



Equipment Validation and Calibration in Pharma: Systematic Review with An Industrial Approach

¹Mis. Shivani Shirbhate, ²Mr. Ujjawal Bhose.

¹Lecturer at Dr. Babasaheb Ambedkar Institute of D-Pharm, ²M- Pharm Student at Wadhawani College of Pharmacy.

¹Department of Quality Assurance, ² Department of Pharmacology,

¹Dr. Babasaheb Ambedkar Institute of D-Pharm, Sewagram, Wardha-442001, India.

²P. Wadhawani College of Pharmacy Yavatmal-445001, India.

Abstract: Equipment validation is a critical process ensuring that instruments function as intended, yielding expected results. Design Qualification (DQ) verifies the suitability of the proposed design for its intended purpose, while Installation Qualification (IQ) confirms compliance with approved design and manufacturer recommendations upon installation or modification. Operational Qualification (OQ) tests equipment performance across anticipated operating ranges, and Performance Qualification (PQ) assesses effective and reproducible performance based on approved methods and specifications. Verification Qualification (VQ) ensures ongoing alignment with user requirements, Safety Qualification (SQ) validates compliance with safety standards, and Maintenance Qualification (MQ) verifies the suitability of proposed maintenance programs. Re-Qualification (RQ) confirms ongoing satisfactory performance, necessitated by factors like relocation or aging. This comprehensive validation process safeguards against deviations, ensuring equipment reliability and product quality across industries.

Key Words: Validation, Calibration, Accuracy, Precision, Traceability, Installation, Performance, Qualification, Uncertainty, Resolution, Sensitivity.

Introduction

The calibration of equipment is an essential practice that must be undertaken regularly to uphold precision and reliability in measurement processes. This necessity arises from the propensity of instruments to deviate over time due to various factors such as harsh operational conditions, mechanical stress, or exposure to extreme temperatures and pressures. The frequency of calibration is contingent upon the tolerance levels required for accurate measurements, with critical objectives demanding more frequent and precise calibration efforts.[1]

While informal checks serve the purpose of ensuring performance requirements are met, a structured and documented approach known as Equipment Qualification holds greater significance. Equipment Qualification encompasses not only the validation procedures conducted during the initial commissioning of a measuring system but also entails regular performance assessments throughout the equipment's operational lifespan. This formal process is imperative not only as a regulatory requirement in certain industries but also for its manifold benefits to analysts.[1]

I. Firstly, Equipment Qualification provides tangible evidence that newly acquired equipment is suitable for its intended application. This is achieved through comprehensive delineation of all requisite characteristics of the measuring system, followed by rigorous validation to ascertain its conformity to these specifications before utilization in analytical procedures. Secondly, Equipment Qualification minimizes the likelihood of erroneous test results by ensuring that the equipment's performance remains suitable for its intended purpose throughout its operational lifespan

II. The documentation generated through Equipment Qualification serves as a valuable troubleshooting tool in the event of any operational issues arising during the equipment's service. By acting as a checklist, it aids in identifying and rectifying the root causes of any measurement-related problems promptly and effectively.

III. Equipment Qualification assumes a pivotal role within a laboratory's quality system by facilitating the development and validation of appropriate test methods and delineating the Quality Control and Quality Assurance measures necessary to ensure the fitness of test measurements for their intended purposes. By confirming that measuring equipment is capable of generating test measurements that meet predefined criteria, Equipment Qualification ensures the integrity and reliability of test results, thus underpinning the quality and credibility of analytical processes within the laboratory setting.[2]

A. Regulatory Requirements of Equipment Qualification:

The regulatory landscape governing pharmaceutical manufacturing underscores the critical importance of ensuring the qualification and maintenance of facilities, systems, equipment, and utilities to uphold data and product integrity. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7a guideline serves as a foundational framework in this regard.

According to the ICH Q7a guideline, facilities, systems, equipment, and utilities must undergo proper qualification and maintenance procedures to ensure the integrity of data and products throughout the manufacturing process. This necessitates adherence to rigorous standards and protocols to validate the performance and reliability of equipment.[3]

In addition to the ICH guidelines, further guidance is provided by the Pharmaceutical Inspection Co-operation Scheme (PIC/S). While acknowledging that it may not always be feasible to conduct detailed Installation Qualification (IQ) for established equipment or comprehensive Operational Qualification (OQ), PIC/S emphasizes the importance of having robust data available to support and verify the operating parameters and limits for critical variables of operating equipment

PIC/S underscores the significance of documenting essential procedures such as calibration, cleaning, preventative maintenance, operating procedures, and operator training for equipment usage. These documented procedures are to be upheld as standard operating procedures (SOPs), ensuring consistency, reliability, and compliance with regulatory requirements.

