FDA Inspections, cGMPs and the New “Health Care Fraud”

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The FDA, Department of Justice (DOJ) and Office of the Inspector General (OIG) have found new common ground in their battle against Health Care fraud: current Good Manufacturing Practices (cGMPs). Massive product recalls, new laws and public outrage have created the impetus for more aggressive inspections to identify cGMP violations, assure product quality and protect the public. Enforcement agencies have taken note of cGMP violations exposed during these inspections, confronting Life Science companies and their executives and managers with new risks and consequences, including the ultimate enforcement hammer: exclusion from the Life Science industry.

This paper identifies six factors driving these new risks, and the issues likely to attract the attention and aggressive scrutiny of an FDA investigator.

Targeting Life Science Companies

The cost of violating the FDA’s cGMPs skyrocketed in 2010. The trend shows no sign of slowing as United States enforcement agencies, state and federal regulators, legislators and even the courts expand the risks and consequences of quality failures in the Life Science industry.

The most visible reflection of the heavy stick coming down on the industry is the False Claims Act (FCA), which the DOJ employed to return more than $2.5 billion to the Medicare Trust Fund through settlements with Life Science companies in 2010. Another billion flooded into state governments after more than 30 state legislatures enacted their own versions of the FCA, often with more stringent requirements than their federal counterpart. Beyond those numbers, hundreds of millions of dollars were paid to whistleblowers – the vast majority being former employees of the prosecuted companies – who filed lawsuits under the qui tam provisions of the FCA. In 2010 FCA recoveries were 60 percent higher than in 2009, according to reports, and the agency raced into 2011 with some 2,000 new criminal and civil investigations pending.
The DOJ, the Health and Human Services’ Office of the Inspector General (OIG) and the FDA have found new, common ground in their battle against Health Care fraud: violations of the FDA’s cGMPs and product quality standards. Several recent actions illustrate this new focus:

- In 2010, a top 10 Pharmaceutical company entered into a record-setting settlement with the DOJ to resolve FCA charges stemming from cGMP violations and resulting quality failures at the company’s Puerto Rico manufacturing plant. The lawsuit alleged that federal health care programs including Medicare and Medicaid paid for drugs that did not comply with FDA quality assurance regulations. The case contains several important elements. The DOJ was joined by 17 states seeking recovery under state FCAs. The DOJ brought criminal charges against the company for adulterated drugs and imposed the largest criminal fine ever assessed for that charge. The settlement did not preclude additional charges against individuals under an ongoing DOJ investigation.

- Two officers of a global Medical Device company signed a consent decree of permanent injunction prohibiting the company from manufacturing and distributing medical devices to new customers. The sale of these systems to existing customers is restricted until the company complies with cGMP and Medical Device Reporting (MDR) requirements. The FDA’s action was based on repeated inspections of the company’s manufacturing facility, where FDA investigators observed a pattern of recurring cGMP violations including deficiencies in processes for corrective and preventive action, nonconforming product, complaints, purchasing, process validations, design controls and adverse event reporting.

- In 2010, the FDA launched its Pharmaceutical Fraud Pilot Program, which focused on “flagrant manufacturing-related violations for biologics, drugs and medical devices.” The first investigations center on cGMPs at two Pharmaceutical manufacturing sites.

**cGMPs and Fraud**

Still reeling from blistering OIG reports and Congressional rebukes about its inspection of Pharmaceutical and Medical Device manufacturing facilities, both foreign and domestic, the FDA increased its staff and the frequency of its inspections. Ironically, the FDA’s Warning Letters did not increase along with the escalating inspection activity. Instead, the FDA continued to emphasize voluntary remediation of cGMP failures by companies. That policy was condemned in 2010 after massive prescription, over-the-counter and medical device product recalls fueled alarm that the FDA was unable to protect patients and consumers from potentially serious health risks posed by poor-quality medical products. Evidence of repeated cGMP violations earning a
light-handed enforcement response has put the agency under the unforgiving attention of the United States Congress, patient protection groups and whistleblowers. With added pressure on the FDA to ensure product quality, inventive legal theories from the DOJ, and the OIG’s court-affirmed exclusionary authority, Life Science companies are on notice that the regulatory, compliance and enforcement landscape has changed.

Inspections Trigger Risk

Beyond the obvious goal of emerging unscathed from an FDA inspection of their manufacturing plants, smart Life Science companies recognize that observations made by FDA inspectors can serve a greater purpose by identifying risks and opportunities to improve both compliance and quality assurance. The FDA's observations may indicate flaws in a discrete, limited process or enterprise-wide problems. Companies that take a proactive approach to compliance and quality by conducting regular, thorough audits of their own facilities will likely identify the same issues and resolve them before an FDA inspection.

