Maintaining the Validated State of Analytical Laboratory Instrumentation in GMP/GLP Environments

Presented by Nick Jones
Analytical Services Director
Pharmaceutical Calibrations and Instrumentation
Agenda

- Introductions
- Individual gain from this class?
- Data Integrity: Regulation and Guidance Overview
- Workshop - Group Discussion
- Break
- Elements of a Good Quality System
- Workshop - Group Discussion
- Q&A
Data Integrity

Research and Development Laboratory

Quality Control Laboratory
Regulations for the Industry

- Code of Federal Regulations (CFR)
  - GLP for Non-Clinical Laboratory Studies
  - Current Good Manufacturing Practices for Finished Pharmaceuticals
  - Medical Device Quality System Regulations

- USP Pharmacopeias

Subpart D: Equipment

Sec. 58.63: Maintenance and Calibration of Equipment

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized.
21 CFR Part 58: GLP for Nonclinical Laboratory Studies

Subpart D: Equipment

Sec. 58.63: Maintenance and Calibration of Equipment

(b) The written standard operating procedures required under Sec. 58.81 (b) (11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedure shall designate the person responsible for the performance of each operation.
21 CFR Part 58: GLP for Nonclinical Laboratory Studies

- Subpart D: Equipment
- Sec. 58.63: Maintenance and Calibration of Equipment

- (c) Written records shall be maintained of all inspections, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of non-routine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.
21 CFR Part 58: cGMP for Finished Pharmaceuticals
- Subpart J: Records and Reports
- Sec. 211.194: Laboratory Records
  - (e) Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160 (b) (4).
Records - Industry Regulations

- 21 CFR Part 11 – Electronic Records; Electronic Signatures
  - Validation of computerized systems
  - Limited and authorized access to computer systems
  - E-records and signatures
  - Electronic audit trail
  - Accurate and complete copies of records,
  - Instant Availability of e-records
Calibration - Industry Regulations

- 21 CFR Part 211: cGMP for Finished Pharmaceuticals
  - Subpart I: Laboratory Controls
  - Sec. 211.160 (b): General Requirements
    - (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.
Training - Industry Regulations

- 21 CFR Part 211: cGMP for Finished Pharmaceuticals
  - Subpart B: Organization and Personnel
  - Sec. 211.25: Personnel Qualifications
    - (a) Each Person…shall have *education, training, and experience*, or any combination thereof, to enable that person to perform the assigned functions. The training shall be in the particular *operations that the employee performs* and in current good manufacturing practice...
Training - Industry Regulations

- 21 CFR Part 820: Medical Device Quality System Regulation
  - Subpart B: Quality System Requirements
    - Sec. 820.25: Personnel
      - (a) Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.
      - (b) Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities, *Training shall be documented.*
Guidelines for the Industry

- GAMP Good Practice Guide
  - Validation of Laboratory Computerized Systems (CSV)
  - Calibration Management

- Analytical Instrument Qualification (AIQ)
  - USP <1058>
GAMP (CSV)

- Validation of Computerized Laboratory Systems
- Moving away from 7 instrument categories to a fully RISK BASED approach
- More Flexible, Will include Examples
- Better USP <1058> Alignment
- Flow chart to support use
Definition of Calibration

- GAMP – Calibration Management
  - The set of operations, which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.
WHERE DOES THIS COME FROM?

- The American Association Pharmaceutical Scientist has produced guidance on analytical instrument qualification (AIQ) that forms the basis for the General Chapter <1058> within the United States Pharmacopoeia (USP). This General Chapter focuses on the instrument with little emphasis on computerized system validation.
USP <1058> AIQ

Figure 1. Components of data quality.
USP <1058> AIQ

- Analytical Instrument Qualification
- Design Qualification
- Installation Qualification
- Operational Qualification
- Performance Qualification
Organizational Quality System

- Based upon industry guidance, all organizations should establish requirements, within their given Quality System, that govern the validation of analytical laboratory instrumentation.
Responsibilities

- Ultimately, the responsibilities of managing the compliance of instrumentation falls to the individual departments:
  - Quality
  - Laboratory Management
  - Chemists / Analysts / Instrument Users
  - Maintenance
  - Information Technology / Support
Recommended Training

- cGMP
- Good Documentation Practices
- Quality System/Validation Requirements
- Calibration Management Requirements
- SOPs
  - Preventive Maintenance
  - Operational Procedures
  - Test Methods
- Site Safety Training
- Operational Manuals
- Manufacturer Training
Definitions

**483s:** A Factory Inspection Form that lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance.

**Warning Letters:** A letter that notifies regulated industry about violations that FDA has documented during its inspections or investigations.

