



## ALERT

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### **TESTING THE LIMITS OF “OFF-LABEL” PROMOTION**

*A cautionary tale involving undercover FBI agents, rogue doctors and whistleblower sales representatives*

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Dr. Peter Gleason, a Maryland psychiatrist, was recently indicted and charged with conspiracy to illegally market the prescription medication Xyrem® for unapproved medical uses on behalf of its manufacturer. Dr. Gleason’s arrest and indictment bring into sharp focus the ever-expanding scope of federal prosecutorial activity involving “off-label” promotion of pharmaceutical products. On April 5, 2006, Dr. Gleason was indicted by a grand jury impaneled in the United States District Court for the Eastern District of New York for promoting Xyrem®, a drug developed by Orphan Medical, Inc., now known as Jazz Pharmaceuticals, Inc (“Orphan”). The prosecution of Dr. Gleason will no doubt test the limits of the complicated drug marketing regulatory scheme. Companies involved in the marketing of prescription drugs, (and now, sales representatives, pharmacies and physicians) should be acutely aware of the government’s view of the promotional activity alleged to be unlawful in this case.

#### **Background**

Xyrem®, also known as sodium oxybate or gamma-hydroxybutyrate (“GHB”), was first approved by the FDA in July 2002 to treat patients with narcolepsy who experience episodes of cataplexy, a condition associated with weak or paralyzed muscles. In November 2005, FDA approved Xyrem® to treat excessive daytime sleepiness (“EDS”) in patients with narcolepsy. Xyrem® has not been approved by FDA for any other medical indications.

GHB became controversial due to reports linking its use as a recreational drug and as a “date rape” drug. In 1990, FDA prohibited the distribution of GHB in interstate commerce, before subsequently approving it for medical use as Xyrem® in 2002. Due to concerns over potential serious risks involving the use of GHB, FDA required that Xyrem®’s label include a ‘black box’ warning. In addition, distribution of Xyrem was tightly restricted. For example, Xyrem was designated a Schedule III Controlled Substance for medical use, and Orphan set tight controls on dispensing. Some of these controls include dispensing through a single, centralized pharmacy, physician and patient education, a physician and patient registry, prescription tracking and detailed patient surveillance. As a condition for approving Xyrem®, the FDA required a four-prong Risk Management Program, a Medication Guide, and post marketing clinical studies.

The FDA’s November 2005 approval for Xyrem® to treat EDS in patients with narcolepsy was contingent on Orphan’s use of agreed-upon labeling text for the Product Package Insert, the Medication Guide and the Xyrem® Success Program for Physicians (Book, Letter, Registration Form, Patient Prescription and Enrollment Form), all of which had to be submitted to the FDA for review and approval no more than 30 days after the materials were printed. We now know that in April 2005, six months *prior to* this second approval, the FDA’s Office of Criminal



Investigations, Special Prosecutions Staff, opened a criminal investigation of alleged off-label promotion of Xyrem®.

### ***Promotion of Xyrem***

The Indictment alleges that Dr. Gleason, together with Orphan sales representatives and other Orphan employees, engaged in a conspiracy to defraud the United States with the goal of expanding the market for Xyrem® by promoting the drug for off-label indications. According to the Indictment, Dr. Gleason gave lectures across the country from 2003-2006, during which he promoted off-label uses of Xyrem®. For these lectures, which Dr. Gleason allegedly characterized as continuing medical education (“CME”), Dr. Gleason was allegedly paid tens of thousands of dollars and was in high demand by Orphan sales representatives because of his proven ability to generate off-label sales of the product. In 2004 alone, the FDA alleged, Dr. Gleason spoke at over 100 events and was paid more than \$70,000.

The government alleges that Dr. Gleason promoted the benefits of Xyrem® for such indications as: chronic pain, weight loss, depression, bipolar disorder, fibromyalgia, insomnia, movement disorders such as Parkinson’s disease, fatigue, and EDS not associated with narcolepsy. It is also alleged that Dr. Gleason advised physicians regarding ways to secure reimbursement of Xyrem® from insurance plans for these “off-label” indications. Specifically, the government alleges that Dr. Gleason advised prescribing physicians who attended his lectures to use alternative diagnosis codes, or even to provide no diagnosis code, which would increase the likelihood of reimbursement by insurance companies.

