Off-Label Promotion under Scrutiny by DOJ

The Department of Justice Is Aggressively Pursuing Healthcare Fraud Allegations

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In a continuing shift of enforcement strategy, the U.S. Department of Justice (DOJ) has firmly taken control of off-label use allegations against pharmaceutical, biotechnology, and medical device manufacturers. Various U.S. attorneys' offices around the country and especially in Washington, DC, now enforce existing legalities in the life science industry through the Food, Drug and Cosmetic Act (FDCA), the Anti-Kickback Statute, and the False Claims Act.

The DOJ, which seems to be taking over from the FDA and even acting inconsistently with the FDA at times, has signaled, via its most recent settlements over the course of the last six months, how its new enforcement procedures will change the way companies promote and market therapeutic products in the future.

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At the same time, however, off-label use of drugs and medical devices is widespread and widely acknowledged to benefit patients. Indeed, some sources estimate that less than 10% of drugs today are being used to treat their approved FDA use. Due to the fact that the FDA does not regulate the practice of medicine once it approves a drug or device for sale for a specific purpose, physicians are permitted to use these therapies in other ways to benefit patients.

The FDA has struggled for years to craft a guidance document that provides clear standards to companies for appropriate promotion, however, its first attempts were tossed out of federal court in the Washington Legal Foundation cases.

Most recently, the FDA has put together a draft guidance that would permit companies to use certain types of materials such as peer-reviewed articles to promote products off-label, a move that so alarmed Rep. Henry Waxman, chairman of the House Committee on Oversight and Government Reform, that he released the draft guidance and his own letter to the FDA Commissioner Andrew C. von Eschenbach on November 30, 2007.

This tension between patient benefit and government enforcement puts companies in a difficult position in disseminating truthful information about their products. Should they stand silent when data is developed that may benefit patients? Or should they risk prosecution for off-label promotion by disseminating scientific information that may indicate important therapeutic options for patients?

The *Jazz Pharmaceuticals* Case

On July 13, 2007, Jazz Pharmaceuticals agreed to pay $20 million in penalties and victim compensation to resolve parallel criminal and civil investigations conducted by the U.S. Attorney's Office for the Eastern District of New York relating to the marketing practices of its wholly owned subsidiary Orphan Medical.

As part of this resolution, Orphan pleaded guilty to felony misbranding, in violation of the FDCA in connection with its illegal promotion of Xyrem, also known as gamma-hydroxybutyrate (GHB), for unapproved uses. According to the government's press release, "GHB is a powerful and fast-acting central nervous system depressant that has been subject to abuse as a recreational drug and is classified by the Department of Health and Human Services (HHS) as a date rape drug."

The government charged that Orphan's criminal misbranding scheme induced physicians throughout the country to write prescriptions for Xyrem that were not reimbursable by private health insurers or public insurance programs like Medicare and Medicaid, thereby causing millions of

dollars in losses to these insurers.

The government's investigation began after a former sales representative for Orphan filed a suit in the Eastern District of New York on behalf of the United States. The False Claims Act authorizes a private citizen to bring an action on behalf of the government for violations of specific statutes. The Jazz case 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 healthcare companies.

Narcolepsy

Xyrem was approved for only two medical indications. The first, approved in July 2002, was for the treatment of cataplexy, a condition characterized by weak or paralyzed muscles associated with narcolepsy. The second use, approved in November 2005, was for the treatment of excessive daytime sleepiness (EDS) in narcolepsy patients.

The drug's black-box warning label, the most serious warning placed in the labeling of a prescription medication, stated that Xyrem is capable of inducing sleep very quickly and causing serious side effects, including difficulty breathing while asleep, confusion, abnormal thinking, depression, nausea, vomiting, and sleepwalking.

Abuse of the drug could cause dependence and craving as well as seizures, coma, and even death. The warning label also indicated that the drug's safety and efficacy were not established in children and that there was only limited experience with the drug in elderly patients.

