Elsevier BusinessIntelligence

"The Pink Sheet"®

Prescription Pharmaceuticals & Biotechnology

November 1, 2010 Volume 72 Number 44

GSK's $750 Mil. DoJ Settlement: When GMP Violations Equal Healthcare Fraud

GlaxoSmithKline's $750 million settlement with the Department of Justice raises a worrisome question for industry: will violations of current good manufacturing practices become a target for whistleblower suits?

The Department of Justice has indicated that it may pursue such cases ("DoJ To Expand Use of False Claims Act To Manufacturing And AER Violations," "The Pink Sheet," Nov. 16, 2009). But GSK's precedent-setting settlement suggests there may be a high bar for charging companies that violate cGMPs with healthcare fraud.

"In this particular case, if you read the facts, they are extreme," said Kenneth Nolan, of Nolan & Auerbach. "And the whistleblower was the most well-positioned whistleblower for this type of case, so it was the perfect storm."

Cheryl Eckard, a former manager of global quality assurance who worked for GSK from 1992 through 2003, filed suit against the company in 2004 alleging numerous problems at GSK's manufacturing plant in Cidra, Puerto Rico, caused false claims to be submitted for defective drugs. She claimed that products manufactured at the site were misidentified because of product mix-ups, that they were contaminated with microorganisms, and that GSK lied to FDA to conceal the problems and obtain approval of the drugs.

FDA cited GSK for several of these problems in a series of inspection reports and a 2002 warning letter to the company (*see chart for timeline of agency actions*).

Alan Minsk, of Arnall Golden Gregory, said receiving a Form 483 of inspectional observations or a warning letter from FDA shouldn't be cause for concern that a False Claims Act case will follow. But he said if a company receives several warning letters or is cited for systemic problems or failure to take corrective action or is subject to a consent decree the government may look at this option.

"The facts would have to be such for [the government] to say 'we gotcha,'" Minsk said.

GSK Pleads Guilty To Adulteration Of Four Drugs

Eckard claimed that 20 drugs were affected by GSK's manufacturing violations. The company pled guilty to distributing four adulterated products into interstate commerce: the injectable anti-nausea drug *Kytril* (granisetron), the anti-infective ointment *Bactroban* (mupirocin), the antidepressant *Paxil CR* (paroxetine) and the diabetes drug *Avandamet* (metformin/rosiglitazone). The drugs were manufactured at the plant between 2001 and 2005.

The $750 million settlement includes a $150 million criminal fine for release of these products and a $600 million civil payment to the federal government and states to resolve claims it caused false claims to be submitted to government healthcare programs for the four products. The federal share is $436.4 million, of which $96 million will go to Eckard. States participating in the agreement will receive $163.6 million.

The Massachusetts U.S. Attorney's Office announced the settlement at an Oct. 26 press conference at the federal courthouse in Boston. Assistant Attorney General Tony West was joined by government officials from DoJ, HHS, FDA and the FBI.

"Whether drugs are contaminated during the manufacturing process, lack the proper mix of ingredients, or are mixed up and put in wrong bottles, the consequences can be real," West said in prepared remarks. "When it comes to the sort of conduct at issue here, we will hold pharmaceutical companies accountable."

West said the settlement is the fourth largest amount ever paid by a pharmaceutical company to the government to resolve criminal and civil allegations relating to the manufacturing and sale of adulterated drugs.

"We regret that we operated the Cidra facility in a manner that was inconsistent with current good manufacturing practice (cGMP) requirements and with GSK's commitment to manufacturing quality," GSK said in a statement. "GSK worked hard to resolve fully the manufacturing issues at the Cidra facility prior to its closure in 2009 and we are committed to continuous improvement in our manufacturing processes."

GSK announced in July that it would record a $2.36 billion legal charge to resolve several litigation matters, including $750 million to settle the government's investigation of its Puerto Rico plant ("Ripping The Bandage Off: GSK Resolves Suits On Many Products For $2.3 Billion," "The Pink Sheet," July 19, 2010).

GSK will also enter into a corporate integrity agreement with HHS' Office of Inspector General, but the company said it is continuing to negotiate the terms.

