War Stories:
Life on the Front Lines -
The Saga Continues

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To paraphrase...

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

George Santayana 1863 – 1952
FDA Inspectional Approach

Publicly available documents detail how FDA conducts inspections, builds cases, and evaluates compliance issues.

- FDA Compliance Programs, such as
  - 7346.832, Pre-Approval Inspections
  - 7356.002, Drug Manufacturing Inspections
  - 7356.002F, Active Pharmaceutical Ingredients
  - 7382.845, Inspection of Medical Device Manufacturers
  - 7383.001, Medical Device Premarket Approval and Postmarket Inspections
  - 7345.848 - Inspection of Biological Drug Products

- Inspection Operations Manual (IOM)
- Compliance Policy Guides
- Regulatory Procedures Manual
FDA Inspectional Approach

“If it isn’t documented, it didn’t happen”

and

“In God We Trust...in all others, verify”
FDA Inspectional Approach

• FDA Investigators spend a considerable amount of time in facilities, which helps them focus on common problem areas

• Investigators often develop the ability to extrapolate findings or make an intuitive leap that permits identification of more significant concerns
FDA Inspectional Approach

Investigators see the forest...not just the trees
FDA Inspectional Approach

• Key Points:
  – An Inspection is a snapshot that typically identifies 10-15% of deficiencies present ~ Beware of developing a false sense of security!
  – FDA-483 observations and Establishment Inspection Reports (EIRs) should be a supplement to, not substitute for, a firm’s internal and external auditing programs
  – Stay current! Use Consent Decrees, Warning Letters, FDA presentations, industry publications, and conferences to understand inspectional trends and enforcement actions
  – Ensure your quality and compliance systems are subjected to routine, strenuous challenges
FDA Inspectional Findings
Development Programs

The ultimate evidence of a rigorous development program is the ability to consistently manufacture high quality product in a commercial setting.

- Product failures, stability failures, recalls, significant complaints, and ADEs/MDRs/BPDRs may cause FDA to question the adequacy of the development program.
Development Programs

• Focus on product design without proper consideration of the manufacturing process

• Insufficient knowledge generated to support commercialization
  – Inadequate assurance that sources of process variability impacting product quality attributes have been identified and controlled
  – Process development studies evaluate target parameters instead of assessing the impact of potential variability that may occur during commercial manufacturing
  – Insufficient manufacturing experience at scale
  – Deficient technology transfer

• Failure to appropriately consider product quality attributes
  – Potent compound handling, microbial control, bioburden / endotoxin control, container/closure compatibility, etc.
Development Programs

- Lack of comparability between the formulation, process, specifications, and controls used to manufacture bioequivalence batch(es) and the proposed commercial process
- Technical rationales used to justify lack of compliance with cGMP requirements
- Inadequate documentation of development activities
- Late stage development couched as process improvement
- Failure to fully integrate key stakeholders such as Quality Assurance, Regulatory Affairs, and Commercial Operations
- Insufficient due diligence when acquiring a product developed by another firm
Development Programs

FDA Warning Letter

“Your experience with the manufacture of (b)(4) mg and (b)(4) mg tablets suggests that product and process development studies were not comprehensive enough to sufficiently understand the interaction between material properties, equipment, and processing parameters in order to establish the right control strategy.”
Facility Maintenance

• The manner in which a firm maintains its facility is often an external manifestation of its quality and compliance mindset

• Facilities must be of adequate design/control to ensure cleanability, microbial control, and prevent inadvertent product contamination

• Carefully observe conditions if materials, product, and/or product contact equipment are open to the surrounding environment
Facility Maintenance

- Flaking paint, rust, peeling caulk, exposed insulation
- 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
- Direct exposure to the outdoors via holes, gaps, torn gaskets, or other disrepair
- Mounted steps crossing filling lines with inadequate protection of open product
Facility Maintenance

FDA Warning Letter

“…dirt, blistering paint, rust, and oil droplets were found to be in close proximity to manufacturing equipment in several building locations. In addition, …operators observed paint chips in the material while manufacturing [API product], which was later rejected. Your variance report, (b)(4) indicates that paint chips could have fallen into the reactor during solid charging… In addition, …implemented corrective actions following the investigation were not effective and you provided no information concerning subsequent corrective actions implemented to reduce the risk of contamination.”
Cleaning Program

- Inadequate development of cleaning program, methodology, procedures, and limits
- Lack of proper employee training and qualification program
- Records do not document execution of required activities
- “Clean” product contact equipment contains previous product residues
- Improper storage of “clean” product contact equipment
- Inappropriate documentation of and/or response to failures
- Cleaning implements are inappropriate, not maintained in a proper state of repair, or improperly stored
Cleaning Program

FDA Warning Letter

“Your firm failed to ensure the non-dedicated (b)(4) was adequately cleaned after use. Specifically,... our inspection found what appeared to be product residue in the (b)(4) despite the “clean” label on the equipment. This represents a potential for cross-contamination of the APIs manufactured in this equipment.

