Pharmaceutical Executive

Off-Label Promotion

A recent court case points to the government's shifting perspective on how it prosecutes companies for promoting off-label. Instead of criminal charges, hefty corporate integrity agreements might be in store.

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Scrutiny of off-label drug promotion is on the rise. Since 2003, the Office of the Inspector General (OIG) has included investigation of pharmaceutical fraud in its annual work plans, and its 2005 plan specifically referenced its intent to assess FDA's oversight and review of permissible and impermissible off-label practices. This suggests the government's scrutiny of off-label drug marketing will continue, but raises a question about the future direction of the government's enforcement efforts.

In recent off-label investigations, the government has relied on two theories under the Food, Drug, and Cosmetic Act (FDCA). The government may claim that a product promoted for off-label use is "misbranded" if it has inadequate directions for the unapproved use or because the company has provided "false and misleading" information regarding the product. Alternatively, the government may charge that promotion of a drug for an unapproved use constitutes the sale of an unapproved new drug, also a misbranding violation.

In any case, the relevant FDCA provisions are complex and ambiguous. That's led the government to develop its prosecution theories for off-label promotion in a number of well-publicized cases in which it has obtained criminal pleas and enormous civil penalties against pharma companies. However, a recent settlement in a major case against Serono suggests the government's position on criminal prosecution may be changing, and that it may rely more heavily on Corporate Integrity Agreements (CIAs) to enforce stricter compliance with the government's view of the law.

The omission of criminal charges for off-label promotion of Serostim is surprising, because the government's earlier plea with Pfizer sent a strong signal that it would criminally charge companies engaged in off-label marketing.

One Issue, Two Rulings

To understand the changing direction of enforcement action, it's helpful to first compare the settlement terms of two off-label promotion suits: Neurontin (gabapentin) and Serostim (somatropin), both negotiated by the United States Attorney's Office for the District of Massachusetts.

Neurontin In 1996, a whistleblower filed a civil *qui tam* action against Warner-Lambert, alleging that the company engaged in off-label promotion of Neurontin, and provided illegal kickbacks to physicians. The government initiated its own investigation and alleged that the company actively promoted Neurontin for off-label uses through its sales reps, medical liaisons, teleconferences, consultants' meetings, and advisory boards. Based on this, the government brought criminal misbranding charges against the company. The case was settled in 2004 when Warner-Lambert (later acquired by Pfizer) pleaded guilty to two criminal FDCA misbranding violations and settled separate civil charges.

To resolve the criminal case, the company pleaded guilty to distribution of an unapproved new drug, based on the theory that the distribution of Neurontin for unapproved uses constituted distribution of an unapproved new drug. The company also pleaded guilty to distribution of a misbranded drug, based on the theory that the FDA-approved package labeling contained inadequate directions for use for the off-label indications. As part of the settlement, Pfizer/Warner-Lambert agreed to pay $430 million in criminal fines and civil payments, and enter into a CIA with OIG. (See "CIA: Head-to-Head Comparison," page 40.)

Serostim Between August 2000 and January 2004, six whistleblowers filed civil complaints against various Serono affiliates, alleging violations of the False Claims Act resulting from illegal marketing of Serostim, an FDA-approved drug for the treatment of AIDS wasting.

The federal government then initiated its own investigation. It alleged that Serono engaged in two ways in improper conduct aimed at creating a bigger market for Serostim. First, Serono attempted

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to promote Serostim for lipodystrophy, an unapproved use. Second, Serono attempted to expand the definition of AIDS wasting to include a loss of body cell mass (BCM), despite an absence of objective weight loss. Serono promoted this new wasting theory through use of bioelectrical-impedance-analysis (BIA) devices that purported to compute a person's BCM. Serono sales reps used the devices to perform BIA tests on patients, provided test results to physicians and patients, and in some instances, interpreted the test results for the purpose of diagnosing wasting and determining whether the patient needed Serostim.

