice called off-label prescribing – without knowing the proper dosing or whether the therapies even work in children.” Dietra Henderson, *Risperdal Use OK’d in Treating Children*, Boston Globe, August 23, 2007.

⁴On appeal, the FDA opined that the challenged provisions in the FDAMA were simply a “safe harbor” ensuring that certain forms of conduct would not be used against manufacturers in misbranding enforcement actions, and that the provisions did not independently authorize the FDA to prohibit or to sanction speech. The Court of Appeals vacated the District Court’s decision without reaching the merits of the First Amendment holding, based on the lack of a constitutional controversy in light of the FDA’s interpretation of the FDAMA. *Washington Legal Foundation v. Henney*, 202 F.3d 331, 335-36 (D.C. Cir. 2000).

⁵In 2003, this health care fraud unit led the nation in healthcare fraud recoveries. Robert S. Bennett and David M. Medearis, *Health Care Fraud: Recent Developments and Timeless Advice*, Texas Medicine, October, 2003. And in June 2005, the Wall Street Journal highlighted the Office’s role in prosecuting healthcare fraud. Harvey A. Silverglate, *Beantown Shakedown, Will the Justice Department Drive Health-Care Business Out of Boston?*, The Wall Street Journal, June 24, 2005.

⁶42 U.S.C. § 1320a-7(a) and corresponding regulations, 42 C.F.R. § 1001.101, provide for **mandatory** exclusion of certain individuals and entities from participation in Medicare and State health care programs for (1) convictions of program-related crimes; (2) convictions relating to patient abuse; (3) felony convictions relating to health care fraud; and (4) felony convictions relating to controlled substances. 42 U.S.C. § 1320a-7(b) and corresponding regulations, 42 C.F.R. § 1001.201, provide for **permissive** exclusion of certain individuals and entities from participation in Medicare and State health care programs for enumerated violations.

⁷The OIG often negotiates CIAs with healthcare organizations as part of the settlement of its investigations. Under a CIA, the organization consents to certain operational obligations in exchange for the OIG foregoing other penalties.