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Manufacturing Practices

cGMP Enforcement and Compliance in the Wake of *Rostholder*



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In January 2013, the Deputy Assistant Attorney General in charge of the Department of Justice ("DOJ") Consumer Protection Branch warned that the DOJ would be taking "an especially hard look whenever patients are placed at an unacceptably high risk of harm by . . . violations of current good manufacturing practices."[1] Within five months of those remarks, the DOJ announced a settlement with the Indian generic drug manufacturer Ranbaxy, which resulted in criminal penalties under the Federal Food, Drug, and Cosmetic Act ("FDCA") and civil penalties under the False Claims Act ("FCA") exceeding $500 million. In December 2013, however, the Fourth Circuit, in *Rostholder v. Omnicare*,[2] struck a significant blow to the DOJ's efforts to penalize pharmaceutical companies for cGMP violations under the FCA.

Since the *Rostholder* decision, the DOJ has continued to pursue pharmaceutical companies for cGMP violations. The DOJ's continued interest in cGMP violations poses challenges for the legal and compliance departments of pharmaceutical companies, which have historically focused on the potential risks arising from off-label marketing and violations of the FCA and federal

[1] *See* "Deputy Assistant Attorney General Maame Ewusi-Mensah Frimpong Speaks at the 2013 CBI Pharmaceutical Compliance Congress," *available at* http://www.justice.gov/iso/opa/civil/speeches/2013/civ-speech-130129.html.

[2] 2014 BL 47153, 745 F.3d 694 (4th Cir. 2014)

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Anti-Kickback Statute (''AKS''), and have paid comparatively less attention to the potential consequences of cGMP violations.

As a result, pharmaceutical companies should ensure that they have robust compliance programs to address cGMP issues before they occur, and that any cGMP violations are investigated and remedied promptly.

I. Statutory Framework

The FDCA bars ''[t]he introduction or delivery for introduction into interstate commerce of any . . . drug [or] device . . . that is adulterated or misbranded.''[3] A drug is ''adulterated'' if ''the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice . . .''[4] Each violation of the FDCA is punishable by a criminal fine of up to $500,000 or twice the gross pecuniary gain or loss, whichever is greater.[5]

Under the FCA, a company may be liable where it ''knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval.''[6] Each violation of the FCA is punishable by a civil fine of not less than $5,500 and not more than $11,000, plus three times the damages sustained by the government as a result of the offense.[7] The FCA also allows private persons to bring *qui tam* actions under the FCA in the name of the government.[8] Plaintiffs who prevail in *qui tam* actions are entitled to anywhere from 15 percent to 30 percent of any proceeds awarded in the suit.[9]

II. The Ranbaxy Case: A Case Study of Pre-*Rostholder* DOJ FCA Action Arising From cGMP Violations

The 2013 case involving Ranbaxy reflects the DOJ's pre-*Rostholder* focus on cGMP violations as a basis for liability under the FDCA and FCA, as well as the DOJ's ability to extract significant penalties from drug manufacturers for such violations. The case is illustrative of the types of problems that can lead to significant penalties and the steps that drug manufacturers must take to avoid Ranbaxy's fate.[10]

On May 13, 2013, the DOJ announced that Ranbaxy USA Inc., a subsidiary of Indian generic pharmaceutical manufacturer Ranbaxy Laboratories Limited, had pled guilty to seven felony counts (three felony FDCA counts and four counts of making false statements to the Food and Drug Administration (''FDA'')) arising out of the manufacture and distribution of adulterated drugs. Pursuant to the agreement, Ranbaxy agreed to pay a criminal fine and forfeiture totaling $150 million, and agreed to settle civil FCA and state law claims for $350 million. The announcement followed on the heels of a consent decree filed by the FDA on Jan. 25, 2012.[11] Pursuant to the consent decree, Ranbaxy was required to comply with detailed data integrity requirements before the FDA would resume reviewing drug applications containing any data or information from three Ranbaxy facilities in India.[12] The consent decree also prevented Ranbaxy from manufacturing drugs at four facilities for introduction into the U.S., or for inclusion in the President's Emergency Plan for AIDS Relief, until drugs could be manufactured at those facilities in compliance with applicable quality standards.[13]

In the press release announcing the guilty plea and civil settlement, the director of the FDA's Office of Criminal Investigations stated, ''[t]he FDA expects that companies will comply with the cGMP requirements mandated by law so that consumers can be assured that their medical products are safe and pure.''[14]