**Consent Decrees:** A final, binding judicial decree or judgment memorializing a voluntary agreement between parties to a suit in return for withdrawal of a criminal charge or an end to a civil litigation.
## Frequency of Observations

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<th>Center Name</th>
<th>FY 2011 # of 483s issued</th>
<th>FY 2012 # of 483s issued</th>
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<td>Veterinary medicine</td>
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<td>Biologics</td>
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<td>237</td>
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<td>Human tissue for transplantation</td>
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## Frequency of Observations FY 2012

### Number of 483’s issued

Inspections ending between 10/1/2011 and 9/30/2012

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<th>Calibration Related 483’s</th>
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<td>Veterinary medicine</td>
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<tr>
<td>Biologics</td>
<td>237</td>
<td>16%</td>
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Frequency of Observations

Calibration Related 483's

- Biologics
- Devices
- Drugs
Frequency of Observations

Cleaning and Maintenance Related 483's

- Biologics
- Devices
- Drugs
Group Discussion

- The FDA is issuing a record number of 483s over the past 3 years with more enforcement officers and activity under current administration.

- Give example of 483 or Warning Letter you experienced. What was the issue and how did you resolve it?
Elements of a Good Quality System

Calibration

Preventive Maintenance

Re-Qualification
Calibration Requirements

- Standard Operating Procedures
- Training
- Acceptance Criteria
- Testing
  - Calibration Interval
  - As Found Testing
  - Adjustments
    - Notification
  - As Left Testing
- Documentation
Preventive Maintenance

- Criteria to consider to define appropriate maintenance activities.
  - Sources of information regarding maintenance frequency.
    - OEM
    - History
  - Impact
    - Instrument failure – QCL vs. R&D
  - Associated Cost
Preventive Maintenance

- Performance of Maintenance Services
  - Standard Operating Procedures
  - Defined Methods
  - Appropriate materials
  - Good Documentation
    - Maintenance Forms / Work Orders
    - Logbooks / Equipment Files
- Training
- Consumable Parts
  - Seals, lamps, filters, etc…
  - Consistency - Like for Like parts replacement
Corrective Maintenance

- Additional Requirements
  - Good Documentation
    - Forms / Work Orders
    - Logbooks / Equipment Files
  - Change Control Operations
    - Parts vs. Components vs. Instrument

- Documented Training
  - Troubleshooting and Diagnosis
Re-Qualification Requirements

- Re-Qualification (RQ) requirements could depend upon the instrument’s environment and local area procedures.
  - Quality Control Laboratory
  - Research and Development Laboratory
How to determine a Requalification event

- Instrument utilization changes
- Maintenance events
- Relocation events
- Based on risk analysis
Service Execution

- Contracted Service Providers
  - OEM
  - Contract Firms, Third Party
- Chemists / Analysts / Instrument Users
- Internal Maintenance Shops Personnel
- Metrology Group

- Advantages and Disadvantages?
Instrument Status

- It is good practice to utilize a procedure-driven system to notify the instrument users prior to, during, and following the execution of any calibration, maintenance, or qualification activities.

- The return of an instrument to service following any calibration, maintenance, or qualification activities should be performed only after the appropriate verification of any executed services.
Point of Use Testing

- User Calibration
  - Check Standards/Samples
- System Suitability
  - Precision / Reproducibility
  - Linearity
  - Check Standards
- Documentation
Instrument/System Changes

- Hardware and Software Changes
- Location
- Policies and Procedures
- System Security
- Asset Control Practices
Procedures drive all aspects of work within a GMP/GLP laboratory including the retirement and/or decommissioning of analytical instrumentation.

- Retirement Plan
- Testing
- Retirement Report
- Change Control
- Inventory
Periodic Review of Systems

- GAMP Validation of Laboratory Computerized Systems
  - A documented assessment of the documentation, records, and performance of computer systems to determine if it is still validated and what actions, if any, are necessary to restore its validated state. The frequency of review is dependent upon the systems complexity, criticality, and rate of change.
  - Concept can be applied to Equipment Validation, SOPs, Test Methods, Training, etc.
Good Documentation

- Record-keeping is key to maintaining the validated state of a GMP/GLP Laboratory.
  - Instrument Use Logbooks
  - Instrument History Files / Folders
  - Data Retention / Security Procedures
  - Maintenance Records
  - Inventory / Instrument Status
  - Going Paperless?
Key Points to Remember

- Industry Standards / Guidance Documents
- Quality System Requirements
- Personnel Roles / Responsibilities / Training
- Good Documentation
Group Discussion

Consider more than the hard costs of your compliance program. What about soft cost?

Best-in-class organizations look beyond the price tag

- Increased efficiency
- Reduced risk
- Benefits to the business bottom line

- Where do you feel your organization lacks efficiency relative to equipment compliance and how can you resolve the issue?
Wrap Up

- Questions ????
- Pittcon Survey

- www pci llc com