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Manufacturing Trouble: Is cGMP the Next Enforcement Frontier?



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I. Introduction

Current Good Manufacturing Practices ("cGMP") may mark the next frontier in health care fraud enforcement. While pharmaceutical and medical device manufacturers have faced scrutiny from the Department of Justice ("DOJ") for decades,[1] those enforcement activities have largely focused on off-label marketing and enforcement of the Anti-Kickback Statute, areas in which most in-house legal and compliance departments are, by now, quite familiar. But many companies view cGMP issues through a regulatory prism, treating them simply as technical, operational concerns that pose relatively little risk of civil liability, let alone federal criminal enforcement. Given DOJ's increased focus on cGMP violations as a potential basis for criminal and civil liability, companies should rethink that approach and refocus their attention and legal resources on cGMP before serious problems arise.

Many pharmaceutical and medical device manufacturers relegate cGMP issues to their quality groups, often with little or no oversight by, or involvement from, their in-house legal departments. Two related developments call this approach into question. First, the Food and Drug Administration ("FDA") recently has ramped up its own enforcement efforts with respect to cGMP deficiencies. In fiscal year 2013 alone, the FDA issued over 5,000 Form 483 observations and approximately 700 non-tobacco Warning Letters, a substantial fraction of which related to cGMP issues. Second, DOJ is flexing its health care enforcement muscle by increasingly eyeing cGMP violations as potential criminal and/or civil violations that fall within its domain. In some respects, the uptick in regulatory activity paves the way for DOJ's expanded enforcement efforts because the FDA's increased documentation of cGMP deficiencies provides DOJ a roadmap for investigating and building cases against pharmaceutical and medical device manufacturers for alleged cGMP violations.

DOJ has made no secret of its intention to aggressively step up enforcement of cGMP. In January 2013, Deputy Assistant Attorney General for Consumer Protection Maame Ewusi-Mensah Frimpong warned that manufacturers who disregard cGMP do so "at their peril" and that the government 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." In August 2013,

[1] In fiscal year 2013, the federal government recovered approximately $4.3 billion dollars in criminal fines and civil settlements related to health care fraud, a substantial portion of which came from pharmaceutical and medical device companies.

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Jeffrey Steger, Assistant Director for DOJ's Consumer Protection Brach, noted that DOJ is working more closely with FDA, and that the government has been receiving an increased number of cGMP referrals from industry whistleblowers. And at the Pharmaceutical Compliance Congress in January of this year, Carmen Ortiz, the United States Attorney for the District of Massachusetts, reportedly noted that investigating the manufacture of adulterated drugs was a top priority for her office. Consistent with this trend, the FDA's Pharmaceutical Fraud Program (''PFP'') opened 23 new criminal investigations in FY 2013, including seven that involve allegedly ''flagrant manufacturing practices.'' The PFP also recently announced that another ongoing investigation of a ''large drug manufacturer for serious and pervasive manufacturing violations'' has begun to ''show promise'' of judicial action, including possible criminal prosecution.

As the government's enforcement priorities evolve, manufacturers must ask themselves if they are ready for increased scrutiny of their manufacturing operations and cGMP compliance programs. Fortunately, there are a number of steps that companies can take now to enhance their manufacturing practices and improve their cGMP compliance programs in ways that will help reduce the risk of DOJ action. After a brief overview of the legal framework for DOJ enforcement of cGMP regulations, we review recent developments in the cGMP enforcement landscape and offer some common-sense strategies that can help manufactures prepare for increased cGMP scrutiny in the years ahead.

II. Legal Framework

A. The Federal Food, Drug & Cosmetic Act

The Federal Food Drug & Cosmetic Act (''FDCA''), prohibits, among other things, the ''introduction or delivery for introduction into interstate commerce'' of any drug or medical device that is adulterated or misbranded. A drug or medical device is ''adulterated,'' if, among other things, it is manufactured in a manner that does not conform with cGMP regulations promulgated by the Department of Health and Human Services. cGMP regulations require companies to have systems in place to assure the proper design, monitoring, and control of their manufacturing processes and facilities. The regulations are designed to be flexible—as they must be—in order to cover a wide variety of manufacturing environments and evolving technical standards. But, this flexibility necessarily leads to ambiguity, and determining exactly what cGMP requires in any given context can be a difficult task. As former FDA chief counsel Peter Barton Hutt has stated, ''it is very difficult, if not impossible, to determine the requirements of GMP compliance simply by looking at the statute and regulations.''

cGMP regulations are primarily enforced by FDA through an administrative regime of inspections, Form 483 observations, Warning Letters, civil injunctions, consent decrees, and civil fines. But the very same cGMP violations that can lead to FDA enforcement action can also carry criminal liability under the FDCA. Even seemingly minor or ''technical'' deviations from cGMP can potentially be prosecuted as criminal misdemeanors. Misdemeanor liability in this context is strict, meaning that the government does not need to prove that the violator intended—or even knew about—the violation. Second-time offenders, and those who act with ''the intent to defraud or mislead,'' are subject to felony criminal liability. Separately, manufacturers can also be subject to criminal liability for making materially false or fraudulent statements to the government, including statements made in connection with New Drug Application submissions, required periodic filings, and even to FDA inspectors during routine inspections.

