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WHITE-COLLAR CRIME

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Crackdown on 'off-label' pitches

Pharmaceutical companies have been penalized for pushing their products for unapproved uses.

By Robert Brady, Meredith Manning and Peter Spivack
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IN A MAJOR SHIFT OF enforcement strategy, the U.S. Department of Justice (DOJ) has firmly taken control of the enforcement against pharmaceutical, biotechnology and medical-device manufacturers. Both "Main Justice" in Washington and various U.S. attorney offices around the country now enforce against these companies through the Food, Drug and Cosmetic Act (FDCA), the Anti-Kickback Statute and the False Claims Act. The DOJ has signaled—via its most recent settlements over the course of two months—how its enforcement will change the way companies promote and market therapeutic products in the future.

On Dec. 21, 2005, the DOJ announced that Eli Lilly and Co. had agreed to plead guilty to a single misdemeanor count and pay $36 million to settle criminal charges and civil allegations related to the company's marketing of its drug Evista, which has been approved for the treatment of osteoporosis in post-menopausal women. Signaling DOJ control over the settlement, the consent decree mirrors the content of corporate-integrity agreements generally drafted by and enforced by the inspector general of the Department of Health and Human Services. *U.S. v. Eli Lilly and Co.*, No. IP05-CR-0206-01-B/F (S.D. Ind. Dec. 21, 2005).

Problems arise from off-label claims for Medicaid repayment.

On Oct. 17, 2005, the DOJ announced that the Swiss company Serono S.A., along with its U.S. subsidiaries, would plead to two felonies and pay $704 million to settle criminal and civil charges related to the marketing of its AIDS-wasting drug, Serostim. This represents the largest settlement to date for promoting a Food and Drug Administration (FDA)-approved product outside its approved indications, or "off-label" promotion. *U.S. v. Serono Laboratories Inc.*, No. 05d CR 10282-RCL (D. Mass. Oct. 12, 2005).

Both cases demonstrate that the DOJ continues to expand the nature and extent of company conduct it will investigate, and that it will pursue those investigations vigorously. The settlements also reveal some clues regarding when the DOJ decides to seek felony charges v. misdemeanor charges against a company for off-label promotion. These cases further highlight the fact that the DOJ is strongly scrutinizing practices in pharmaceutical, biotech and medical-device companies that traditionally have not been investigated by the FDA.

Health care companies' promotional activities continue to be a major focus of DOJ enforcement actions. In 2004, Pfizer Inc. entered into a $430 million settlement with the DOJ to settle charges that it had illegally promoted its anti-epileptic drug, Neurontin, for an array of unapproved uses, including pain and bipolar disorder. The charges arose out of a qui tam, or whistleblower, lawsuit brought under the federal civil False Claims Act (FCA) by a former employee who painted a picture of a "comprehensive scheme" devised by the company to promote Neurontin for off-label uses. *U.S. ex rel. Franklin v. Parke-Davis*, No. 96-11651-PBS (D. Mass. filed Aug. 22, 1996; settlement agreement May 13, 2004).

The FCA authorizes a private citizen to bring an action on behalf of the government for violations of specific statutes. The Neurontin case stands for the novel proposition that a company's off-label promotion is a violation of the FCA if the promotion results in submission of an off-label claim for

Robert Brady, Meredith Manning and Peter Spivack are partners at Hogan & Hartson in Washington. Brady held several leadership positions at the FDA. They can be reached, respectively, at rpbrady @hhlaw.com, mmanning@hhlaw.com and psspivack@hhlaw.com. Associates Stephanie Solomon and Alison Stanton assisted in the preparation of this article.

reimbursement to a federal health care program. The Neurontin case may have established a new standard that it need only be "reasonably foreseeable" that a company's conduct will result in a false Medicaid claim.

The Neurontin case also demonstrates that a disgruntled former employee can pose a substantial threat to a company. According to published reports, there are upwards of 200 pending qui tam cases involving allegations of off-label promotion by health care companies.

