Preparing for GMP Inspections – It’s much more than an audit!

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Disclosures

- I am currently a Senior Technical Advisor at F. Hoffman La Roche.
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- The following are my views and not necessarily the views of the Food and Drug Administration Alumni Association (FDAAA), FDA, or Roche.
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• Reactive vs. Proactive Compliance
  – What they look like
• Inspection vs. Compliance risk?
• Proactive Inspection Management Model
  – Issue Identification and remediation
  – Role of Audit
  – Senior Management Involvement
• Pre-Approval Inspection Preparation
• Pre-Approval Inspection Follow Up
Learning Objectives

• Understand the differences between reactive and proactive compliance
• Understand how inspection risk and compliance risk are different
• Gain insight into one approach to a proactive compliance model
  – Understand one role of Audit in a proactive compliance program
• Understand needs for Pre-Approval Inspection Preparation
• Understand needs for Pre-Approval Inspection Follow Up
The Pre-Approval Inspection
• Federal Food, Drug, and Cosmetic Act, Section 505(d)(3):
  – Grounds for refusing application; approval of application; "substantial evidence" defined. If the Secretary finds, that … (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity;

• 21 CFR Part 210 and 211
  – Good Manufacturing Practice for Finished Pharmaceuticals
• ICH Q7
  – Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

• CPGM 7346.832, Pre-Approval Inspections
  – 2.1 SCOPE - A pre-approval inspection (PAI) is performed to contribute to FDA’s assurance that a manufacturing establishment named in a drug application is capable of manufacturing a drug, and that submitted data are accurate and complete.
• Approximately 1 – 3 months following submission, FDA will conduct a pre-approval inspection (PAI).
• FDA will send a team of individuals to conduct the pre-approval inspection. The team may include:
  – Lead investigator
  – Analyst
    • Microbiologist
    • Chemist
  – Computer Specialist
  – Reviewer from Headquarters

• They will determine if:
  – The site is ready for commercial manufacturing
  – the information submitted is consistent with site records
  – the information submitted is complete and accurate
– Is essentially the Six System GMP inspection
– Will review “pivotal”, “qualification” or “biobatches”
  • Focus on change control, deviation and trend evaluations
  • Process validation reviewed against batch records
– More focus on Laboratory system and stability
  • Will evaluate sampling and testing of components, WIP, and product and procedures for release.
– High focus on your Supplier Qualification program
– Facility and equipment procedures with a focus on contamination controls
– Quality System review – batch release, discrepancy management, investigation completeness, complaint and ADE handling.
They will review records and procedures
  - Verify that the formulation, manufacturing and/or processing methods, and analytical (or examination) methods are consistent with descriptions contained in the CMC section of the application for the biobatch (and other pivotal clinical batches, when applicable), the proposed commercial scale batch, and the API(s).

Data Integrity

They will audit the raw data
  - Authenticate and verify that all relevant data (e.g., stability, biobatch data) were submitted in the CMC section of the application such that CDER product reviewers can rely on the submitted data as complete and accurate.
Reactive versus Proactive Compliance
• Issues generally identified after major discrepancy or during audit
  – Issues identified after work completed
  – Auditors seen as opponent, not partner, by broader organization
• Inspection Management involves defending and/or re-work
• Audit findings may not address the most non-compliant areas
  – Snap shot in time
  – Limited audit time
  – Inconsistencies in auditor experience
• Quality and Operations partner to identify non compliances real time
  – Drives compliance self awareness
  – Drives accountability for issue mitigation
  – Can identify issues before work is done
• Quality and Operations partner to prioritize remediation
  – Risk Ranking of issues to drive resource allocation – one list to rule them all!
• Quality and Operations partner to best present significant issues (i.e., investigations)
  – Are aware of significant issues before inspection, so can prepare and practice presentations
• Senior Management aware of compliance / inspection risk at sites
  – Helps fulfill ICH Q9 and 10 obligations
Pre-Approval Inspection Preparation
• Establish an inspection management team for managing preparation and inspection.
  – Accountable for all facets of inspection management process.
    • Proactive risk management process with individual accountabilities defined
    • Inspection procedures defined and implemented (document tracking, roles and responsibilities. Inspection room conduct, etc).
      - Trained on inspection procedures and policies.
      - Trained on managing inspectors.
    • Functional area and senior management support
    • Routine updates to senior management
1. **Product Description**
   - Technology Transfer
   - Development

