Cautionary Tales: Ignore at Your Own Peril

Vicky C. Stoakes
President, IntegRx, Inc.
To paraphrase…

*Those who fail to learn from the mistakes of others are destined to repeat them*

~ *George Santayana (1863 – 1952)*
The “C” in cGMP

FDA regulatory requirements and expectations are continuously evolving

- FDA expects firms to comply with “current” expectations
- Maintaining the status quo can equate to falling behind

“…the "C" in CGMP stands for "current," requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment that may have been "top-of-the-line" to prevent contamination, mix-ups, and errors 10 or 20 years ago may be less than adequate by today's standards… It is important to note that CGMPs are minimum requirements.”

The “GMP” in cGMP

Some Good Manufacturing Practices (GMPs) have not significantly changed over time…

That being said, the Agency does more fully articulate its expectations based on increased knowledge and experience.
A Reality Check

• Each Inspection is a snapshot that typically identifies a limited number of existing deficiencies
  – Beware of developing a false sense of security
  – Inspections should be a supplement to, not substitute for, your own efforts to strenuously challenge the adequacy of your Quality and Compliance Systems on an ongoing basis

“True wisdom is knowing what you don't know”

~ Confucius (551 – 479 BC)
Maintaining cGMP Compliance

Publicly available documents provide insight as to FDA expectations, inspectional processes / objectives, and deficiencies that may warrant regulatory action

– FDA Compliance Programs, such as:
  • 7346.832, Pre-Approval Inspections
  • 7356.002, Drug Manufacturing Inspections
  • 7356.002F, Active Pharmaceutical Ingredients
  • 7345.848, Inspection of Biological Drug Products

– Inspection Operations Manual (IOM)
– Compliance Policy Guides
– Regulatory Procedures Manual
Maintaining cGMP Compliance

Additional Resources:

- Laws / Regulations / Guidance
- Judicial Decisions
- Import Alerts
- Warning Letters
- FDA presentations / webinars
- www.fda.gov
- Conferences / Courses
- Consent Decrees
- Complete Response Letters
- Enforcement Activities
- FDA 483 Observations
- FDA Policy Documents
- FDA Email Updates
- Industry Publications
Maintaining cGMP Compliance

Firms must not only know the cGMP requirements and expectations, but must also appropriately

Disseminate
Evaluate
Apply

these concepts to their own operations as well as those of contractors performing regulated activities
Cautionary Tales
Data Integrity

CP 7346.832, Pre-Approval Inspections

Provides possible indications of data integrity problems, including:

• Alteration of raw, original data and records
• References to failing bio-studies
• Discrepancies (e.g., color, shape, embossing) between biostudy samples and reserve samples
• Inconsistencies in manufacturing documentation (e.g., identification of actual equipment used) and other information in the submission
Data Integrity

CP 7346.832, Pre-Approval Inspections

Provides examples of data integrity problems that have been previously observed, including:

• Manipulation of a poorly defined analytical procedure and associated data analysis in order to obtain passing results
• Creating acceptable test results without performing the test
• Backdating stability test results to meet the required commitments
• Reworking or process modifications not adequately justified and appropriately reported
• Determination that a site does not actually manufacture the drug as described in records or submissions
Data Integrity

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drugs

Enforcement Activities by FDA

Consent Decree for [Redacted] Facility

- FDA Form 483 (PDF - 8.44MB) (1/11/2014)

Import Alert and Consent Decree for [Redacted] Facility

- FDA Press Release: FDA prohibits manufacture of FDA-regulated drugs from [Redacted] plant and issues import alert (9/16/2013)
- FDA Form 483 (PDF - 2MB) (9/11/2012)
- FDA Form 483 (PDF - 765KB) (12/7/2012)

Department of Justice Action Against [Redacted]

- DOJ News Release: Generic Drug Manufacturer [Redacted] Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, CGMP Violations and False Statements to the FDA (5/13/2013)
Data Integrity

Consent Decree for [Redacted] Facilities and [Redacted] in [Redacted]

- FDA News Release: Department of Justice files consent decree of permanent injunction against [Redacted] (1/25/2012)

Application Integrity Policy Action for [Redacted], Facility


Application Integrity Policy List

Import Alert for [Redacted] Facilities

- FDA News Release: FDA Issues Warning Letters to [Redacted] and an Import Alert for Drugs from Two [Redacted] Plants in [Redacted] (9/15/2008)
- List of Drugs Manufactured at the [Redacted]
- Questions and Answers
  - Warning Letter
  - Warning Letter [Redacted] in [Redacted]

Additional Warning Letters

- [Redacted] (12/21/2009)
- [Redacted] (6/15/2006)
- [Redacted] (10/11/2002)
Data Integrity

FDA Warning Letter

“Your firm did not have proper controls in place to prevent the unauthorized manipulation of your laboratory’s raw electronic data. Your HPLC computer software lacked active audit trail functions to record changes to analytical methods... In addition, your laboratory systems did not have access controls to prevent deletion or alteration of raw data...”

“...Moreover, the gas chromatograph (GC) computer software lacked password protection allowing uncontrolled full access to all employees. ”
Data Integrity

FDA Warning Letter, continued

“... However, your response lacks sufficient detail of the systems and controls you will implement. Simply turning on audit trail functions is inadequate…”

“...provide specific details about the comprehensive controls in place to ensure the integrity of electronic raw data generated by all computerized systems during the manufacture and testing of your drugs. Your response should demonstrate an understanding of your processes and the appropriate controls needed for each stage of manufacturing and testing that generates electronic raw data. Your response should also describe the controls and procedures you will implement to retain and archive the raw data you generate.”
Data Integrity

• Determine if organizational functions and contractors performing regulated activities have adequate systems, knowledge, and resources to ensure data integrity as pertain to their area(s) of responsibility
  – Auditing is only one component of a systematic approach
  – Build integrity into the process via: Corporate culture; Quality systems and procedures; Computer System Validation and 21 CFR Part 11 compliance; Training; Oversight and monitoring; etc.