Most notably, the government alleged that Ranbaxy falsified stability testing data, and that ''in many instances, the stability test results for certain drugs for different time intervals (e.g., three, six, and nine months) actually were conducted on the same day or within a few days of each other.''[15] The government also alleged that Ranbaxy intentionally departed from the stability testing protocols it disclosed to the FDA by storing samples in a four-degree Celsius refrigerator prior to testing, rather than at conditions approximating those under which the drug could be expected to be held once it was marketed.[16]

The FDA's investigation of Ranbaxy followed warnings from Ranbaxy's own external consultants regarding the company's cGMP issues. In October 2003, for example, an audit report sent to Ranbaxy's director of regulatory affairs advised that ''formalized training, as required by the cGMPs . . . was essentially nonexistent'' and that ''[n]umerous discrepancies were found in the source data.''[17] In February and March 2005, consultants similarly advised that Ranbaxy's facilities suffered from defects that ''if not addressed, could potentially result in regulatory action and/or a significant FDA 483 observation.''[18] The problems identified by the consultant allegedly included manufacturing and laboratory procedures, site-wide documentation practices and stability program issues.[19] The consulting report specifically noted that ''[a] procedure on good documentation practices was found to be lacking at all the sites'' and that Ranbaxy's stability department was understaffed.[20] The consulting firm proposed con-

[3] 21 U.S.C. § 331(a).
[4] 21 U.S.C. § 351(a)(2)(B).
[5] 21 U.S.C. § 331(a); 18 U.S.C. § 3571(c),(d).
[6] 31 U.S.C. § 3729(a)(1)(A).
[7] 31 U.S.C. § 3729(a)(1).
[8] 31 U.S.C. § 3730(b)(1).
[9] 31 U.S.C. § 3730(d)(1),(2).
[10] Ranbaxy is not the only drug manufacturer to face substantial penalties for cGMP violations. *See* http://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-pay-750-million-resolve-criminal-and-civil-liability-regarding.
[11] DOJ files consent decree of permanent injunction against Ranbaxy, *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289224.htm.
[12] *Id*.
[13] *Id*.
[14] Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA, *available at* http://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false.
[15] Criminal Information ¶ 16.
[16] Criminal Information ¶ 17.
[17] Criminal Information ¶ 19.
[18] Criminal Information ¶ 20.
[19] *Id*.
[20] *Id*.

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ducting a series of training programs at Ranbaxy, but Ranbaxy never offered any of those programs.[21]

Years before the criminal and civil settlement, the FDA advised Ranbaxy on multiple occasions that its procedures failed to align with cGMP. In February 2006, for example, inspectors documented eight cGMP violations at Ranbaxy's Paonta Sahib facility, including: (1) failure to include a complete record of data obtained during laboratory tests; (2) failure to establish and follow an adequate written testing program; and (3) failure to provide the quality control unit with adequate laboratory resources, including personnel and equipment, for conducting stability testing.[22]

The FDA identified similar violations at Ranbaxy's Dewas facility in February and March 2006, including: (1) failure to maintain complete testing data; (2) failure to maintain batch production and control records; and (3) failure to investigate other batches of drugs demonstrated to have discrepancies to determine whether those other batches suffered from the same defects.[23] A subsequent inspection of the Dewas facility in January and February 2008 identified ''serious deviations'' from cGMP, including: (1) failure to establish separate areas for manufacture and processing of certain products to prevent contamination; (2) failure to maintain procedures to review unexplained discrepancies in batches; and (3) failure to maintain and follow adequate written procedures designed to prevent microbiological contamination.[24]

In addition to the significant criminal and civil penalties Ranbaxy agreed to pay as part of the plea, the cGMP violations also caused the FDA to withdraw tentative approval of two Abbreviated New Drug Applications (''ANDA'') that it had previously granted to Ranbaxy, including approval of a generic version of the acid reflux drug Nexium. In February 2015, the U.S. District Court for the District of Columbia upheld the FDA's decision to withdraw the tentative approvals and rejected Ranbaxy's argument that the FDA had no authority to withdraw such approvals once granted.[25] In its decision, the court characterized the FDA's original decision to approve the ANDAs as an ''egregious error'' in light of Ranbaxy's cGMP violations, and held that the FDA possesses inherent authority to correct such mistakes by withdrawing tentative approval.[26] The decision is currently on appeal.

III. The *Rostholder* Case and the Limitation on the Use of the FCA to Punish cGMP Violations

While the Ranbaxy case demonstrates the DOJ's historic willingness to use both the FDCA and the FCA to extract substantial penalties from drug manufacturers, a recent decision from the U.S. Court of Appeals for the Fourth Circuit limits the use of the FCA as a means of penalizing cGMP violations.