The indictment also alleges that Dr. Gleason routinely provided physicians with model Xyrem® prescription forms that contained suggested diagnosis codes, such as the code for EDS, to ensure the reimbursement for off-label uses. The government alleges that Dr. Gleason’s knowledge of the approved indication is indicated by the fact that these model prescription forms all contained a “Physician Declaration” section that explicitly stated: “I understand that Xyrem® is approved for the treatment of cataplexy in patients with narcolepsy, and that the safety or efficacy has not been established for any other indication.” This declaration was required by the FDA as part of the Success Program Prescription and Enrollment form.

On the company side, the government also alleges that Xyrem® sales representatives were under enormous pressure to increase sales of the product. A regional sales manager allegedly told sales representatives to “get the business” by any means possible, that “they had all sold products off-label before,” and that “there was no reason to object to that method now.” The regional sales manager allegedly told the sales representatives about Dr. Gleason, who would come and “work magic” in their territories.

The FBI’s Assistant Director-in-Charge said publicly that Dr. Gleason’s conduct was just like that of a “carnival snake-oil salesman.”

### ***The Investigation***

In recent years, the FDA, Office of Criminal Investigations, has established a Special Prosecutions Staff in Beltsville, Maryland specifically to investigate, among other conduct, potential illegal off-label promotion of approved drugs. A Special Agent with that office, in a



then-sealed Affidavit in Support of an Application for Arrest Warrant, said that in April 2005 a “confidential source” provided information regarding illegal off-label promotional activity by Orphan and Dr. Gleason. The Special Agent states that the “confidential source” was a sales representative responsible for the marketing and sales of Xyrem® in Alabama and Tennessee.

Orphan’s “confidential source” sales representative alleged that in 2003 Orphan had shifted its focus away from approved indications for the drug toward unapproved indications. She alleged to the FDA that starting in 2004 a Regional Sales Manager specifically encouraged the promotion of off-label indications of Xyrem® for fibromyalgia, and that the Vice President of Marketing was complicit in the promotion of off-label sales. This “confidential source” described to the FDA information allegedly discussed in internal sales conference calls, at two 2004 National Sales Meetings, at a CME program sponsored by Orphan and at a promotional dinner event organized by the “confidential source.” She also reportedly provided the government with recordings of her conversations with Dr. Gleason at promotional events, her discussions with other Orphan sales representatives, lectures given by Dr. Gleason, and conversations between herself, Dr. Gleason and Orphan’s sales managers. Further, she provided the government with e-mails between herself and the Regional Sales Manager, and between herself and Dr. Gleason, as well as other records from events during 2003, 2004 and early 2005.

Starting in August 2005, the FDA also ran an undercover operation through a cooperating witness (“CW”), who is identified as a physician who had pleaded guilty in 2003 to health care fraud but, as of February 2006, has not been sentenced. On August 2, 2005, this CW recorded a lecture that was monitored by the FDA Special Agent and other Special Agents (FBI and/or HHS). This CW also recorded meetings, at his office, with a sales representative (and Dr. Gleason on November 2) that were monitored by the FDA Special Agent and other Special Agents. These two meetings appear to be the only events specified in the Indictment and Sealed Affidavit that took place within the Eastern District of New York, where Dr. Gleason was charged and arrested.

### ***The Indictment***

The Indictment against Dr. Gleason charges the following five counts: Conspiracy to introduce a misbranded drug into interstate commerce, in violation of 21 U.S.C. §331(a) and 333(a)(2) (Food, Drug, and Cosmetic Act); Health care fraud conspiracy, in violation of 18 U.S.C. §1347 (health care fraud), §1349 (attempt and conspiracy); Introduction of a misbranded drug into interstate commerce, in violation of 21 U.S.C. § 331(a) and 333(a)(2) and 18 U.S.C. §2 (aiding and abetting); and; Health care fraud, in violation of 18 U.S.C. §2, §1347. The Indictment also seeks criminal forfeiture of all property constituting or derived from proceeds traceable to his offenses. If convicted, Dr. Gleason faces a maximum sentence of five years incarceration on Count One, ten years incarceration on Count Two, three years incarceration on Count Three and ten years incarceration on Count Four. On each count of conviction Dr. Gleason also faces a maximum fine of \$250,000.

### ***Analytical Background***

Generally speaking, enforcement in this area reflects the tension, as stated by a now-former top Department of Justice official, between the axiom that “once a product is approved [by the FDA for any indication], a physician relying on his or her own medical judgment may prescribe that



product for any medical use without violating federal law” with the dictate that the “introduction into interstate commerce [by a manufacturer] of a drug or other product with the intent to market or promote it for an off-label or unapproved use is illegal and can be prosecuted.” Throw in the mix that the Medicare and Medicaid programs explicitly and intentionally pay for specified off-label uses, the commercial free speech rights of manufacturers, and the critical need for full and unrestricted scientific and clinical exchange of information, and it becomes even harder to balance on the enforcement tightrope.