A disgruntled former employee can impose a substantial threat.

Small sales not immune

Additionally, it is not necessarily the size of the market for a particular product that puts a company at risk of DOJ investigation. For example, Novo Nordisk A/S recorded only $2.6 million in sales of an insulin product for the first nine months of 2005, but it recently announced receipt of a subpoena from the U.S. attorney for the Eastern District of New York requesting documents related to that product's marketing and promotion. Thus, health care companies in markets of all sizes need to be wary of the current enforcement environment.

The Serono case arose from three qui tam actions filed by former sales representatives against the company for false Medicaid claims. The complaints alleged that Serono sales representatives used a bioelectrical impedance analysis (BIA) test to "measure" patients' body mass wasting and manipulated the BIA readings to suggest that patients without AIDS wasting be prescribed Serostim. The whistleblowers also alleged that Serono offered prescribers trips to Cannes, France, in exchange for writing a certain number of prescriptions for Serostim within a set period of time.

Serono Labs pleaded guilty to two felony counts: conspiracy to distribute an unapproved and adulterated medical device; and conspiracy to pay illegal remuneration to health care providers to induce referrals to pharmacies for Serostim—payment for which was made by Medicaid. The charging document describes the basis for these charges.

Count one charged that through use of unapproved diagnostic software (a device under the FDCA), Serono launched a campaign to convince prescribers that "body cell mass"—rather than weight loss, which the company had used as the clinical endpoint in its clinical investigations supporting approval of the drug—was the true measure of AIDS wasting. Around the time of Serostim's approval, protease inhibitors also were approved by the FDA. These drugs dramatically reduced the number of patients suffering from AIDS wasting, and thus, the demand for Serostim. By "redefining AIDS wasting," the government asserted, the company aimed to artificially expand the Serostim market.

Count two asserted that, to further boost lagging sales, the company initiated what it called a "6m-6 Day Plan" through which representatives were instructed to offer financial incentives to high prescribers to meet a targeted sales increase of $6 million within six days. Physicians were offered all-expense-paid trips to the International Conference on Nutrition and HIV Infection in Cannes in exchange for the increased prescribing of Serostim.

Serono's criminal penalties for these violations totaled $137 million.

Under a civil settlement agreement, Serono will pay more than $560 million to settle liabilities relating to payments made by state Medicaid and federal health care programs for Serostim during the time of the illegal conduct. The government agreed to allow Serono-owned companies other than Serono Labs to continue receiving reimbursement under federal health care programs. The government released Serono from civil claims related to the Serostim promotional conduct.

Serono entered a corporate integrity agreement (CIA) obligating the company to establish a comprehensive compliance program and develop policies and procedures spanning a variety of topics. The Serono CIA is similar to one in place between the government and Pfizer as a result of the Neurontin case, but there are some notable differences. First, the Serono CIA has a heightened focus on the funding and conduct of medical education programs. Second, Serono is obligated to implement policies relating to compensation to ensure that financial incentives do not encourage improper promotional, sales and marketing practices. Finally, the Serono CIA prohibits medical information staff from responding to requests for off-label information unless the request is made in writing.

In its case, Lilly agreed to plead guilty and to pay $36 million in connection with its illegal promotion of its pharmaceutical drug Evista. In pleading guilty to a misdemeanor count of misbranding Evista, the Indianapolis-based company agreed to pay a $6 million criminal fine and forfeit to the government an additional sum of $6 million. In addition, Lilly agreed to settle civil FDCA liabilities by entering into a consent decree and disgorging $24 million.

A better deal for Lilly

The government alleged that the first year's sales of Evista in the United States

were disappointing compared to Lilly's original forecast. In October 1998, the company reduced the forecast of Evista's first year's sales in the United States from $401 million to $120 million, and an internal business plan noted a "disappointing year versus original forecast." Thus, according to the DOJ, Lilly sought to broaden the market for Evista by promoting it for unapproved uses.