In essence, adherence to regulatory requirements for equipment qualification entails meticulous documentation, validation of critical operating parameters, and implementation of standardized procedures to ensure the integrity, reliability, and compliance of equipment used in pharmaceutical manufacturing processes. Compliance with these regulations is essential to safeguarding product quality, patient safety, and regulatory compliance within the pharmaceutical industry.[3]

B. Regulatory Requirements of Equipment Qualification in Accordance with ICH Q7a Guideline:

The regulatory framework established by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7a guideline sets forth stringent mandates concerning the qualification and maintenance of facilities, systems, equipment, and utilities within pharmaceutical manufacturing settings. The primary objective of these regulations is to ensure the integrity of data and products throughout the manufacturing process, thereby upholding the highest standards of quality, safety, and efficacy in pharmaceutical products.

According to the ICH Q7a guideline, facilities, systems, equipment, and utilities must undergo rigorous qualification procedures to validate their suitability and functionality for intended purposes. This entails comprehensive assessment and documentation of critical parameters, ensuring that the equipment operates within predefined specifications and limits. Additionally, facilities must be maintained in a manner that preserves data and product integrity, with adherence to established protocols for cleaning, maintenance, and calibration.[1],[3]

Furthermore, the guideline emphasizes the importance of maintaining standardized operating procedures (SOPs) for equipment usage. These SOPs encompass a range of procedures, including calibration, cleaning, preventative maintenance, and operator training. By documenting and implementing these procedures as SOPs, pharmaceutical manufacturers ensure consistency, reliability, and compliance with regulatory requirements throughout the equipment's operational lifespan.

It is crucial to note that while the ICH Q7a guideline provides overarching principles for equipment qualification and maintenance, additional guidance is available from regulatory bodies such as the Pharmaceutical Inspection Co-operation Scheme (PIC/S). PIC/S acknowledges the challenges associated with conducting detailed Installation Qualification (IQ) and Operational Qualification (OQ) for established equipment. However, it underscores the necessity of having robust data available to support and verify the operating parameters and limits for critical variables of operating equipment.[3]

the regulatory requirements outlined in the ICH Q7a guideline is imperative for pharmaceutical manufacturers to ensure the integrity, reliability, and compliance of equipment used in manufacturing processes. By meticulously qualifying and maintaining facilities, systems, equipment, and utilities, manufacturers uphold the highest standards of quality assurance and regulatory compliance, thereby safeguarding the integrity and safety of pharmaceutical products for patients worldwide.

C. Qualification of Utilities and Equipment:

The qualification process for utilities and equipment within pharmaceutical manufacturing facilities involves meticulous assessment and validation to ensure their suitability, reliability, and compliance with regulatory standards. This comprehensive procedure encompasses several key steps aimed at verifying the selection, construction, installation, and operational performance of utilities and equipment to support manufacturing processes effectively.[2]

1. Selection and Design Considerations:

The qualification process begins with a thorough evaluation of the specific requirements and intended uses of utilities and equipment. This includes consideration of factors such as operating principles, construction materials, performance characteristics, and capacity to ensure compatibility with manufacturing processes and regulatory standards.

2. Compliance with Design Specifications:

Utilities and equipment are meticulously verified to ensure compliance with design specifications. This entails confirming that utility systems and equipment are built and installed according to predefined criteria, including proper materials, capacity, and functionality. Additionally, calibration and proper connection of equipment are verified to ensure accuracy and reliability in operation

3. Operational Verification:

A crucial aspect of equipment qualification involves verifying that utility systems and equipment operate in accordance with process requirements across all anticipated operating ranges. This comprehensive assessment includes challenging the equipment or system functions under loads comparable to those expected during routine production. Furthermore, interventions, stoppages, and start-ups are simulated to assess equipment performance under realistic production conditions. This ensures that operating ranges can be maintained for the required duration during routine production operations.

The qualification of utilities and equipment is essential for ensuring the integrity, reliability, and compliance of pharmaceutical manufacturing processes. By adhering to stringent qualification protocols, manufacturers can mitigate risks, maintain product quality, and uphold regulatory compliance, thereby ensuring the safety and efficacy of pharmaceutical products for patients.

Validation of Laboratory Equipment.[1],[4]

Equipment qualification is a comprehensive process that goes beyond simple calibration. It encompasses several stages, each verifying a different aspect of the instrument's suitability for its intended purpose:

Design Qualification (DQ): This stage involves reviewing the design specifications of the friability tester to ensure it aligns with established standards and test requirements. Factors like drum size, rotation speed, and material compatibility are evaluated.

Installation Qualification (IQ): During IQ, the physical installation of the tester is verified. This includes checking for proper electrical connections, grounding, and placement within the laboratory environment.

Operational Qualification (OQ): OQ focuses on testing the operational functionality of the friability tester. This includes verifying the accuracy of the speed control mechanism, timer, and drum rotation. The example you provided falls under this category, outlining the specific procedures for checking the rotation speed at different settings.