In *Rostholder*,[27] a relator alleged that Omnicare, Inc., failed to ensure that penicillin and non-penicillin drugs were packaged in complete isolation from one another, as required by cGMP. The relator sought to bring claims under the FCA, alleging that Omnicare knowingly or recklessly violated cGMP, which rendered the drugs adulterated and ineligible for reimbursement, and thus that any reimbursement for the drugs was ''false or fraudulent'' under the FCA. The Fourth Circuit rejected that argument, noting that a defendant is liable under the FCA only where it has made a ''false statement'' or engaged in a ''fraudulent course of conduct.'' However, drugs are eligible for reimbursement under Medicare and Medicaid so long as they have been approved by the FDA; neither statute expressly bars reimbursement for drugs manufactured in violation of cGMP. Because compliance with cGMP is not required for reimbursement under Medicare and Medicaid, Omnicare did not make any false statement merely by distributing adulterated products that were reimbursed, and the relator could not state a claim under the FCA. The Fourth Circuit worried that ''[w]ere we to accept relator's theory of liability based merely on a regulatory violation, we would sanction use of the FCA as a sweeping mechanism to promote regulatory compliance, rather than a set of statutes aimed at protecting the financial resources of the government from the consequences of fraudulent conduct.''[28]

In the wake of *Rostholder*, the DOJ and relators face significant obstacles in their efforts to transform cGMP violations into the basis for substantial civil liability under the FCA. Indeed, since the *Rostholder* decision, the DOJ has not brought any action against a pharmaceutical company alleging FCA liability based on cGMP violations. Similarly, relators have been challenged in their efforts to bring suit against pharmaceutical companies under the FCA for cGMP violations. In *United States ex rel. Campie v. Gilead Sci., Inc.*,[29] the realtors alleged that Gilead Sciences Inc. obtained reimbursement under Medicare and Medicaid in violation of the FCA for contaminated and defective drugs. The district court found that the relators failed to state a claim under the FCA and dismissed the realtors' suit.[30] The district court explained that the FCA is not ''an all-purpose, anti-fraud statute . . . It does not stand for the proposition that a falsehood told to a governmental regulatory agency can form the basis of FCA liability simply because the fraudulently induced action of that agency was part of a casual chain that ultimately led to eligibility for payment from the payor agency.''[31]

IV. Post-*Rostholder* cGMP FDA & DOJ Actions

In the wake of *Rostholder*, the FDA and DOJ have continued to bring actions against pharmaceutical companies for violations of cGMP.[32]

A. March 10, 2015, Consent Decree of Permanent Injunction Against Specialty Compounding

On March 10, 2015, a federal district court in the Western District of Texas entered a consent decree of

[21] Criminal Information ¶ 21.
[22] Criminal Information ¶ 13.
[23] Criminal Information ¶ 14.
[24] Criminal Information ¶ 15.
[25] *See Ranbaxy Laboratories, Ltd. v. Burwell*, 2015 BL 65027, No. 14-1923(BAH) (D.D.C. March 11, 2015).
[26] *Id.* at *3, *102.
[27] 2014 BL 47153, 745 F.3d 694 (4th Cir. 2014).
[28] *Id.*
[29] 2015 BL 2670, No. C-11-0941 (N.D. Cal. Jan. 7, 2015).
[30] *Id.* at *8.
[31] *Id.* at *13.
[32] *See* http://www.justice.gov/opa/pr/mcneil-ppc-inc-pleads-guilty-connection-adulterated-infants-and-childrens-over-counter-liquid.

permanent injunction against Specialty Compounding LLC, its pharmacist-in-charge and co-owner, and its Managing Partner and co-owner, to prevent the distribution of adulterated and misbranded drugs.[33] The DOJ filed a complaint seeking the entry of the consent decree at the request of the FDA.[34] According to the complaint, Specialty Compounding manufactured sterile and non-sterile drugs at a facility in Texas, and distributed the company's drugs to hospitals, surgery centers and health clinics in Texas and throughout the U.S. One of the sterile injectable drug products manufactured by Specialty Compounding tested positive for bacterial growth.[35] Moreover, in August 2013, the FDA received reports from two Texas hospitals that 17 patients had developed bacterial infections after receiving infusions of calcium gluconate manufactured by Specialty Compounding.[36] That same month, Specialty Compounding ceased sterile drug manufacturing operations, and recalled all lots of its unexpired sterile drug products distributed since Feb. 1, 2013.[37] Pursuant to the terms of the permanent injunction, Specialty Compounding and its co-owners cannot resume production of sterile drug products until they receive written approval from the FDA that they are in compliance with the remedial provisions of the permanent injunction, which include compliance with the FDCA and its regulations.[38]