The direct financial consequences of a FDCA conviction or plea can be devastating. Significantly, the statute provides the same range of potential penalties for selling a drug or device manufactured with a minor cGMP deviation as for selling one that wholly fails to meet its FDA-approved specification. Any criminal conviction or plea—even a misdemeanor—is punishable by a criminal fine of $500,000 per violation, or twice the pecuniary gain or loss associated with the criminal conduct, whichever is greater. The government can also enforce compliance by seeking a lengthy term of probation or requiring that a company enter into a Corporate Integrity Agreement as a condition of settlement. These nonmonetary remedies can require companies to revamp their compliance programs, hire independent monitors, and impose onerous self-reporting obligations. They can also include expedited procedures for imposing additional penalties in the event new violations are discovered. Depending on the nature of the conviction, the government can also seek, in certain circumstances, to debar or exclude an offender from participation in federal healthcare programs—the effective death knell for most pharmaceutical and medical device companies.

B. The False Claims Act

The government may also choose to litigate cGMP violations under the federal False Claims Act (''FCA''). The FCA imposes civil liability on those who ''knowingly present[] or cause to be presented'' to the government ''false or fraudulent claim[s] for payment.'' In the cGMP context, the government has alleged that claims submitted to federal healthcare programs for reimbursement of adulterated products not manufactured in conformance with cGMP are false, and that pharmaceutical manufacturers knowingly cause the submission of those false claims when they ship adulterated products in interstate commerce. Violators are subject to a penalty of $5,500 to $11,000 for each false claim they present or cause to be presented, plus up to treble damages. A unique *qui tam* provision that allows individuals to bring FCA actions in the name of the United States and collect fifteen to thirty percent of the government's recovery creates a powerful incentive for employees and other company insiders to become whistleblowers when they learn of potential compliance issues.

Recently, however, the United States Court of Appeals for the Fourth Circuit rejected a relator's legal theory that cGMP violations can form the basis of an FCA action. In *United States ex rel. Rostholder v. Omnicare, Inc.*, 745 F.3d 694 (4th Cir. 2014), *cert denied*, No. 13-1411 (Oct. 6, 2014), a former pharmacist and operations manager for an Omnicare subsidiary alleged that the company violated cGMP by packaging both penicillin and non-penicillin products in the same building, with inadequate separation and controls to prevent cross-contamination. The relator alleged that drugs

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manufactured in facilities with cGMP violations were adulterated under the FDCA, and that claims submitted to Medicare and Medicaid for reimbursement of such adulterated drugs were therefore false. While the government declined to intervene in the case, it filed a statement of interest, in which it argued that certain types of cGMP violations, particularly those that render a drug useless or give rise to discrepancies in the composition of the drug, are material to the government's reimbursement decision and can therefore serve as the basis of a false claim.

The Fourth Circuit acknowledged that the relator's alleged cGMP violations rendered the drugs adulterated, but found that such violations were not, by themselves, sufficient to trigger FCA liability. According to the court, an FDA-approved drug is reimbursable under the Medicare and Medicaid statutes, and ''the submission of a reimbursement request for [an FDA-approved] drug cannot constitute a 'false' claim under the FCA on the sole basis that the drug has been adulterated as a result of having been processed in violation of FDA safety regulations.'' *Rostholder* at 701-02. The court also expressed general discomfort with the idea of using the FCA to enforce cGMP violations, stating:

> Were 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. When an agency has broad powers to enforce its own regulations, as the FDA does in this case, allowing FCA liability based on regulatory noncompliance could ''short circuit the very remedial processes the Government has established to address non-compliance with those regulations.''

Rostholder at 702 (quoting *U.S. ex rel. Wilkins v. United Health Grp., Inc.*, 659 F.3d 295, 310 (3d Cir. 2011)).

Although the significance of the *Rostholder* decision remains to be seen, it seems unlikely to deter the government from pursuing FCA actions premised upon cGMP violations, particularly where those violations materially affect the strength, quality, or purity of a drug. It is also unclear what impact the decision will have in other circuits that, unlike the Fourth Circuit, recognize the more lenient ''implied certification'' theory of liability. On October 6, 2014, the Supreme Court denied certiorari in the *Rostholder* matter, leaving this issue unresolved for now.

