cGMP “Pitfalls" in the QC Laboratory- Preparing the QC Laboratory and Staff for an FDA Inspection

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Regulations

- 21 CFR
  - Part 211, Subpart B – Responsibilities of a Quality Control Unit
  - Part 211, Subpart I - Laboratory Controls
- 21 CFR
  - Part 11

Regulations

- United States Pharmacopoeia – USP
  - Reference Standards
  - Assays
  - Test Methods

FDA Guidance

- “Guidance for Industry” – Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production

FDA Guidelines

- Guideline for Industry
  - International Conference for Harmonization - ICH

FDA Guidelines

- International Conference for Harmonization – ICH
  - Stability Testing of New Drug Substances and Products
  - Validation of Analytical Methods

What This Means

- The Quality Control Laboratory serves one of the most important functions in Pharmaceutical production/control
- A significant portion of FDA regulations/requirements pertain to the QC and Product Testing

Preparing for the Inspection

- Preparing the Laboratory for the Inspection

Areas to “troubleshoot”

- Laboratory Equipment
  - Calibration
  - Preventative Maintenance
  - Validation

Areas to “troubleshoot”

- Standard Operating Procedures – SOP’s
  - Laboratory Records
  - Logs
  - Data Sheets

Areas to “troubleshoot”

- Out of Specification (OOS)
  - Laboratory Errors
  - Investigations
  - Documentation
  - Investigation Timeframes

Areas to “troubleshoot”

- Training
  - Documented Program

Areas to “troubleshoot”

- Analytical Method Validation
- Reagents, Solutions and Reference Standards

Areas to “troubleshoot”

- Development “work” - GMP “work”
  - Documentation
  - Laboratory Notebooks

Laboratory Equipment

- Is all the QC equipment controlled and utilized by QC personnel
- Is there a Equipment List
- Is the Laboratory Area (with all the equipment) of a suitable size 211.42 (a)

Laboratory Equipment

- Calibration Program
  - Is it written down
  - Suitable calibration intervals
  - Provisions for remedial Action
  - Tracking capabilities
  - Is Equipment “tagged”

Laboratory Equipment

- Maintenance
  - Is there a program
  - Responsibility
  - Record Keeping

Laboratory Equipment

- Validation
  - Does the lab have equipment that requires Validation (PQ)
  - Master Validation Plan

Standard Operating Procedures – SOP's

- SOP's in QC Laboratory
  - Accessible to QC staff
  - Current version

Standard Operating Procedures – SOP's

- Laboratory Records (raw laboratory data)
  - Bound or prenumbered sheets
  - Not loose or scraps of paper
  - Review of data (acceptability)

Standard Operating Procedures – SOP's

- Laboratory Logs
  - "Sequence" dates in log – analysis dates versus manufacturing dates
  - Equipment usage logs for all equipment
  - Equipment usage logs current

Out of Specification (OOS)

- Laboratory Errors
  - Laboratory Errors should be relatively rare. Frequent errors suggest a problem:
    - Inadequate training
    - Poorly maintained equipment
    - Improperly calibrated equipment

Out of Specification (OOS)

- Laboratory Investigations
  - Analyst and Supervisor – “roles”
  - Informal Investigation
  - Formal Investigation –extending beyond the QC laboratory

Out of Specification (OOS)

- Investigation Documentation
  - Investigation or Failure Report
  - Corrective Action

Out of Specification (OOS)

- Investigation Timeframes
  - All failure investigations should be performed within 20 business days of the problem.
  - Includes implementation time frame for corrective action

Training

- GMP's require an "active" training program
- Documented evaluation of the training of QC analysts – "Task Training"

Analytical Method Validation

- Compendial Methods – must demonstrate that the method works under actual conditions of use.
- System suitability does not constitute method validation

Reagents, Solutions and Reference Standards

- Proper storage of
- Reuse of solutions –stability
- Appropriate identification
- Expiration “justifications”

Reagents, Solutions and Reference Standards

- Reagent and Solution preparation
  - Complete and accurate documentation
  - Highly unlikely that analysts can “accurately and consistently weigh” to the same gram or microgram

Development vs. GMP

- Use of Laboratory Notebooks
  - Documented methods
  - Documented materials
  - Traceability to equipment

Preparing QC Personnel for the Inspection

- Training the staff

Preparation for an inspection

- Clean and organize your work area
- Don’t store items on the floor
- No loose data, post-its, or writing data on your hand
- Know where SOPs, logbooks, and controlled forms applicable to your work are kept
- Clean lab coats
- Neatness counts

Conduct of the Inspection

- Inspectors are looking for issues & deficiencies, despite how they present their approach to the inspection
- Inspectors can inspect all areas of the labs that apply to the scope of the inspection; accompanied by your QA
- May read SOPs, review data, watch analyses, question analysts

Conduct of the Inspection

- The inspection covers the lab, the data, and the compliance program, not the individuals in the lab
- The inspection should **never** be taken personally

Questions by the inspectors

- Inspectors may ask questions to learn how the lab or compliance program operates
- May ask the same question in different ways
- Remember: the inspectors have to learn the processes of a lab that is new to them, prior to making an assessment of the lab

Answering the Questions

- Think before you answer
- Answer questions accurately and truthfully
- Don’t be intimidated or defensive
- Know your work and be confident of your answers
- Be professional
- If you don’t know the answer, it is acceptable to ask your supervisor
- Acceptable to reply that don’t know, but you can find out

Your role in the Inspection

- Things not to do:
  - Don’t have food in the lab
  - Joke with inspectors
  - Have clutter in your work area
  - Quote what the SOP says, unless you’re 200% certain you know what you’re talking about

- Any Questions