In addition, your firm failed to perform adequate cleaning validation studies for your non-dedicated equipment. For example, your firm failed to perform recovery studies to ensure product residues could be detected during the cleaning validation studies.”
Microbial Control

Non-Sterile APIs for Use in Sterile Products Non-Sterile Finished Products

- Inadequate understanding of cGMP expectations and lack of appropriate Microbiology expertise
- No comprehensive bioburden / microbial control strategy
  - Facility / equipment design and control
  - Product contact utilities
  - Environmental monitoring
  - Manufacturing process attributes
  - Cleaning / sanitization
  - Materials / packaging
  - Training/ gowning / practices
  - Testing / specifications
- Inadequate response to gram negative / objectionable organisms
- Preservative systems used to kill microorganisms present due to poor cGMP practices
Microbial Control
Non-Sterile APIs for Use in Sterile Products Non-Sterile Finished Products

FDA Warning Letter

“... the purpose of adding preservatives to drug and cosmetic products is not to kill microorganisms present in your finished products due to poor manufacturing practices, but rather to prevent the growth of microorganisms in products manufactured in compliance with good manufacturing practices”
cGMP Investigations

- Investigations are not timely, thorough, and well documented

- Failure to establish and justify investigational scope
  - Impact on marketed product, other susceptible batches/products, continued production, etc.

- Inadequate justification/documentation to support conclusions

- True root cause not identified and CAPAs not implemented to prevent recurrence

- Lack of CAPA effectiveness checks
cGMP Investigations

FDA Warning Letters

“Your firm failed to conduct adequate investigations that included scientific justification to support conclusions. In addition, the investigations did not include proper corrective actions.”

“...your firm has failed to thoroughly investigate the recurrence of environmental excursions in your facility and has failed to verify the effectiveness of prior corrective actions that addressed similar environmental excursions”
cGMP Investigations

FDA Warning Letters

“Timely assessment of quality indicators, such as OOS findings and complaints, is essential to detecting and determining the scope of product or process deficiencies.”

“…you failed to investigate unexplained discrepancies and conduct or document complete investigations ...[drug product tablets]... contained metal slivers compressed into the tablets. The apparent cause was improper set up of the compression machine. Your firm failed to document a root cause and conduct corrective actions for this event.”
Electronic Records
Integrity and Maintenance

- Continues to be a significant FDA priority
  - Investigators receive specialized training to detect data integrity, data manipulation, and fraud
  - Compliance Programs highlight the data integrity audit as a primary inspectional objective
  - Center issued directed inspection assignments
  - Violations identified during numerous recent FDA Inspections, resulting in Warning Letters, Import Alerts, and Consent Decrees
Electronic Records
Integrity and Maintenance

• Insufficient procedures, actions, and controls to ensure the integrity and proper maintenance of computerized electronic data
  – Instruments do not allow unique user name and password authentication
  – User roles and responsibilities have not been established to prevent personnel from modifying, overwriting, and/or deleting original raw data files
  – No system for maintaining original electronic data when such capability exists
“For High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) systems (and other computerized systems involving user inputs, outputs, audit trials, etc.), the predicate rules, such as 21 CFR 211.68 and 21 CFR 211.180(d), require the electronic records themselves to be retained and maintained in accordance with those regulations...The printed chromatogram would also not be considered an “exact and complete” copy of the electronic raw data used to create the chromatogram... The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity. Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21 CFR Part 211. The electronic records created by the computerized laboratory systems must be maintained ... and readily available for review by, for example, QC/QA personnel or the FDA investigator.

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124787.htm#3
Electronic Records
Integrity and Maintenance

• Inadequate review and approval processes
  – Personnel not trained to identify modern data integrity issues
  – SOPs do not address detection of data integrity and data manipulation
  – No evaluation of audit trails and revision histories
  – No system to identify unreported data

There should be a documented data integrity policy that establishes zero tolerance for violations and requires immediate reporting of any potential integrity issues
Accountability

• Contract facilities are not regarded as an extension of the manufacturer's own facility
  – The manufacturer and contractor share responsibility for product quality; however the manufacturer is ultimately responsible

• If things go wrong:
  – Finger pointing is not a recommended strategy
  – “I am just the contractor” is not a valid defense
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…”
FDA will attempt to determine whether your quality organization is struggling to bear its regulatory responsibilities without adequate support.
What is Your Quality Culture?

Characteristics of Challenged Organizations

• Quality does not have the necessary authority and resources
• Quality is perceived as a “negative cost center” that interferes with the ability to accomplish business objectives
• Responsibility for quality belongs to a limited group

Characteristics of High Performing Organizations

• Quality has necessary authority and resources and exercises them appropriately
• Quality is perceived as adding value to the product and corporate brand
• Responsibility for quality belongs to every employee

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What is Your Quality Culture?

Characteristics of Challenged Organizations

- Significant issues are not escalated to executive management awareness
- Highly politicized atmosphere with a tendency to downplay compliance concerns
- Organizational silos with limited communication

Characteristics of High Performing Organizations

- Executive management creates an atmosphere that fosters escalation of issues
- Open environment where personnel are encouraged to uncover and communicate compliance concerns
- Highly interactive team approach
What is Your Quality Culture?

Characteristics of Challenged Organizations

• Personnel ratings / rewards discourage quality minded performance
• Decisions do not reflect the total cost of quality throughout the lifecycle

Characteristics of High Performing Organizations

• Personnel ratings / rewards encourage quality minded performance
• Decisions consider total cost of quality throughout the lifecycle
Your Attitude Determines Your Altitude

In order to achieve and sustain FDA compliance, it is essential to establish a culture of quality.
Final Thoughts…

• Executive management must be fully engaged and committed to establishing and maintaining an appropriate culture of compliance

• FDA understands that you will encounter challenges; your reputation within FDA is dependent upon your response

• Remember, this is not a war… The primary objective of both FDA and Industry is to ensure patients are provided safe and effective products