Lilly's strategic marketing plans and promotion touted Evista as effective in preventing and reducing the risk of diseases for which the drug's labeling lacked adequate directions for use. Lilly's Evista brand team and sales representatives promoted Evista for the prevention and reduction in risk of breast cancer even after the FDA rejected Lilly's proposed labeling that Evista reduced "the frequency of newly diagnosed breast cancer" in those taking Evista compared to placebo. Lilly also promoted Evista for the reduction of cardiovascular disease.

Although not charged in the information, it is notable that a federal court granted AstraZeneca PLC a preliminary injunction against Lilly in 1999 under the Lanham Act to block the firm from promoting a breast cancer claim for Evista. *Zeneca Inc. v. Lilly & Co.*, No. 99 Civ. 1452 (S.D.N.Y. July 19, 1999). AstraZeneca's Nolvadex (tamoxifen) is approved for reducing the risk of breast cancer.

The information alleges much of the same conduct that AstraZeneca raised in its Lanham Act suit—that Lilly used a number of tactics, including:

■ One-on-one sales pitches to physicians by sales representatives promoting off-label uses for Evista. Sales representatives were trained how to prompt questions by doctors on unapproved uses.

■ Encouraging sales representatives to send unsolicited medical letters to doctors on their sales routes to promote the drug for an unapproved use.

■ Organizing a "market research summit" during which Evista was discussed with physicians for unapproved uses, including reducing the risk of breast cancer.

■ Creating and distributing to sales representatives an "Evista Best Practices" videotape, in which a sales representative states that "Evista truly is the best drug for the prevention of all these diseases," referring to osteoporosis, breast cancer and cardiovascular disease.

The complaint for permanent injunction alleges that Lilly used additional tactics, including organizing "consultant meetings" for physicians at which unapproved uses for Evista were discussed.

The consent decree imposes a broad range of obligations on Lilly, similar to a CIA, including implementing effective training and supervision of its marketing and sales staff for Evista, and ensuring that any future off-label marketing conduct is detected and corrected. Lilly agreed to be permanently enjoined from promoting Evista for any unapproved use. Lilly also agreed to use an independent review organization to assess and evaluate its policies and procedures for promoting Evista and for complying with the consent decree. Unlike the Serono CIA, however, most of the obligations under the consent decree are limited to the promotion of a single drug, Evista.

Importantly, the consent decree obligates Lilly to submit to the government all market research conducted by or for the Evista brand team or Lilly Market Research to measure physician recall of marketing messages by Lilly sales representative for Evista, along with any summaries, reports or presentations of such data. The consent decree obligates the company to obtain quarterly information on the interaction between their sales reps and physicians and provide it to the government.

The DOJ is watching

The Serono settlement confirms that the DOJ will vigorously prosecute anti-kickback cases. In fact, the presence of the kickback element in the Serono case appears to be the major differentiation in the conduct alleged in the Serono and Lilly charging documents.

From the perspective of compliance with the FDCA, both cases demonstrate that the DOJ will not only prosecute promotion of unapproved drugs (or promotion of approved drugs for unapproved uses), but will thoroughly examine marketing efforts such as Serono's efforts to alter a diagnostic method to convince physicians to use a drug in a wider patient population and Lilly's promotional activities couched as "market research." The cases also signal that the DOJ continues to closely scrutinize those activities considered "nonpromotional"—such as support for medical education and responses to unsolicited requests for information. A component of any post-approval advertising promotion compliance program should be a thorough corporate understanding of the labeling negotiations between the company and FDA.

Finally, the Serono case is the first known instance of the DOJ asking a company to evaluate or assess incentive compensation. The Lilly case is the first in which the DOJ has addressed market research as a potential promotional tool. Both settlements demonstrate that the DOJ continues to learn about the methods companies use to promote drugs, biologics and medical devices, and that it will continue to apply that knowledge to other companies. NLJ