Performance Qualification (PQ): (Optional) This final stage demonstrates that the friability tester, when used within a defined process, can consistently produce reliable results. This might involve testing reference materials with known friability values and comparing the obtained results to established specifications.[3]

D. Elements of Equipment Qualification in Scientific Language:

1. Design Qualification (DQ):

Design Qualification entails the systematic verification, documentation, and validation of the proposed design of equipment and systems to ensure their suitability and efficacy for the intended purpose within pharmaceutical manufacturing processes. This process involves comprehensive assessment and evaluation to ascertain that the design meets predefined criteria and regulatory standards.[5]

- a. Design Qualification (DQ) is the initial step in ensuring that equipment and systems used in pharmaceutical manufacturing are suitable for their intended purpose. It's a documented process that verifies the design meets all the necessary requirements before the equipment is even built or installed.
- b. **Scenario:** A pharmaceutical company needs a new mixing tank to blend active ingredients for a new drug.
- c. **DQ Activities:**
 - i. **User Requirements Specification (URS):** The company starts by developing a URS document. This document outlines the specific needs and functionalities required of the mixing tank. It might include details like:
 - Desired mixing capacity (volume)
 - Required mixing speed and intensity
 - Compatibility with the materials being mixed (e.g., stainless steel)
 - Cleaning and sanitation procedures
 - Control features (temperature, pressure)
 - ii. **Reviewing Design Documents:** The company's engineering team or a qualified vendor will then review the design documents for the mixing tank. These documents might include:
 - Engineering drawings and specifications
 - Material selection details
 - Control system schematics
- d. **Verification against URS:** During the review, the team will compare the design documents against the URS to ensure the design meets all the specified requirements.
- e. **Regulatory Compliance:** The DQ process will also involve verifying that the design adheres to relevant regulatory standards for pharmaceutical equipment. This might include standards set by agencies like the FDA or EMA.
- f. **Documentation and Approval:** Once the design review is complete, all findings and verifications are documented in a DQ report. This report will be reviewed and approved by a qualified team before proceeding to the next stage (Installation Qualification - IQ).

By following these steps, the company can ensure the new mixing tank design is suitable for its intended purpose, meets all user requirements, and complies with regulatory standards. This helps to minimize risks and ensure a smooth transition to the next stages of equipment qualification (IQ and OQ).

2. Installation Qualification (IQ):

Installation Qualification involves the documented verification that the equipment and system, as installed or modified, comply with the approved design specifications and the manufacturer's recommendations. This phase ensures that the equipment is correctly installed, calibrated, and configured according to predefined criteria to facilitate proper functioning and compliance with regulatory requirements.[5]

- a. Installation Qualification (IQ) is the second phase of equipment qualification, following Design Qualification (DQ). It focuses on verifying that the equipment or system has been installed and configured correctly according to the approved design specifications and manufacturer's instructions.

- b. **Scenario:** Continuing with the example from the DQ section, the new mixing tank has been delivered and installed at the pharmaceutical company's facility.

IQ Activities:

- i. **Verification of Delivery:** The IQ process begins with verifying the complete delivery of the mixing tank and all its components, as per the packing list.
 - ii. **Inspection for Damage:** The tank is thoroughly inspected for any physical damage that might have occurred during transportation or installation.
 - iii. **Installation Verification:** The team checks if the tank is installed in the designated location, ensuring proper clearance and accessibility for operation and maintenance.
 - iv. **Utility Connections:** They verify that all necessary utilities (e.g., power, water lines) are connected correctly to the tank, adhering to the manufacturer's specifications.
 - v. **Calibration Checks:** Calibrations are performed on any critical instruments or controls associated with the mixing tank, such as temperature sensors, agitator speed gauges, or pressure gauges. Calibration certificates are verified to ensure the instruments are within the required tolerance limits.
- c. **Documentation and Approval:** Similar to DQ, all findings and verifications during IQ are documented in an IQ report. This report includes details like:
- Installation procedures followed
 - Verification results (pass/fail)
 - Calibration certificates

Once the IQ report is complete, it's reviewed and approved by a qualified team before proceeding to the next phase (Operational Qualification - OQ).

By performing a thorough IQ, the company can ensure the mixing tank has been installed correctly, all components are present and functional, and the equipment is ready for further testing in the OQ phase. This helps to minimize the risk of issues arising during operation and ensures the equipment performs as intended.