Until 1999, FDA enforcement regarding the labeling and promotion of approved drugs generally proceeded and was resolved through the use of warning letters or, if necessary, enforcement by the FDA Office of Chief Counsel and the Office of Consumer Litigation (OCL) of the Justice Department. According to recent remarks by the Director of OCL, when criminal enforcement was appropriate in the 1990’s, misdemeanor charges were the norm. Meanwhile, in the 1990’s in other areas of health care, the civil False Claims Act (along with its *qui tam* provisions) and the criminal Anti-Kickback Statute were proving to be enormously powerful enforcement tools, racking up record financial recoveries and significant criminal convictions.

In 1999, however, the landscape began to change. The FDA Office of Criminal Investigations and the Department of Justice resolved through a criminal plea agreement and civil settlement charges that Genentech illegally marketed Protropin for treating children with growth failure for reasons other than the lack of adequate growth hormone, children with a rare form of juvenile obesity, and a small number of burn patients. In 1985, FDA had approved and labeled Protropin only for the long-term treatment of children who have growth failure due to the lack on adequate endogenous growth hormone secretion.

The FDA Office of Criminal Investigations called this case “the first-ever criminal prosecution of a drug company for violating FDA’s rules against promoting a drug for unapproved uses,” and Genentech paid a criminal fine of \$30 million and a civil settlement of \$20 million. This civil settlement, significantly, was predicated on the theory that the illegal off-label promotion caused financial harm to the state Medicaid programs that paid claims submitted for non-approved uses, thus violating the False Claims Act. Thus, the traditional use of the criminal Food, Drug, and Cosmetic Act and the aggressive use of the civil False Claims Act, statutes enforced by separate components of the Department of Justice, were conjoined.

Following the Genentech matter, the Department of Justice resolved a series of three major off-label cases against pharmaceutical manufacturers. The first two reflected the “health care fraud” model of FDA enforcement: significant roles for *qui tam* “whistleblowers” seeking a share of recoveries; emphasis on civil recoveries (and False Claims Act releases); heavy criminal financial penalties; and stringent compliance requirements. The most recent resolution followed the more traditional model of criminal enforcement by the FDA and the Department of Justice with a criminal plea, Consent Decree, and no civil False Claims Act recovery or releases (or “whistleblower” rewards).

In May 2004, to resolve a *qui tam* action filed in 1996, Pfizer (for predecessor company Warner-Lambert’s conduct) agreed to plead guilty and pay more than \$430 million to resolve criminal charges (\$240 million) and civil liabilities (\$190 million) in connection with the off-label promotion of Neurontin (approved for anti-epileptic use). The investigation into Warner-Lambert began



when a former medical liaison for the company, David Franklin, M.D., brought a *qui tam* action under the False Claims Act alleging improper promotional activities. In that case, the government alleged the company paid physicians to attend seminars about off-label uses, to write articles and conduct studies about the effects of Neurontin, and to speak at events about the drug. In charges similar to those raised in the case against Dr. Gleason, the government alleged that the company paid certain doctors between \$50,000 and \$250,000 over time for delivering favorable messages regarding off-label uses for the drug. The government also alleged in that case that the company paid kickbacks to physicians to encourage them to prescribe the drug, especially for off-label use. Ultimately Dr. Franklin himself received about \$24.6 million of the civil recovery.

In December 2005, to resolve a number of *qui tam* actions, Serono Laboratories pled guilty and agreed to pay a total of \$704 million to settle criminal charges (\$136 million) and civil liabilities (\$567 million) related to allegations that Serono was engaged in the illegal off-label promotion of Serostim (approved for AIDS-wasting), conspired to distribute an unapproved and adulterated medical device, and conspired to pay illegal kickbacks. The government alleged that one New York doctor, Mikhail Makhlin, for example, illegally prescribed over \$11.5 million worth of the drug, which was paid for by Medicaid. In April 2005, eight months prior to the corporate resolution, the Department of Justice had indicted four former executives of Serono Inc. (a former marketing vice president, a former vice president for sales, and two regional sales directors) for allegations of offering kickbacks to doctors for Serostim prescriptions.

Most recently, the government demonstrated its commitment to prosecuting off-label promotion of approved drugs, even in the absence of *qui tam* filings, kickback allegations, or demonstrated financial harm to federally-funded health care programs. In December 2005, the government obtained a guilty plea under the Federal Food, Drug and Cosmetic Act to one count of misbranding from a pharmaceutical company allegedly engaged in off-label promotion. The company agreed to pay a \$6 million criminal fine, a \$6 million forfeiture, and \$24 million in equitable disgorgement pursuant to a Consent Decree of Permanent Injunction.