Ingredients For A Qui Tam Suit: GSK's Cidra Plant Violations

GlaxoSmithKline's violations of current good manufacturing practices at its former Cidra, Puerto Rico plant were the basis of a False Claims Act suit and the company's $750 million settlement with the Department of Justice. Below is a timeline of FDA inspections and actions in response to the manufacturing problems. GSK closed the plant in 2009.

FDA Action	Deficiencies Cited
February – April 2002 Inspection	Failure to reject drug products that did not meet established specifications and quality control criteria, which led to release of Bactroban contaminated with Pseudomonas fluorescens; failure to conduct a recall of the lot until the issue was brought up during the inspection and a conference call with FDA staff; failure to investigate and evaluate the reason for recurrent contamination of Bactroban and its impact on the safety and efficacy of the drug.
July 2002 Warning Letter	Adulteration of certain drug products manufactured at the site because, among other reasons, SB Pharmco failed to conduct timely investigations and take corrective actions. For example, FDA cited delayed investigations involving water sampling and media fill vials.
October 2002 Inspection	Procedures designed to prevent microbiological contamination of drug products were not followed.
October – December 2003 Inspection	Failure to take corrective action against all lots of Avandamet with content uniformity problems; lack of appropriate procedures and controls to prevent product mix-ups, which occurred repeatedly from 2001 through 2003; informing FDA that the mix-ups were isolated incidents unrelated to the manufacturing operation.
September - November 2004 Inspection	Failure to take adequate actions to prevent the Paxil CR split tablet defect; content uniformity failures with Avandamet; inappropriate procedures for cleaning and maintenance of equipment to prevent product mix-ups.
March 2005 Seizure of Paxil CR and Avandamet Tablets	FDA said the violation of manufacturing standards may have resulted in production of poor-quality drug products that could potentially pose risks to consumers. It determined that GSK's product recall was insufficient.
April 2005 Consent Decree	Among other things, the decree required GSK to retain experts to review its investigation of Paxil CR tablet splitting problems and Avandamet content uniformity failures to determine if the probable root causes had been identified and appropriate corrective and preventive actions taken.

Corporate Integrity Agreement v. Consent Decree

GSK previously had to modify its behavior under a 2005 FDA consent decree. The decree enjoined GSK employees from causing adulterated products from the Cidra plant to be introduced into interstate commerce. It also required GSK to retain experts to investigate Paxil CR tablet splitting and Avandamet content uniformity problems.

Nolan said that corporate integrity agreements are much broader in scope than consent decrees, which focus on manufacturing infractions. For example, the CIAs that Allergan and several other companies have entered into include provisions for board review of compliance programs, management certifications and employee training. Nolan represented whistleblowers who filed one of three qui tam suits that led to DoJ's $600 million settlement with Allergan ("Botox Reimbursement Training Is Driving Factor In Allergan Settlement With DoJ," "The Pink Sheet" DAILY, Sept. 1, 2010).

The government's criminal complaint against GSK's Cidra plant, SB Pharmco Puerto Rico, cites the history of problems FDA discovered in a series of inspections. It states that Bactorban was continuously contaminated with microbes and that contaminated batches of both Bactorban and Kytril were distributed in the market.

The complaint says Paxil CR tablets were defective because the active ingredient layer separated from the inactive ingredient, or barrier layer. It also states that GSK failed to report the defect to FDA and that after the agency cited it in 2004 for failing to take corrective actions the company released adulterated lots.

Among other violations, the complaint cites field alert reports of product mix-ups during the manufacturing and packing process.

Eckard's civil complaint alleged that GSK received complaints that consumers had found tablets of a different drug type or different strength in the same bottle. The complaint said an internal investigation identified *Avandia* (rosiglitazone) mixed with *Tagamet* (cimetidine) and Paxil with Avandia, among other mix-ups.

Product Diversion To Black Markets Alleged

In addition to manufacturing problems, the complaint also alleges that employees at the Cidra plant skimmed product during manufacture, including reject product, and diverted it to black markets in Latin America. The product was allegedly then channeled back into the U.S.

A private investigative firm looked into these allegations, which were made by a current and a former Cidra employee, and identified connections between a senior manager at Cidra and companies alleged to distribute the product on the black market, the complaint states. It says one of these companies was identified as Mova Pharmaceuticals, a contract manufacturer in Caguas, Puerto Rico.

The complaint says GSK closed its investigation into these allegations in April or May of 2003 for lack of sufficient evidence.

By Brenda Sandburg