In October 2005, Serono settled and pleaded guilty to two criminal conspiracy charges: conspiracy to introduce into interstate commerce adulterated medical devices (the BIA devices, which had not been FDA-approved for such use), with intent to defraud and mislead; and conspiracy to offer illegal remuneration to physicians to induce them to refer individuals to particular pharmacies to fill Serostim prescriptions, for which payments were made under state Medicaid programs. As part of the plea and settlement agreements, Serono agreed to pay $704 million in criminal fines and civil payments, and enter into a CIA with OIG.

Criminal vs. Civil Charges

While the government previously charged Pfizer with criminal misbranding violations under the FDCA, it did not charge Serono with any criminal misbranding violations, and Serono did not admit criminal liability with respect to such allegations. Although the government alleged in the civil settlement agreement that Serono had engaged in off-label promotion of Serostim, it entered into a side agreement with Serono, specifically declining criminal prosecution for, among other things, off-label promotion of the AIDS wasting drug.

The omission of criminal charges for off-label promotion of Serostim in Serono is somewhat surprising, because the government's earlier plea and settlement agreement with Pfizer sent a strong signal that it would bring criminal charges against companies engaged in off-label marketing practices. It raises the question as to whether the government's view of the scope of criminal liability for off-label marketing is changing.

Indeed, Serono clearly sends the message that civil consequences for off-label marketing will be severe for the pharma industry. The criminal fine of almost $137 million imposed in the Serono settlement pales in comparison to the civil portion of the settlement ($567 million), which was based on off-label marketing allegations. In addition, the Serono CIA is more onerous than Pfizer's in its application to off-label marketing practices.

Off-label marketing is likely to remain a focus of OIG's investigative efforts, and equally likely are future settlements and CIAs involving onerous off-label marketing restrictions and obligations. Even if the number of criminal misbranding prosecutions for off-label marketing decreases, it is likely that these practices will be deterred by the threat of enormous civil penalties and onerous CIAs. PE

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CIA: Head-to-Head Comparison

Although Serono escaped criminal prosecution for its off-label marketing efforts for Serostim, the company's CIA restrictions were more onerous than those imposed on Pfizer as part of the Neurontin settlement. Here's a snapshot, and a side-by-side comparison, of some of the more relevant CIA provisions.

Pfizer	Serono
→ maintain a Code of Conduct relating to full compliance with all FDA requirements	→ implement and maintain a Code of Conduct relating to full compliance with all FDA requirements
→ maintain written policies and procedures relating to methods for marketing, selling, promoting, advertising, and disseminating information on off-label uses in compliance with all applicable FDA requirements	→ implement and maintain written policies and procedures relating to methods for marketing, selling, promoting, advertising, and disseminating information on off-label uses in compliance with all applicable FDA requirements, including procedures for responses to requests for information on off-label uses
→ maintain written policies and procedures to address the manner in which the company's medical information unit will respond to information requests for off-label uses	→ implement and maintain written policies and procedures to address the manner in which the company's medical information unit will respond to information requests for off-label uses
→ provide training on off-label issues	→ provide training on off-label issues
→ engage an independent review organization (IRO) to review sales, marketing, and product services activities	→ engage an IRO to assess and evaluate its systems, processes, policies, and practices related to promotional and product services-related functions
→ conduct internal investigations, and make internal and external disclosures regarding off-label marketing in certain circumstances	→ conduct internal investigations, and make internal and external disclosures regarding off-label marketing in certain circumstances
	→ implement a compensation policy to ensure that financial incentives do not inappropriately reward sales reps for engaging in improper promotion, sales and marketing activities
	→ document all inquiries to its medical information unit regarding Serostim
	→ review the medical information unit inquiry reports for Serostim semi-annually, and assess whether an undue amount of off-label requests originate from any particular sales territory, or whether the information suggests the occurrence of improper off-label promotion

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