

- Prosecutors facing hurdles in proving off-label promotion is a crime
- Large financial settlements, CIA's the national trend
- Smart drug companies should assess off-label implications of their promotional activities

Civil or Criminal? Current Perspectives on Off-Label Drug Promotion

A drug company and its employees may find themselves in the cross-hairs of off-label drug promotion when the Food and Drug Administration ("FDA") approves the labeling of a drug, and new uses for the drug are discovered that go beyond the uses described on the FDA-approved label. It is the government's position that doctors may prescribe drugs for "off-label" uses, but drug companies and their employees are prohibited from promoting drugs for such uses. Therein lies the unique nature of this purported crime - a doctor may properly prescribe a drug for "off label" uses, while a sales representative may go to jail for telling the doctor about the drug's "off label" uses.

Prosecutors face many hurdles in this area. One stumbling block is that there is no statute stating that off-label drug promotion is a crime. Accordingly, prosecutors have had to argue that off-label drug promotion causes the introduction of a "misbranded" drug in violation of 21 U.S.C. § 331(a) and 352, or causes the introduction of an "unapproved new drug" in violation of 21 U.S.C. § 331(d) and 355(a). In order to bring felony charges under either of these statutes prosecutors must prove "intent to defraud or mislead," a burden substantially greater than simply showing that a drug company provided information on a drug's off-label use.

Another stumbling block is that off-label drug prosecutions may be found to fly in the face of a drug company's First Amendment right to engage in commercial speech. The one decision that reached this conclusion, *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), caused the FDA to downplay its enforcement of the Food and Drug Administration Modernization Act's ("FDAMA's") restriction of a drug company's ability to distribute clinical reports on off-label drug uses.

The U.S. Attorney's Office for the District of Massachusetts is a national leader in the area of healthcare fraud prosecution. However, that office has not indicted many cases involving facts that arguably could support charges of off-label drug promotion. Rather, these cases have 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 and the U.S. Attorney's Office has secured significant financial settlements without having to litigate off-label drug charges.

Examples of such District of Massachusetts cases include:

Bristol-Myers Squibb Company and Apothecan, Inc.

In September 2007, Bristol-Myers and its subsidiary Apothecan 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"). The agreement settled purported 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; and three separate violations of the False Claims Act. Under the agreement, Bristol-Myers and Apothecan agreed to pay in excess of \$515 million. Bristol-Myers also entered into a Corporate Integrity Agreement ("CIA") with the OIG relating to off-label promotion.

Pharmacia & Upjohn Company LLC and Pfizer, Inc.

In March, 2007, the U.S. Attorney's Office entered into a 36-month deferred prosecution agreement with Pharmacia, a subsidiary of Pfizer, arising out of its promotion of its human growth hormone product, Genotropin, for off-label uses such as anti-aging, cosmetic use and athletic performance enhancement. Pharmacia agreed to pay \$15 million. Pfizer entered into a five-year CIA, which also applied to Pharmacia, and required Pharmacia to establish a training program on marketing and promotion of drugs and dissemination of information on off-label uses.

Schering Sales Corporation, a subsidiary of Schering-Plough Corporation

In August 2006, Schering pled guilty to an Information that charged that Schering conspired with others to make false statements to the FDA in order to avoid scrutiny by the FDA 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 these drugs for unapproved uses, which involved training of its sales force to seek off-label sales, and compensation of its sales force for off-label sales. Yet, Schering was only charged with engaging in a conspiracy to make false statements to the FDA in response to an inquiry regarding the pervasiveness of its off-label promotion and the remedial action it had taken to prevent such promotion. Schering paid a \$180 million fine and had its preexisting CIA expanded to incorporate requirements relating to off-label drug promotion.

Serono Laboratories Inc.

In October 2005, Serono pled guilty to charges that it conspired with a medical device manufacturer to market computer software devices for unapproved uses in order to increase the market for its drug, Serostim. Although the government also contended that Serono promoted the sale and use of Serostim for off-label uses, Serono was not criminally charged and did not plead guilty to off-label promotion of Serostim. Serono paid \$704 million in criminal fines and civil payments and entered into a five-year CIA that included stringent obligations regarding off-label promotion.

Even on a nationwide basis, there are few cases that have been charged criminally. Those few cases have involved particularly egregious facts in which the prosecution alleged that the perpetrators engaged in blatantly false representations or the off-label use posed a significant risk to the health and safety of the public. Under such circumstances, the subject speech may arguably be untruthful and misleading and therefore outside the bounds of First Amendment protection. Examples of cases that were charged criminally include:

Purdue Frederick Company, Inc.

In May 2007, Purdue pled guilty to felony misbranding of OxyContin in the Western District of Virginia. Purdue admitted that it fraudulently marketed OxyContin by falsely claiming that OxyContin was less addictive, less subject to abuse and diversion, and less likely to cause tolerance and withdrawal symptoms than other pain medications, when there was no medical research to support these claims. Purdue paid over \$590 million in criminal and civil fines and entered into a five-year CIA that included obligations to stem off-label drug promotion.

Dr. Peter Gleason, David Tucker and Orphan Medical, Inc.

Since April 2006, the U.S. Attorney's Office for the Eastern District of New York has pursued criminal prosecutions relating to the off-label promotion of the drug, Xyrem, commonly known as the "date rape" drug after having been used in sexual assaults. In April 2006, Dr. Peter Gleason, a licensed psychiatrist, was indicted for misbranding Xyrem. The indictment alleged that Gleason was paid substantial sums by the manufacturer, Orphan Medical, Inc., to give lectures that deceptively promoted off-label uses of Xyrem. In March 2007, David Tucker, a Regional Sales Manager at Orphan, pled guilty to introducing a misbranded drug

into interstate commerce. Tucker was accused of listening without objecting, as Gleason made misleading statements about Xyrem. Finally, in July 2007, Orphan pled guilty to introduction of a misbranded drug into interstate commerce. Orphan and its parent, Jazz Pharmaceuticals, Inc., paid \$20 million in criminal and civil fines and entered into a five-year CIA that included obligations to prevent off-label promotion.

Eli Lilly and Company

In December, 2005, Eli Lilly pled guilty to distribution of a misbranded drug, Evista, in the Southern District of Indiana. The Information alleged that Eli Lilly sold and promoted Evista for unapproved uses, including prevention and reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease. Eli Lilly promoted such uses despite the FDA's rejection of its request to include language on its label claiming benefits in treating breast cancer. Eli Lilly paid \$36 million in criminal and civil fines and entered into a consent decree of permanent injunction that enjoined it from selling or promoting Evista for any unapproved use and required that Eli Lilly maintain a compliance program to prevent future off-label promotion.

Warner-Lambert

In May 2004, Warner-Lambert pled guilty to distribution of Neurontin in the District of Massachusetts. The Information alleged that Warner-Lambert promoted Neurontin for unapproved uses despite the lack of clinically controlled data describing the efficacy of Neurontin in treating these conditions, and despite the FDA's rejection of Warner-Lambert's application for approval of one of those indications. Warner-Lambert's parent company, Pfizer Inc., paid \$240 million in criminal fines and had its existing CIA amended and expanded to include numerous requirements relating to its marketing activities and dissemination of off-label information.

It appears that the government is limiting its criminal prosecution of off-label drug promotion to particularly egregious cases. Nonetheless, companies have been assessed significant fines and been subjected to stringent CIA requirements in civil settlements with the government. Financial penalties in these cases have reached over \$100 million dollars. Accordingly, drug companies would be well served to assess their promotional activities that may relate to off-label drug uses.

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