3. Operational Qualification (OQ):

Operational Qualification focuses on the documented verification of equipment and system performance to ensure they function as intended throughout anticipated operating ranges. This entails rigorous testing to validate the functionality, reliability, and performance of the equipment under varying operational conditions, ensuring consistency and compliance with predefined specifications.[5]

- a. Operational Qualification (OQ) is the third and final phase of equipment qualification, following Design Qualification (DQ) and Installation Qualification (IQ). It focuses on verifying that the equipment actually performs as intended under real-world operating conditions.
- b. Scenario: Continuing with the new mixing tank example, the company is ready to test its functionality.
- c. **OQ Activities:**
 - i. **Test Procedures:** The company develops documented test procedures specifically designed to assess the mixing tank's performance across its anticipated operating range. These procedures might include:
 - Testing the mixing capabilities at different speeds and intensities
 - Verifying temperature control accuracy within the specified range
 - Evaluating cleaning and sanitation procedures for effectiveness
 - Assessing the functionality of alarms and safety features
 - Testing the performance of the control system and user interface
 - ii. **Test Execution:** The documented test procedures are then executed by qualified personnel. During testing, data is collected and recorded to demonstrate the equipment's performance.
- d. **Data Analysis:** The collected data is analyzed to ensure it meets the predefined acceptance criteria established for each test. This might involve comparing data against pre-defined limits or reference values.
- e. **Deviation Management:** Any deviations from the acceptance criteria are documented and investigated. Depending on the severity of the deviation, corrective actions might be required before proceeding.
- f. **Documentation and Approval:** Similar to DQ and IQ, all OQ activities, test results, and data analyses are summarized in an OQ report. This report is reviewed and approved by a qualified team before the mixing tank can be considered fully qualified and operational for production purposes.

By performing a comprehensive OQ, the company can ensure the mixing tank performs consistently and reliably under expected operating conditions. This helps to minimize the risk of product quality issues and ensures the equipment meets all the necessary requirements for pharmaceutical manufacturing.

4. Performance Qualification (PQ):

Performance Qualification involves the documented verification that the equipment and system, when connected together, can effectively and reproducibly perform based on approved process methods and product specifications. This phase verifies the capability of the equipment to consistently produce desired results within predefined specifications over an extended period, mimicking real-world operational conditions.[5]

- i. Performance Qualification (PQ) is the final, and often optional, stage of equipment qualification in some regulatory frameworks. It follows Design Qualification (DQ), Installation Qualification (IQ), and Operational Qualification (OQ). PQ focuses on demonstrating that the entire system, including the qualified equipment and the established processes, can consistently produce the desired product quality under real-world manufacturing conditions.
- ii. **Scenario:** Continuing with the new mixing tank example, the company has completed DQ, IQ, and OQ, and is ready to test the tank's ability to produce a specific drug product.
- iii. **PQ Activities:**
 - i. **Production Simulation:** The company simulates a real production run using the mixing tank and established process procedures. This might involve using a batch of non-potent materials that mimic the actual drug ingredients.
 - ii. **Data Collection:** Throughout the simulated production run, data is collected on various parameters, such as:
 - Mixing efficiency and uniformity
 - Temperature control during the process
 - Cleaning effectiveness after the run
 - Product quality attributes (e.g., potency, uniformity) of the final product
 - iv. **Data Analysis:** The collected data is analyzed to ensure it meets the predefined acceptance criteria for the drug product. This analysis verifies if the mixing tank, when integrated with the established process, can consistently produce high-quality product within specifications.
 - v. **Deviation Management:** Any deviations from the acceptance criteria are documented and investigated. Depending on the severity, corrective actions or process adjustments might be necessary before proceeding.
 - vi. **Documentation and Approval:** Similar to previous stages, all PQ activities, data collection, and analyses are documented in a PQ report. This report is reviewed and approved by a qualified team before the mixing tank and associated process are officially considered qualified for production of the specific drug product.
 - vii. **Importance of PQ:** While not always mandatory, PQ provides an additional layer of assurance that the equipment and processes can consistently deliver the desired product quality. This can be particularly crucial for high-risk or complex drug products.

5. Verification Qualification (VQ):

Verification Qualification encompasses the documented verification that the equipment and system, when connected together, continue to meet user requirements and produce expected results. This phase ensures that the equipment remains state-of-the-art and operates in accordance with predefined criteria and regulatory standards, maintaining reliability and effectiveness.[3],[5]

- a. Verification Qualification (VQ) resonates with the importance of ongoing equipment performance monitoring, it's not a recognized stage within the standard equipment qualification process outlined by ICH Q7a or other major regulatory frameworks in the pharmaceutical industry. Here's a breakdown to clarify the concept of VQ within the equipment qualification landscape. This is an ongoing activity that ensures equipment continues to perform as expected and meets established criteria throughout its operational life. It's not a distinct stage but rather an essential part of maintaining the "qualified state" of the equipment achieved through formal qualification.
- b. **Verification Activities:**
 - **Routine Calibration:** Regularly checking and adjusting critical instruments or controls on the equipment to ensure accuracy remains within acceptable ranges.
 - **Cleaning Verification:** Performing tests after cleaning procedures to confirm the equipment is free of contaminants that could impact product quality.
 - **Process Performance Monitoring:** Tracking key process parameters during production runs to identify any deviations or trends that might indicate potential equipment issues.
 - **Preventive Maintenance:** Performing scheduled maintenance activities to prevent equipment failures and ensure smooth operation.
 - **Maintaining Equipment Performance and Regulatory Compliance:**
 - Regularly verifying performance helps identify potential problems before they escalate into major issues, safeguarding product quality and production efficiency. Continuous verification helps manufacturers demonstrate adherence to regulatory requirements for equipment performance and data integrity.