### **Gleason**

The Gleason case differs from these prior cases in several notable ways, including the government's initial focus on bringing criminal action against an independent contractor physician; allegations that the doctor affirmatively misled other physicians in the course of his off-label promotion; and the government's focus on a drug that the FDA expressly considers inherently dangerous. The latter two points may help explain the unusual step of criminally prosecuting the doctor before taking any apparent action against the company. On the other hand, manufacturers should not be lulled into a sense of comfort by these distinctions. Even though only a single physician has been indicted, and his conduct as alleged may appear particularly egregious, the case nevertheless should set off alarm bells for all pharmaceutical manufacturers. Specifically, and critically for pharmaceutical companies of all sizes and products, it reflects the government's willingness to focus on:

- The *criminal* prosecution of potential off-label violations;
- Undercover operations;
- A "pure" off-label case, without kickback allegations;



- A small company and a drug with limited sales;
- The provision of guidance to doctors on getting drug claims reimbursed for off-label uses; and
- Alleged misconduct as to which FDA could have but has not issued a warning letter.

The case also reflects the importance of whistleblowers to government prosecution. As reflected in the discussion above of previous cases, many of these cases are brought to the government by *qui tam* relators. While nothing expressly indicates that this investigation developed out of a *qui tam* case, the “confidential source” on which the government relied for its arrest warrant affidavit could well be a *qui tam* relator. She had been employed as a sales representative for the company for several years in Alabama and Tennessee, yet the indictment against Dr. Gleason (a Maryland physician) was brought in Brooklyn. While it is possible that she simply approached the FDA with her concerns and the FDA found an interested audience in Brooklyn, it seems far more likely that the “confidential source” approached a member of the relator’s bar, who chose to file the *qui tam* complaint on her behalf in the Eastern District of New York based on that office’s experience in pharmaceutical fraud cases. Such complaints are filed and remain under seal while the government investigates. Ultimately, *qui tam* relators are entitled to 15-25% of the government’s recovery in cases in which the government decides to intervene, which can provide a huge financial incentive for a disgruntled employee or former employee to file a complaint.

The prosecution of Dr. Gleason also points out the need for pharmaceutical manufacturers to pay close attention to the laws and regulations governing CME presentations and other exchanges of information with physicians through company-sponsored events. While physicians have a First Amendment right to discuss off-label uses, FDA has stated that discussions of off-label uses are not permissible in company-sponsored and company-controlled programs. More generally, several government agencies and industry groups including FDA, the Department of Health and Human Services Office of Inspector General, Pharmaceutical Research and Manufacturers of America, and the Accreditation Council for Continuing Medical Education have issued guidance requiring that educational programs funded by pharmaceutical companies maintain independence from the pharmaceutical company sponsors with respect to choices of speaker and educational content. It would be problematic under any of this guidance for a pharmaceutical company to expressly pay a physician to lecture on the off-label uses of the company’s drug.

In summary, what lessons can be learned from the Gleason case, and what can pharmaceutical companies expect in the future? First, this enforcement activity is just the tip of the iceberg. The government has confirmed that it has over 150 investigations of pharmaceutical companies in the pipeline, involving 500 or more products. These investigations can take many years to investigate and resolve and, even absent any identified wrongdoing, are enormously costly to defend. Second, enforcement activity is not restricted to large companies, or products with a significant amount of federal reimbursement through Medicare or Medicaid. Third, enforcement clearly has two prongs—traditional criminal enforcement under the Federal Food, Drug and Cosmetic Act, and the False Claims Act model with more emphasis on financial harm and civil recoveries. Under both models, patient harm (or patient benefit), financial benefit (corporate or individual), and the scientific or clinical foundation for off-label discussions may be critical factors. Fourth, the need for companies to implement effective risk reduction strategies with



respect to off-label uses of products, and to re-evaluate these policies and programs as enforcement in this area continues to evolve, is critical.

Understanding the conduct of concern in the prosecutions and resolutions to date, the compliance measures required as part of the resolutions, and underlying federal policy goals provides a context for compliance programs and risk reduction strategies. The prosecution of Dr. Gleason and investigation of Orphan involve factors that differ substantially from prior off-label promotional cases that have been resolved, and the outcome of this investigation will undoubtedly have a significant impact on compliance and enforcement.

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