III. DOJ's Approach to cGMP Enforcement Is Familiar

The approach DOJ appears to be taking with respect to the prosecution of cGMP cases is in many ways consistent with that which it has used to prosecute other forms of healthcare fraud. Among other things, DOJ appears to be focused not on technical cGMP violations, but on cases that involve real quality issues, actual product adulteration, and/or a risk of patient harm. This focus is particularly evident in two of the most heavily covered cGMP cases in years, as well as a recent complaint filed in the District of New Jersey.

First, in October 2010, SB Pharmco Puerto Rico Inc. (''SB Pharmco''), a subsidiary of GlaxoSmithKline (''GSK''), pleaded guilty and agreed to pay $750 million in criminal fines, forfeitures and civil damages to resolve charges of misbranding and distributing adulterated products stemming from cGMP violations involving the manufacture of Paxil CR and Avandamet and violations of the False Claims Act.[2] Specifically, the government claimed that the Paxil CR manufacturing process allowed certain two-layer tablets to split, resulting in the distribution of some Paxil CR tablets that lacked any active ingredient, and some that lacked any controlled release mechanism. The government similarly alleged that certain tablets of Avandamet did not contain the FDA-approved mix of active ingredients.

Then, in May 2013, generic manufacturer Ranbaxy Laboratories, Ltd. pleaded guilty and agreed to pay $150 million in criminal penalties, plus $350 in civil damages and penalties, to resolve charges of misbranding, distributing adulterated products, making false statements, and violations of the FCA relating to significant cGMP violations at several of its Indian facilities. The alleged cGMP violations included, among other things, Ranbaxy's submission of false stability study data to FDA, ''nonexistent'' cGMP training, and numerous deficiencies in Ranbaxy's internal investigations, recordkeeping, stability assessment program and cross-contamination prevention controls.

And as recently as October 2, 2014, DOJ filed a complaint for permanent injunction in the District of New Jersey against a medical device manufacturer, Pharmaceutical Innovations, Inc. (''PII''), and its owner, Gilbert Buchalter for, among other things, violations of cGMP. DOJ alleged that, despite multiple meetings with the FDA, the issuance of multiple Form 483 observations, and a Warning Letter, PII failed to comply with cGMP regulations regarding process validation, production and process controls, corrective and preventative actions, and purchasing controls. In addition to the cGMP failures, DOJ also alleged that PII failed to properly alert the FDA when it became aware that sixteen surgical patients at a Michigan hospital developed infections traced to a PII ultrasound transmission gel.

In contrast to the GSK, Ranbaxy and PII cases, in which product adulteration allegations raised safety and efficacy questions, the DOJ has declined cases where the alleged cGMP violations at issue presented less serious risks to product safety or quality.

IV. Recent Developments in cGMP Enforcement

While much of the recent attention in the cGMP enforcement sphere has focused on the GSK, Ranbaxy, and *Rostholder* cases, a number of other recent events provide valuable insights into the government's view of the importance of cGMP compliance. In one recent case, FDA announced that it was withholding approval of a new drug until its manufacturer corrected previously identified cGMP deficiencies at the proposed manufacturing facility. Those deficiencies, which FDA had detailed in a Warning Letter, included the failure to investigate critical deviations and to reject products that did not meet specification. Significantly, FDA did not request any additional studies concerning, and has not expressed any significant concerns about the new drug's safety or efficacy. Thus, FDA's decision, while

[2] In the related *qui tam* action, GSK agreed to pay $600 million to settle FCA and related state law claims involving allegations that it sold drugs whose strength, purity, and quality differed materially from their FDA-approved specifications.

not unprecedented, reflects the seriousness of the government's commitment and its willingness to put cGMP compliance above other financial and public health interests.

The government has also recently signaled an intent to hold distributors accountable for overseeing manufacturing operations performed by third party contractors. In the spring of 2013, FDA sent Warning Letters to five dietary supplement distributors citing their failure to implement and maintain an adequate quality release program for supplements manufactured for them by third-party contract manufacturers. Citing *United States v. Park*, 421 U.S. 658 (1975), FDA admonished each company that, ''[a]lthough your firm may contract out certain dietary supplement manufacturing operations, it cannot, by the same token, contract out its ultimate responsibility to ensure that the dietary supplement it places into commerce (or causes to be placed into commerce) is not adulterated for failure to comply with dietary supplement CGMP requirements.'' Thus, the government asserted, the distributors are ''responsible for ensuring that the product is not adulterated for failure to comply with dietary supplement CGMP requirements, regardless of who actually performs the dietary supplement CGMP operations.'' Although the government had not yet pursued this expansive theory of liability in a criminal cGMP case, these Warning Letters demonstrate the risks that companies who lack their own manufacturing operations can face as government scrutiny of cGMP increases.