• Solicit advice: legal, third party consultants, software vendors

• Take a global, holistic approach to remediation

• Attend the Data Integrity Panel Discussion for further recommendations
Facility Compliance Status

FDA CDER Summary Review

Prior to NDA submission, FDA inspections revealed cGMP violations at the drug substance and product manufacturing site. After NDA submission, a Warning Letter was issued. FDA could not establish that drug substances and finished products were not longer deemed adulterated before the PDUFA goal date. Compliance made a withhold approval recommendation and the application received a complete response due to product quality issues.
Pharmaceutical company announced that FDA issued a Complete Response Letter to its NDA. The company had received a final approval for the product. However, FDA rescinded its earlier approval, citing that the compliance status of the manufacturing facility was not acceptable on the date of approval.
Facility Compliance Status

- Rigorously evaluate and monitor the compliance status of facilities before and throughout the submission process.
- Recognize significant cGMP observations before regulatory action is taken and assess the potential impact from a compliance perspective.
- Know when to involve legal counsel and/or independent experts.
- Be cognizant of significant potential compliance risks, develop appropriate remediation strategies, and consider developing contingency plans.
Accountability

FDA Warning Letter

“Although you have agreements with other firms that may delineate specific responsibilities to each party (e.g., quality control responsibilities), you are ultimately responsible for the quality of your products. Regardless of who manufactures your products or the agreements in place, you are required to ensure that these products meet predefined specifications prior to distribution and are manufactured in accordance with the Act and its implementing regulations…”
Accountability

FDA Warning Letter

“FDA considers contractors as extensions of the manufacturer’s own facility. Your failure to comply with CGMP may affect the quality, safety, and efficacy of the products you test for your clients. Your clients (e.g., drug manufacturers, application sponsors), in turn, must provide you with all of the scientific data and information needed to support reliable method implementation”
Accountability

The Supreme Court addressed the duty imposed on responsible corporate officials in the case of United States v. Park (1975):

• “The [FDCA] imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will insure that violations will not occur.”

• “The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding, and perhaps onerous, but they are no more stringent than the public has a right to expect of those who voluntarily assume positions of authority in business enterprises whose services and products affect the health and well-being of the public that supports them.”

• The Court did not impose on the Government a duty to prove that the defendant had a consciousness of wrongdoing.
Accountability

• Examine systems and procedures to assure critical compliance issues are escalated to the attention of Executive management

• Evaluate whether Quality has necessary authority and resources and exercises them appropriately

• Determine if employee staffing, experience, and training are adequate to meet regulatory obligations

• Assure responsibility for quality belongs to every employee

• Assure personnel ratings / rewards consistently encourage quality and compliance minded performance

• Assess the adequacy of contractual provisions pertaining to regulated activities and Quality Agreements

"Accountability breeds response-ability."

Stephen R. Covey (1932 – 2012)
FDA Warning Letter

“...Failure to properly maintain, repair, and keep clean buildings used in the manufacture of APIs in a manner that prevents contamination where open equipment is used. ...holes in the walls and roof which allowed pigeons access near production equipment in multiple manufacturing areas... Gaps and holes in outside walls for piping and air ducts which allow contaminants to enter the building.

... Failure to properly maintain equipment used in the manufacture of APIs and minimize the risk of contamination, where open equipment is used. ... rust, dirt, lubrication leaks, and exposed insulation material on and around open drug manufacturing equipment.”
FDA Warning Letter, continued

“...We note that you continued to manufacture product intended for the U.S. market even after you recognized that your facility and equipment were in disrepair and not compliant with CGMP requirements. ... Your response should also include your plan to ensure your facility and equipment will be proactively maintained in such a way that your product is continually manufactured under CGMP conditions.”
Facility / Equipment Maintenance

• Use a fresh perspective to re-evaluate facilities / equipment for other such objectionable conditions, including:
  – Wooden pallets in poor physical condition
  – Insects, dust, construction debris
  – Disintegrating / brittle plastics or coatings
  – Roof leaks, leaking pipes, dripping condensation onto raw materials or open product
  – Mounted steps crossing manufacturing lines with inadequate protection of open product

“You can observe a lot by watching”

Yogi Berra (1925-2015)
Facility / Equipment Maintenance

• Evaluate product quality complaints ~ the intersection of opportunity and actuality

• Determine true root cause by assessing factors, such as:
  • Resource allocation
  • Supervision and Quality Oversight
  • Adequacy and frequency of scheduled maintenance activities
  • Training

– Be aware that the manner in which a firm maintains its facility / equipment is often an external manifestation of its quality and compliance mindset ~ Is an unintended message being sent?
Final Thoughts...

Consider whether your firm and contractors routinely operate in firefighting mode.

If so, this may negatively impact the ability to stay current in a complex and continuously evolving regulatory environment.
Final Thoughts...

Communicate findings to Senior Management

- When current expectations are met or exceeded:
  
  **Take Credit!!!**

  (without developing a false sense of security)
  (Or becoming complacent)

- When current expectations are not met:
  
  - Prepare a documented remediation strategy, including timelines for completion and assignment of responsibilities
  - Request and justify resources to achieve timely, effective, and sustainable remediation