Calibration and validation

Calibration

Definition:

- Calibration is the documented comparison of the measurement provided by an instrument or system against a known standard.
- It ensures the instrument provides accurate and traceable measurements within specified limits.

Purpose:

- To ensure accuracy and precision of analytical instruments.
- To maintain traceability to national or international standards.
- To detect instrument drift or inaccuracies over time.
- To ensure data integrity and compliance with regulatory guidelines.

ICH Guidelines on Calibration:

The ICH does not provide specific standalone guidelines solely on calibration but refers to it in broader contexts like:

A. ICH Q7 (GMP for Active Pharmaceutical Ingredients):

- Section 5.4: "Instruments and equipment should be calibrated according to a written program, which includes specific directions, schedules, limits for accuracy and precision, and actions to be taken when limits are not met."
- Calibration records must be maintained and readily available.

B. ICH Q10 (Pharmaceutical Quality System):

- Promotes a system-based approach, where calibration is part of the maintenance and performance monitoring system.

USFDA Guidelines on Calibration

A. 21 CFR Part 211 – cGMP for Finished Pharmaceuticals:

- **211.68**: Automated, mechanical, and electronic equipment must be calibrated routinely.
- **211.160(b)(4)**: Laboratory instruments and equipment must be calibrated at suitable intervals.
- **211.63**: Equipment must be of appropriate design and properly maintained, which includes regular calibration.

B. FDA Guidance Documents:

- "Process Validation: General Principles and Practices (2011)" mentions that instruments used for measuring and monitoring critical process parameters must be calibrated.

USFDA Guidelines on Calibration

Elements of Calibration (As per ICH & USFDA)

A. Certified Reference Standards

- Use certified, traceable, and stable standards (e.g., NIST).
- Store under appropriate conditions to ensure integrity.

B. Frequency of Calibration

- Defined in SOPs based on time or usage.
- Recalibrate after repairs, relocation, or major maintenance.

C. Calibration Documentation

- Each log should include:
  - Instrument ID
  - Calibration date
  - Personnel name
  - Reference standard used
  - Results and acceptance criteria
  - Deviations and corrective actions (if any)

D. Acceptance Criteria

- Set pre-defined measurement tolerances.
- If failed:
  - Investigate root cause
  - Invalidate affected data
  - Recalibrate and document actions

E. Labeling

- Clearly indicate status (e.g., "Calibrated", "On Hold", "Out of Service").

Calibration Process Steps

1. **Selection of Calibration Standard:**
   - Use reference standards with known and traceable values (e.g., NIST-traceable).
2. **Performance of Calibration:**
   - Measure known standards and compare with the instrument response.
   - Adjust the instrument to correct any deviations.
3. **Documentation:**
   - Record calibration data, date, personnel, standard used, and result.
4. **Evaluation and Acceptance Criteria:**
   - Ensure instrument response falls within pre-defined limits.
5. **Labeling:**
   - Indicate calibration status (e.g., calibrated/on hold/out of service).

Examples in Instrumentation:

- **UV-Vis Spectrophotometer:** Calibration with potassium dichromate solution.
- **HPLC:** Calibration of flow rate, detector response, injection volume.
- **pH Meter:** Calibration using buffer solutions (pH 4.0, 7.0, 10.0).
- **Mass Spectrometer:** Calibration with a standard tuning solution.

Validation

Definition:

- Validation is a documented process of demonstrating that a method, process, or system consistently produces results that meet predetermined specifications and quality attributes.

Types of Validation:

1. **Analytical Method Validation**
   - Demonstrates that the method measures what it is intended to measure with accuracy and precision.
2. **Process Validation**
   - Confirms that the manufacturing process consistently yields a quality product.
3. **Equipment Validation**
   - Ensures that an instrument performs reliably over time.
4. **Cleaning Validation**
   - Verifies the effectiveness of cleaning procedures in removing residues to acceptable levels.

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