6. Safety Qualification (SQ):

Safety Qualification involves the documented verification that the equipment and system, as installed or modified, comply with safety requirements pertaining to process, facility, and personnel. This phase ensures that the equipment is designed, installed, and operated in a manner that minimizes risks to personnel, facilities, and products during pharmaceutical manufacturing processes.[4][7]

7. Maintenance Qualification (MQ):

Maintenance Qualification focuses on the documented verification that the proposed maintenance program for the equipment and system is suitable for the intended purpose. This phase ensures that the maintenance procedures and schedules are adequately designed and implemented to support the reliability, functionality, and longevity of the equipment throughout its operational lifespan. [4][7]

8. Re-Qualification (RQ):

Re-Qualification involves the documented verification that the systems, when connected together, continue to perform satisfactorily following relocation, major modifications, or aging. This phase ensures that the equipment remains compliant with regulatory standards and continues to meet predefined criteria for performance, reliability, and effectiveness. Re-qualification is necessary to maintain the integrity and effectiveness of pharmaceutical manufacturing processes over time. [4][5]

Imagine relying on a ruler that stretches or a stopwatch that runs a little too fast. In countless industries, precise measurements are paramount, and that's where instrument calibration comes in. It's the process of regularly checking and adjusting instruments to ensure they provide accurate and reliable readings. Calibration is crucial for several reasons:

- **Maintaining Accuracy over Time:** All instruments are susceptible to drift, meaning their readings can deviate from the true value over time. Regular calibration corrects for this drift, ensuring measurements remain consistent and trustworthy.
- **Identifying Potential Issues:** Calibration can often uncover hidden problems with instruments before they significantly impact results. A sudden shift in calibration values might indicate a malfunction or internal damage, prompting further investigation and repair. [7]
- **Meeting Regulatory Requirements:** Many industries, particularly those heavily regulated like pharmaceuticals or engineering, have strict guidelines for instrument calibration. Regular calibrations ensure compliance with these regulations and maintain data integrity. [7]
- **Enhancing Process Control and Quality Assurance:** Accurate measurements are vital for process control in various fields. From monitoring temperatures in chemical reactions to verifying the dimensions of manufactured parts, calibration ensures processes run smoothly and products meet quality standards. [7]
- **Improved Decision-Making:** Reliable data from calibrated instruments empowers informed decision-making. This can involve anything from optimizing production processes to ensuring the safety and efficacy of medical treatments.

a. When is Calibration Needed?

There are several situations that call for instrument calibration:

- **New Instruments:** Brand new instruments need to be calibrated before their initial use to establish a baseline for accuracy.
- **Scheduled Intervals:** Instruments should be calibrated at predetermined intervals based on manufacturer recommendations, industry standards, or the criticality of the measurements they take. These intervals can be based on time elapsed, usage (operating hours), or a combination of both. [8]
- **Unexpected Events:** If an instrument experiences a shock, vibration, or any other unusual event that could potentially affect its accuracy, calibration is advisable to ensure readings haven't been compromised.
- **Questionable Observations:** If you suspect an instrument might be providing inaccurate readings, even without any specific incident, calibration is necessary to verify its performance. [8]

b. The Calibration Process:

There are two main approaches to instrument calibration: [8]

- i. **Internal Calibration:** Qualified personnel within an organization can perform internal calibration using reference standards with known traceability to national or international standards. This is suitable for less critical instruments or those with frequent calibration requirements.
- ii. **External Calibration:** External calibration involves sending instruments to specialized laboratories accredited by governing bodies. This approach is often used for high-precision instruments or those requiring adherence to strict regulations.

c. Keeping Track of Calibration Status:

A crucial element of any calibration program is maintaining proper documentation. Calibration tags attached to the instruments typically include details like:

- Instrument name and model
- Date of procurement
- Date of last calibration
- Due date for the next calibration
- Signature of the calibrator with the date of calibration

By following these practices, organizations can ensure their instruments are consistently calibrated, providing them with the confidence that their measurements are accurate and reliable. This, in turn, contributes to better decision-making, improved product quality, and overall operational efficiency.

d. Calibration: Maintaining Measurement Accuracy

Calibration is a specific step within the operational qualification (OQ) stage. It focuses on ensuring the instrument's measurements (in this case, rotation speed) are accurate and traceable to national or international standards. Here's an updated approach to the calibration procedure for the friability tester:

Example 1. Calibration Procedure with respect to Friability Tester:

Reference Standard: Obtain a certified reference standard tachometer or speed sensor with a known level of accuracy.

- i. **Test Procedure:** Mount the reference standard tachometer on the friability tester's drum or shaft, ensuring proper alignment.