V. Mitigating the Risks

As the government sharpens its focus on cGMP, an increasing number of companies will find their manufacturing, quality, and compliance programs under scrutiny from a variety of government agencies, including FDA and DOJ. Companies would be well served to take a hard look at their manufacturing, quality and cGMP compliance programs now, before they come under the microscope of a government investigation, to ensure that they are prepared. Fortunately, companies can take a variety of steps to enhance their manufacturing practices, quality systems and compliance programs in order to help reduce the risk of an investigation and bring any investigations that do arise to a swift, and hopefully favorable, conclusion.

A. Prioritize and Incentivize cGMP Compliance

Any successful compliance program begins with the ''tone at the top,'' and cGMP compliance is no different. Senior management must make cGMP compliance a priority and continually reinforce its importance. While proper messaging is important, prioritizing and reinforcing cGMP means more than just ''talking the talk.'' It also means ensuring that the company has an independent quality assurance function, backed by adequate funding and resources, and staffed with dedicated employees who have received proper cGMP training. It means ensuring that every employee who touches the manufacturing process and supply chain understands that cGMP compliance is a key part of his or her job. And it means creating appropriate mechanisms and incentives to encourage all employees to detect, report, and correct cGMP issues when they arise.

B. Understand Your Products and How They Are Made

Robust and effective cGMP compliance also requires a deep scientific and technical understanding of every product the company manufactures, and every process used to manufacture each product. It requires a fundamental understanding of which process parameters are key to successful manufacturing and which variables drive process failures. Achieving this depth of understating can be challenging for companies that manufacture legacy products, particularly where robust development data are not readily available. But even where such data are limited, companies must be vigilant about identifying, investigating, and correcting manufacturing deviations and monitoring manufacturing trends to help detect process problems before they affect product quality. Companies must also effectively monitor, track, and investigate any customer complaints that involve product quality.

C. Take a Holistic Approach

Companies must take a holistic approach to cGMP compliance. Modern pharmaceutical and medical device companies often operate through a multinational network of corporate entities, divisions, and business units, each with its own corporate structure, operating budget, and management authority. But the government often takes a more monolithic view of these organizations, and can be unsympathetic to claims of corporate separateness. For example, the government often expects companies to assess whether cGMP issues identified at one site are present at others, and if so, to remedy those issues even where they fall under the purview of a legally separate entity.

D. Prioritize Responses to FDA Observations and Whistleblower Complaints

Companies must also take seriously any issues identified by government inspectors or their own employees. Rarely does DOJ surprise a company by investigating an issue that is completely new or foreign to key members of its manufacturing, quality or compliance groups. Indeed, most of DOJ's recent cGMP investigations have focused on problems that were the subject of repeated Form 483 observations, FDA Warning Letters and/or employee complaints. Internal whistleblower complaints are also important. Such complaints played a key role in the Ranbaxy case, as the company's failure to promptly and thoroughly investigate and respond to whistleblower complaints provided impetus for DOJ action.

To help reduce the risk that problems identified by FDA inspectors and employee whistleblowers will result in a DOJ investigation, companies should:

- Foster an open an collaborative corporate culture, in which management respects and encourages employee feedback, and in which employees feel comfortable reporting issues to their managers without fear of retaliation;
- Maintain clear, transparent dialogue with FDA, both during inspections and in response to any resulting Form 483 observations;
- Prioritize the remediation of issues identified during FDA inspections and devote adequate re-

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sources to remediation so that such issues are corrected in a timely fashion;

- Make internal cGMP compliance and investigation policies transparent to employees;
- Ensure that employees have anonymous channels for reporting cGMP issues that they do not feel comfortable reporting to their managers;
- Investigate reports of cGMP violations thoroughly, credibly and objectively;
- Where necessary, hire outside consultants with appropriate technical expertise and/or knowledgeable attorneys to lead or assist in investigating cGMP problems; and
- Drive investigations to completion, and implement recommended remedial actions, including disciplinary actions, where necessary and appropriate.

E. Integrate Legal Into Key Aspects of cGMP Compliance Program

Finally, in light of the current enforcement environment and the potential risks involved, now is the time for companies to integrate in-house counsel into their cGMP compliance programs, much as they have done in the sales and marketing spheres over the past decade. Among other things, counsel can bring considerable expertise to bear in identifying and assessing enforcement risks associated with cGMP issues, and by reviewing and commenting on FDA communications to help avoid unintentional admissions or misstatements. Members of the legal department can also oversee, advise on, or even conduct internal investigations of whistleblower complaints and help guide other cGMP-related investigations. And, in-house attorneys can draw upon their networks of experienced outside counsel to obtain more particularized advice, to conduct larger investigations, and to defend the company in the event a DOJ investigation does arise.