What are some of the most common signals to an inspector – whether an in-house auditor or an FDA inspector – of potential noncompliance with cGMP requirements? Recent FDA Warning Letters point out six key observations that can easily trigger broader questions and concerns about cGMP compliance and product quality:

1. **Unqualified Employees:** “Operators ... were observed demonstrating incorrect aseptic techniques to prevent product contamination.” The FDA specifically requires companies to ensure that each person engaged in the manufacture, processing, packing or holding of a drug has the necessary training, education and experience to perform the assigned job [21 CFR 211.25(a)]. **Seeing one employee perform a job incorrectly will trigger the inspector's concerns that other employees are poorly trained to perform their assigned functions and that quality issues may exist at multiple points in the facility.**

2. **Repeat Violations:** In 2010, a company failed to identify organisms recovered from a sterility test. The FDA noted that the 2010 violations were identical to violations observed during a December 2008 inspection. Even though the product in question was voluntarily recalled, the company's failure to correct the earlier violation suggested that other remedial measures may have been ignored at the facility. **Inspectors who identify repeated and unresolved violations at one site often aim their attention on the company's other facilities, especially those with similar products or processes, to determine whether the violation represents a systemic quality failure.**
3. **Supply Chain Liabilities**: A contract testing laboratory showed multiple deviations that caused its client’s APIs to be adulterated. Although it was only one of numerous deviations noted during the inspection, the failure of the lab’s quality unit to report accurate results to its client stood out as an issue of particular concern to the FDA inspector. The FDA identified this serious concern after comparing the raw data and reported results for several samples, which revealed the documentation errors. The errors also alerted the FDA that other activities by the quality unit could signal quality problems. Among the other issues identified by the FDA: a validation study was incomplete and protocols were missing, there was no procedure to investigate and document Out-of-Specification (OOS) test results at the time of performance, and the lab had not calibrated testing equipment as described in the operation manual for the instruments. Even though the contract manufacturer committed the violations, the brand company holds ultimate responsibility for the quality of the product. As many recent recalls have demonstrated, it doesn’t matter where in the supply chain a problem occurs. Liability stays with the sponsor company.

4. **Workforce Knowledge**: A Class II Medical Device company’s explanation for its failure to have test records readily available for the required period of time and in the required locations was that an employee had taken the records home and could not locate them. This response did not instill confidence in the inspector about the firm’s integrity, honesty or competence. The FDA’s Warning Letter noted, “Based on the deviations described, it appears that your firm’s personnel lack a fundamental understanding of cGMPs or have not been trained to perform their duties in accordance with cGMPs.” It would be surprising if the FDA did not question the competence of the total workforce or the lab’s ability to achieve cGMP compliance in any of its operations. It would also be surprising if the FDA inspectors did not follow up with inspections of the lab’s customers, since those companies used the Active Pharmaceutical Ingredients (APIs) in their final products.

5. **Root Cause Analysis**: Internal company investigators identified an equipment malfunction as the root cause of a discolored drug, but the investigation did not extend to other lots that were manufactured on the nondedicated filling line. As a result, the company released products at risk of cross contamination. The company failed to thoroughly investigate and correlate consumer complaints about the discolored drug product. Only after the FDA identified deficiencies in the company’s investigation and management of consumer complaints did the company initiate a recall of products associated with the equipment failure – one year after identifying the root cause of the discoloration. As an explanation for continued
rejise of the product, the company’s investigation concluded that administering
Health Care Professionals (HCPs) would identify any discoloration and prevent
use of the product. The FDA had a curt response, “It is unacceptable to rely on the
HCP to fulfill your Quality Control Unit responsibilities.” A particularly disturbing
aspect of this company’s noncompliance is this notation by the FDA, “This is a repeat
observation from the March inspection.”

6. **SOP Compliance:** An FDA investigator identified a firm’s failure to audit the
third party component manufacturer of a medical device, as required by the
company’s own SOPs. When advised of the observation during the inspection,
the company conducted an audit of the subcontractor and identified “critical and
major deficiencies.” As a result of its failure to assure compliance of its contractor,
the company submitted data to the FDA that was inaccurate. In response to the
FDA’s complaint, the company updated its SOP to ensure all components and
subcontractors were completely qualified prior to submitting samples for release,
but the FDA insists, “… we will verify the adequacy of your compliance with your
procedures during the next inspection.” The company’s updated SOPs may resolve
the specific observations identified by the FDA but they will not prevent harsh
scrutiny in future inspections of all operations.
**Inspection Warning Signs**

FDA inspectors are experienced in identifying “warning signs” and following through on them to determine the underlying problems. Fewer employees than expected performing a required task will signal inadequate staffing. Employees performing their jobs incorrectly will indicate a breakdown in oversight and inadequate training. SOPs that are not easily accessible, both to employees during work hours and to the FDA during an inspection, suggest that workers will complete tasks “on the fly” if they are unsure of proper procedures. Documents that are “unavailable” are effectively “non-existent.” Inadequate testing, qualification of suppliers, response to complaints, prompt completion of corrective and preventive action plans – these all point to the potential for larger problems at the facility and throughout the organization.

It is important to remember that a 483 from the FDA documents the observations of the inspector. The company’s response, complete with a clear program for addressing each observation, is required within 15 days. Missing that deadline or answering inadequately will produce a Warning Letter, which triggers additional risk and legal liability. Warning Letters are also publicly accessible documents, documenting the FDA’s complaints and the company’s response. Because of that documentation, companies will be hard-pressed to find cover in the “we didn’t know” response. More to the point, recent amendments to the False Claims Act and the DOJ’s interpretation of the Act make clear there is no safety in “not knowing” for companies, their officers and their managers. Even beyond the risk of DOJ prosecution, consumers take a dim view of companies that take their responsibilities for quality lightly.

The regulatory risks and legal liabilities for Pharmaceutical and Medical Device companies have never been greater. And the most common trigger for igniting those risks is the FDA’s inspection of facilities for cGMP compliance.
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