- ii. **Comparison and Adjustment:** Run the friability tester at the designated speeds (25 RPM and 100 RPM) and compare the readings from the reference standard with the tester's built-in display. If there are discrepancies exceeding the acceptable tolerance limits (e.g., $\pm 2\%$ for speed), adjustments to the tester's calibration settings might be necessary.
- iii. **Documentation:** Record all calibration details, including the date, reference standard used, observed readings, and any adjustments made. This data provides a traceable record of the calibration process.
- iv. **Frequency and Additional Considerations:**

The frequency of calibration for a friability tester typically follows the recommendations outlined in the manufacturer's instructions. However, a good practice is to perform calibration at least annually or more frequently depending on usage and criticality of the test. Additionally, calibration should also be conducted:

- After any repairs or maintenance procedures on the tester.
- If the tester experiences any shocks, vibrations, or other events that could potentially affect its performance.
- If the user observes any unusual behavior or inconsistencies in the test results.

v. **Maintaining Calibration Status:**

- Similar to your example, a "Calibration Status" label should be affixed to the instrument, indicating the date of the last calibration and the due date for the next one. Electronic calibration management systems can also be used to track calibration records and generate reminders for upcoming calibrations.
- Qualification and calibration program for friability testers, laboratories can ensure the accuracy and reliability of their test results. This contributes to the overall quality and consistency of pharmaceutical products reaching consumers.[9]

Example 2. Calibration Procedure with respect to Hardness Testers

Hardness testing is a vital quality control procedure in various industries, measuring the resistance of a material to deformation. Accurate and reliable hardness testers are essential for ensuring product quality and consistency. This is where proper calibration comes in.

- **The Importance of Calibration:**
- Over time, the internal components of a hardness tester can experience wear and tear, potentially affecting the accuracy of its force measurements. Regular calibration helps to:
- **Maintain Measurement Accuracy:** Calibration ensures the tester's readings are consistent with known standards, preventing false acceptance or rejection of materials based on inaccurate hardness values.
- **Traceability to Standards:** Calibration procedures use certified standard weights with traceable links to national or international measurement standards, guaranteeing the reliability of the test results.
- **Compliance with Regulations:** Many industries, particularly those with strict quality control requirements, have regulations mandating periodic calibration of testing equipment. Calibration ensures compliance with these regulations.

a. **The Calibration Process:**

The procedure you provided outlines a common method for calibrating force gauges used in hardness testers. Here's a breakdown of the steps:

- i. **Preparation:** Ensure the force gauge is clean and free of any debris that might affect its performance.
- ii. **Zero Adjustment:** With the gauge held vertically, adjust the zero point on its scale to ensure it accurately reflects no applied force.
- iii. **Weight Application:** Starting with the lightest weight (e.g., 1.0 kg), hang it from the hook of the force gauge.
- iv. **Reading and Comparison:** Record the force value displayed on the gauge and compare it to the weight's nominal value. The tolerance limits you provided (e.g., ± 0.25 kg for larger weights and ± 0.1 kg for smaller weights) define the acceptable range of deviation.
- v. **Adjustment (if necessary):** If the displayed value falls outside the tolerance limits, adjustments to the gauge's calibration mechanism might be required to bring it back into specification.
- vi. **Repeat for Different Weights:** Repeat steps 3-5 for each of the standard weights (2.0 kg, 5.0 kg, 10.0 kg, 20.0 kg, and 30.0 kg) in your calibration set.
- b. **Documentation:** Record all calibration details, including the date, weights used, observed readings, and any adjustments made. This data provides a traceable record of the calibration process.
- c. **Frequency and Additional Considerations:**
The recommended frequency of calibration for a hardness tester's force gauge typically falls within the range of **every 3 to 12 months**. The specific timeframe depends on several factors, including:
 - **Manufacturer's recommendations:** Always refer to the manufacturer's instructions for your specific hardness tester model, as they might have specific calibration frequency guidelines.
 - **Frequency of use:** More frequent use of the tester generally warrants more frequent calibration.
 - **Criticality of application:** For applications where precise hardness measurements are crucial, more frequent calibration might be necessary.
 - **Beyond Calibration: Maintaining Instrument Performance**
 - In addition to calibration, here are some additional practices to ensure the continued performance of your hardness tester:

- d. **Proper Handling and Storage:** Follow the manufacturer's instructions for proper handling and storage of the tester to minimize wear and tear.
- e. **Preventative Maintenance:** Regular preventative maintenance can help identify and address potential issues before they escalate into major problems affecting calibration or performance.
- f. **User Training:** Proper user training ensures operators understand how to use the tester correctly and identify any signs of malfunction.[10]

Example 3. Calibration Procedure with respect to Disintegration Apparatus

The disintegration test is a crucial quality control procedure for evaluating how quickly a tablet or capsule breaks down in an aqueous environment. A well-calibrated disintegration tester is essential for obtaining reliable and consistent results. Here's a breakdown of the calibration procedures you outlined, along with some additional insights:

a. Calibration for Number of Oscillations per Minute:

This procedure verifies the basket movement speed of the disintegration tester, which is a critical factor in the disintegration process.