2. **Process**
   - Manufacturing Instructions
   - Historical Batch Performance
   - Process Development
   - Support Validations
   - Process Equipment

3. **Analytical**
   - Lab Practices
   - Analytical Equipment
   - Lab Investigations and Method Issues
   - Method Validation and Qualification:

4. **Facility**
   - Systems and Utilities
   - PM / Calibration
   - Change Over / Cleaning
   - Support Equipment (i.e., freezers, stopper and glass washers etc)
   - Environmental Monitoring

5. **Quality and Compliance**
   - Quality Systems & SOP’s
   - Quality Agreements
   - Investigations / Deviations
   - CAPA Closeouts
   - Batch History & Quality Trends
   - Change Control
   - Training
   - Raw Material and Components
   - Storage and Warehousing

6. **Storage and Distribution**
   - Shipping Procedures
   - Shipping Validation

7. **Stability**
• They are not the same thing
  – Compliance risk is gap between company and anticipated regulatory interpretations of the regulations
    • Beware - very rarely does an individual compliance gap lead to a patient safety issue
    • That is not a reason to ignore the issue
  – Inspection risk not only encompasses the compliance gap, but also the likelihood that the issue will be reviewed during an inspection, and how comfortable you are presenting the issue to regulators
    • An inspection risk can still exist after a compliance risk is removed – for example, an investigation can lead to CAs that prevent recurrence of an issue, but the regulators may still find fault with the investigation, or even the event that caused the investigation.
• Inspection Management group leads team of area SMEs
  – Meet on routine schedule
    • May increase as anticipated inspections approach
  – Teams establish criteria for what goes on “risk log” (see SIMP categories, for example)
  – Develop laundry list of all “known” compliance gaps
    • Is a living document, updated on some frequency
• Compliance gaps risk ranked using standardized criteria
  – Helps prioritize work
  – Things to consider when risk ranking
    • compliance, frequency, visibility, significance of issue, quality of investigation
• Attack inspection readiness based on risk ranking
  – Responsible person for issues identified and accountable
  – Team agrees on strategies
    • Mitigate unacceptable risks – CAPAs where appropriate
    • Prepare defenses for risks being accepted and / or for investigations
  – Re-score issue once mitigation activity complete
    • Is residual risk acceptable?
The role of “self audit”

- Independent Audit helps identify “unknown” gaps
- Audit findings automatically move on to inspection management risk log
  - Proactive: if site has already identified issue and developed remediation plan, this is highlighted in audit report and not tracked as part of audit findings
- Prioritized with other “known” risks
  - Helps site establish timelines in response to finding

The role of “mock audit”

- Mock Audits help train SMEs in inspection presentation skills
- Mock Audits help practice presenting developed strategies
- Are not generally aimed at uncovering new issues
• Sites present compliance risks and decisions for endorsement
  – Drives accountability across organization for inspection outcomes
  – Drives resource management decisions – based on risk profile, resources can be (re)allocated
• Senior Management engaged and aware of Compliance and Inspection risks
• Drives continuous improvement
  – set goals for compliance risk reduction
    • Recommended to use multiple tiered goals – heavily weighted to compliance risk
  – Monitor and improve compliance savvy of broader organization
Pre-Approval Inspection Follow Up
• The inspection is but one part of the approval process
• Lead investigator will make a recommendation at the conclusion of the inspection.
  – Recommend Approval
    • Indicates that the inspection found no fatal issues
    • Response to observations is important
  – Recommend Withholding of Approval
    • Investigators feel site is not GMP compliant, information in CMC is not consistent with site records, or information submitted is not accurate and complete.
    • Response to observations is critical

• The Center Reviewer makes the ultimate decision on whether to approve or withhold.
  – If inspection is the cause of the withhold decision, a re-inspection will generally be required before approval is granted.
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