The government alleged that, through sales representatives and at least one medical professional, Orphan engaged in a scheme to expand the market for Xyrem by promoting the drug to physicians for off-label medical uses including fatigue, insomnia, chronic pain, EDS (before EDS became an approved indication), weight loss, depression, bipolar disorder, and movement disorders such as Parkinson's disease.

Specifically, Orphan sales representatives in the Eastern District of New York and across the United States, with the knowledge and approval of Orphan sales managers throughout the country, frequently made sales calls on physicians who did not specialize in narcolepsy in order to promote Xyrem for the treatment of conditions not related to the approved use. They also distributed written materials concerning off-label uses that did not adhere to FDA guidance designed to prevent their improper use by drug manufacturers in promoting their products.

The government also alleged that Orphan relied on a psychiatrist to give talks around the country promoting Xyrem to physicians for off-label uses and paid him tens of thousands of dollars for these engagements.

With the approval of Orphan sales personnel, the psychiatrist allegedly made misleading statements about Xyrem in the course of promoting the drug for off-label use, including minimizing the dangers of a Xyrem overdose and suggesting that the drug was customary and safe to use on children and the elderly. He also suggested that the drug's active ingredient, GHB, was not really a date-rape drug.

Also, the psychiatrist, again with the approval of Orphan sales personnel, allegedly advised physicians how to conceal off-label Xyrem prescriptions in order to obtain reimbursement from insurers for unapproved uses that were not medically accepted and generally not reimbursed. As a result of its guilty plea, Orphan was excluded from federal healthcare reimbursement by the Office of Inspector General for HHS.

In order to resolve the case, Jazz entered into a nonprosecution agreement with the government. Jazz has agreed to guarantee Orphan's obligation to pay criminal restitution to public and private insurers of approximately $12.2 million and a criminal fine of $5 million. Jazz will provide ongoing cooperation to the government in connection with its investigation and prosecution of the underlying illegal marketing scheme. Pursuant to the civil settlement agreement, Jazz and Orphan agreed to pay $3.75 million, plus interest.

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Jazz also agreed to implement the terms of a corporate integrity agreement required by the Office of Inspector General for HHS and take other proactive and remedial measures, including the implementation of a code-of-conduct prohibiting promotion for unapproved or off-label use and requiring compliance training for promotional speakers and sales representatives.

Jazz also agreed to replace the former Orphan regional sales managers who were responsible for overseeing the conduct of sales representatives in their respective territories.

In October 2005, the DOJ announced that Serono must pay $704 million to settle criminal charges and civil allegations related to the company's marketing practices for its AIDS wasting drug, Serostim.

This represents the largest settlement to date concerning allegations of illegal off-label promotion and is among the largest concerning healthcare fraud. Serono pleaded guilty to two felony counts of conspiracy: conspiracy to distribute an unapproved and adulterated medical device and conspiracy to pay illegal remuneration to healthcare providers to induce referrals to pharmacies for Serostim, payment for which was made by Medicaid.

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.

The first count charged that, through the use of unapproved diagnostic software, 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 investigations was the true measure of AIDS wasting.

Around the time of Serostim's approval, protease inhibitors were also approved by the FDA. These drugs dramatically reduced the number of patients suffering from AIDS wasting, thus, the demand for Serostim. By redefining AIDS wasting, the government asserted that 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 increased prescribing of Serostim. Serono's criminal penalties for these violations totaled $137 million.

Under a civil settlement agreement to resolve False Claims Act allegations, Serono will pay more than $560 million to settle liabilities relating to payments made by state Medicaid and federal healthcare 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 healthcare 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.

Science and the DOJ

From the perspective of compliance with the FDCA, these 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 attempts to alter a diagnostic method to convince physicians to use a drug in a wider patient population. 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.

These cases along with other 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.

These settlements also demonstrate that it is critical for companies to understand the new theories that the DOJ is using to prevent off-label promotion so that they can carefully scrutinize their own practices. GEN

CORRECTION

In the May 1 issue of *GEN*, in an article on "Introducing In Vitro ADMET Studies Earlier," the phrase "The A in ADMET" was used without crediting pION, the service mark owner. *GEN* regrets the error.