- **Pre-calibrated Stopwatch:** It's important to ensure the stopwatch used is indeed pre-calibrated and traceable to a national standard for time measurement.
- **Number of Measurements:** While five repetitions are a good starting point, some guidelines recommend taking ten readings to improve the statistical significance of the data.
- **Tolerance Limits:** The specified range of 29 to 32 oscillations per minute ensures consistency with the USP (United States Pharmacopeia) and other regulatory standards.

B. Calibration for Temperature:

This procedure verifies the accuracy of the internal temperature sensor and heating system of the disintegration tester.

- **Alternative Approach:** While your procedure outlines manual temperature measurement, some testers have built-in calibration features that allow for direct adjustment of the temperature sensor.
- **Calibration Standards:** The pre-calibrated thermometer used should be traceable to national or international temperature standards.
- **Temperature Uniformity:** In addition to measuring the temperature in beakers A and B, some guidelines recommend checking the temperature uniformity across multiple locations within the bath to ensure consistent heating throughout.

C. Timer Calibration:

This procedure verifies the accuracy of the internal timer used in the disintegration tester.

- **Tolerance Limits:** The ± 1 minute tolerance limit ensures the timer operates within an acceptable range for test validity.
- **Multiple Time Points:** Consider performing timer calibration at different time intervals (e.g., 15 minutes, 30 minutes) to assess its accuracy across various test durations.

D. Sieve Integrity Test:

This procedure verifies the physical integrity and mesh size of the sieves used in the disintegration test, which are crucial for capturing disintegrated fragments.

- **Calibration Tool:** A vernier caliper is a good option, but some labs might prefer using pre-calibrated sieves with certified mesh sizes.
- **Mesh Size Specifications:** The specified aperture size (1.8 – 2.2 mm) and wire diameter (0.57 to 0.66 mm) ensure compliance with established standards for disintegration testing.

E. Additional Considerations:

- **Calibration Records:** Maintain detailed records of all calibration procedures, including dates, observations, and any adjustments made. This data provides a traceable audit trail for regulatory purposes.
- **Reference Standards:** Ensure all reference standards used for calibration (stopwatches, thermometers, vernier calipers) have valid calibration certificates from accredited laboratories.
- **Frequency of Calibration:** The recommended frequency of calibration for a disintegration tester is typically **every 3 to 6 months**, depending on manufacturer recommendations, usage frequency, and criticality of testing.[11]

Example 4. Calibration Procedure with respect to Calibration and Suitability Testing of Dissolution Testers

Dissolution testing plays a crucial role in the pharmaceutical industry, assessing the rate at which a drug releases from its dosage form (tablet, capsule) into a simulated digestive fluid. Accurate and reliable results from dissolution testing are essential for ensuring the bioavailability and efficacy of medications. This is where proper calibration and suitability testing of dissolution testers come in.

Part A: Calibration Procedures

- a. **Temperature Calibration:** This procedure verifies the accuracy of the internal temperature sensor and heating system of the dissolution tester.
- b. **Measurement Comparison:** The temperature of the water bath and each individual vessel is measured using a calibrated thermometer and compared to the values displayed on the instrument.
- c. **Acceptance Criteria:** The measured temperatures should fall within $\pm 0.5^\circ\text{C}$ of the set point (37°C), which aligns with typical human body temperature and simulates physiological conditions for drug dissolution.

- d. **RPM Calibration:** This procedure verifies the accuracy of the motor speed control mechanism of the dissolution tester, which is crucial for maintaining consistent agitation throughout the test.
- e. **Calibration Speeds:** The apparatus is calibrated at two commonly used speeds (50 RPM and 100 RPM).
- f. **Measurement Techniques:** The actual rotation speed is measured using either a calibrated stopwatch or a tachometer. These readings are then compared to the values displayed on the instrument.
- g. **Acceptance Criteria:** The measured RPM should be within ± 1 RPM for 50 RPM and ± 2 RPM for 100 RPM. These tolerances ensure consistent agitation and maintain the validity of dissolution testing data.