B. Jan. 30, 2015, FDA Warning Letter to Apotex

On Jan. 30, 2015, the FDA issued a Warning Letter[39] to Apotex, the Canadian-based manufacturer of vaccines distributed in the U.S. and elsewhere, in connection with the FDA's June 23 to July 1, 2014, inspection of Apotex's manufacturing facility located in Bangalore, India.[40] During that inspection, investigators from the FDA identified significant violations of cGMP regulations for finished pharmaceuticals, causing the drugs to be adulterated under the FDCA.[41] More specifically, the Warning Letter noted Apotex's failure to: 1) ensure that laboratory records included complete data derived from all tests necessary to ensure compliance with established specifications and standards; 2) exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records; 3) establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile; and 4) follow written procedures applicable to the quality control unit, and the related failure of the quality control unit to review and approve all drug product production and control records to determine compliance with all established, approved written procedures before a batch is released or distributed.[42]

The FDA concluded that Apotex's internal investigation of these issues had failed to address or resolve the foregoing issues.[43] As such, the FDA has demanded that Apotex provide to the agency: 1) a comprehensive evaluation of the extent of the inaccuracy of recorded and reported data; 2) a risk assessment of the potential effect of the observed failure on the quality of drug products; and 3) a management strategy for Apotex that includes details of a global corrective and preventative action (''CAPA'') plan.[44] The FDA stated that until Apotex completes all corrective actions and the FDA has confirmed those actions and Apotex's compliance with cGMP, the FDA may withhold approval of any new applications or supplements listing Apotex as a drug product manufacturer.[45] The FDA further warned that Apotex's failure to correct the violations may result in the FDA continuing to refuse admission of articles manufactured at the Bangalore facility into the U.S.[46]

V. Best Practices for cGMP Compliance in the Wake of the Ranbaxy Case and the *Rostholder* Decision

While *Rostholder* suggests that the DOJ may not be able to use cGMP violations as a basis for FCA liability as it did with respect to Ranbaxy, it is likely that the DOJ will continue to focus on cGMP violations, and may bring criminal charges and civil suits where it has reason to believe that significant violations exist. It is therefore critical that legal and compliance teams at drug manufacturers take steps to monitor cGMP issues and to actively address any problems that arise. As the most recent cases brought by the DOJ indicate, companies are most likely to face criminal or civil charges for cGMP violations where the violations are pervasive or countenanced by senior personnel, where companies fail to support or actively impede audit and compliance personnel, where cGMP violations remain uncorrected despite multiple FDA Warning Letters or Form 483s and where companies actively mislead the FDA about their manufacturing and testing processes and compliance with cGMP. Thus, it is recommended that pharmaceutical companies take the following actions to avoid or minimize any criminal or civil liability:

- maintain an active compliance program to detect and rectify cGMP violations;
- implement and maintain a robust internal audit program;
- foster a culture of compliance and encouraging employees to come forward with any violations that they observe;
- ensure that all relevant employees are aware of cGMP requirements, and provide regular compliance training;

[33] Federal judge enters consent decree against Specialty Compounding LLC, *available at* http://www.fda.gov/NewsEvents/Newsroom?pressAnnouncements/ucm437682.htm.

[34] *Id*.

[35] District Court Enters Permanent Injunction Against Texas Pharmacy and Senior Executives to Present Distribution of Adulterated and Misbranded Drugs, *available at* http://www.justice.gov/opa/pr/district-court-enters-permanent-injunction-against-texas-pharmacy-and-senior-executives.

[36] *Id*.

[37] *Id*.

[38] *Id*.

[39] Warning Letters are the FDA's principal means of obtaining ''prompt voluntary compliance'' with the FDCA. FDA Regulatory Procedures Manual, ''4-1-1 Warning Letter Procedures,'' *available at* http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm#SUB4-1.

[40] FDA Warning Letter, Apotex Research Private Limited 1/30/15, *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm432709.htm.

[41] *Id*.

[42] *Id*.

[43] *Id*.

[44] *Id*.

[45] *Id*.

[46] *Id*.

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- implement and monitor quality agreements with all suppliers;
- implement and maintain a robust program to address consumer complaints regarding product quality;
- implement and maintain a robust program to address and remediate cGMP-related issues, including CAPA plans; and
- respond promptly and thoroughly to any FDA Warning Letters or Form 483s.