Part B: Apparatus Suitability Test

This test verifies the overall performance of the dissolution tester and its ability to generate reliable results. There are two approaches depending on the type of tablet being tested:

- a. **Disintegrating Type:**
 - i. **USP Dissolution Calibrators:** These are standardized tablets containing a specific drug (prednisone in this example) with well-defined dissolution characteristics.
 - ii. **Dissolution Media:** The test is typically conducted using distilled water to minimize potential interactions with the media composition.
 - iii. **Acceptance Criteria:** The measured concentration of prednisone released from the tablets at specified time points and agitation speeds should fall within the ranges specified in the certificate of analysis for the calibrator tablets. This ensures the dissolution tester is functioning correctly and can generate consistent results for disintegrating tablets.
- b. **Non-disintegrating Type:**
 - i. **Salicylic Acid Tablets:** These tablets are used for suitability testing of dissolution testers intended for non-disintegrating dosage forms.
 - ii. **Phosphate Buffer Media:** This media simulates the slightly acidic environment of the stomach.
 - iii. **Acceptance Criteria:** Similar to the disintegrating type test, the measured concentration of salicylic acid released from the tablets at specified time points and agitation speeds should fall within the ranges defined for this specific calibrator. This confirms the suitability of the tester for non-disintegrating tablets.
 - iv. **Frequency of Calibration and Suitability Testing**
The recommended frequency for calibration of a dissolution tester is typically **every 3 months** or after any maintenance work is performed. This ensures the instrument maintains its accuracy and performance over time. Additionally, **suitability testing** should be conducted **periodically** (e.g., every 6 months or with each new batch of drug product) to verify the ongoing performance of the dissolution tester.[12]

Example 5. Calibration Procedure with respect to Calibration Procedure for Tap Density Testers

Tap density is a crucial parameter in the pharmaceutical industry, characterizing the packing behaviour of powders and granules. An accurate and reliable tap density tester is essential for obtaining consistent and meaningful results.

- a. **Pre-Calibration Steps:**
 - i. **Tapping Height Measurement:** Using a ruler, ensure the tapping height mechanism of the tester is precisely set to either 3mm or 14mm, as these are common industry standards.
 - ii. **Calibrated Cylinder:** The test utilizes a calibrated cylinder with a known volume (typically 250 mL, but other volumes might be used). It's crucial to obtain this cylinder from a qualified supplier who can provide certification of its volume accuracy.
 - iii. **Cylinder Length Measurement:** While not directly involved in the calibration process itself, measuring the cylinder length can be helpful for reference and troubleshooting purposes.
 - iv. **Calibration Procedure:**
 - v. **Setting Tap Count:** The tester allows you to program a specific number of taps for the test. This will depend on the specific standard or method being followed.
 - vi. **Start Tapping:** Once the tapping height, cylinder, and tap count are set, initiate the tapping cycle.
 - vii. **Tap Number Counting:** Using a stopwatch set to one minute, count the actual number of taps delivered by the tester during the cycle. This allows you to verify if the programmed tap count matches the actual operation of the instrument.
 - viii. **Allowed Tap Number Error Range:** Different international standards (e.g., USP, Ph. Eur.) might have slightly different acceptable tolerances for the number of taps delivered within a minute. Consult the relevant standard to determine the allowable error range for your specific application.
- b. **Post-Calibration Step:**
 - i. **Weighing the Tapping Device with Cylinder:** This step, while not directly related to calibration, can be a useful part of routine maintenance. Weighing the entire tapping device with the cylinder assembled can establish a baseline weight. Deviations from this baseline weight in future measurements might indicate loose components or potential issues within the tester.
 - ii. **Additional Considerations:**
 - iii. **Reference Standards:** It's recommended to consult and follow the guidelines set forth in relevant international standards (e.g., USP, Ph. Eur. 2.9.34) for tap density testing. These standards provide detailed procedures and acceptance criteria for calibration.

- iv. **Frequency of Calibration:** The recommended frequency for calibration of a tap density tester typically falls within the range of every 3 to 12 months. This can vary depending on factors like usage frequency, manufacturer recommendations, and criticality of the application.
- v. **Documentation:** Maintain detailed records of all calibration procedures, including dates, observations, and any adjustments made.[13]

Conclusion: The validation of equipment in various industries, including pharmaceuticals and manufacturing, is a multifaceted process essential for ensuring reliable and consistent performance. Through the systematic verification phases outlined, including Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), Verification Qualification (VQ), Safety Qualification (SQ), Maintenance Qualification (MQ), and Re-Qualification (RQ), organizations can establish confidence in the functionality, compliance, and ongoing performance of their equipment. By adhering to rigorous validation protocols, industries can mitigate risks, maintain product quality, and uphold regulatory compliance standards. Moreover, this comprehensive validation process not only safeguards against deviations but also contributes to enhanced operational efficiency and product integrity. Thus, equipment validation serves as a cornerstone in ensuring the reliability, safety, and efficacy of processes and products across diverse industrial sectors. Furthermore, the validation process is not a one-time event but rather a continuous endeavour, as evidenced by the need for periodic re-qualification (RQ) due to factors such as relocation, major modifications, or aging. This ongoing commitment to validation ensures that equipment remains in a state of optimal performance, aligned with evolving user requirements and industry standards. By maintaining meticulous records of validation activities and adhering to recommended calibration frequencies, organizations can uphold the integrity of their operations and sustain high levels of quality assurance. In summary, equipment validation is indispensable for achieving and maintaining operational excellence, regulatory compliance, and the delivery of safe and effective products to consumers.

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