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EQUIPMENT QUALIFICATION AND MAINTENANCE IN PHARMACEUTICAL MANUFACTURING: STRATEGIES FOR EFFICIENCY AND COMPLIANCE

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ABSTRACT

Efficient equipment qualification and maintenance are crucial elements in ensuring the quality, safety, and compliance of pharmaceutical manufacturing processes. This review article examines various strategies employed in the industry to enhance efficiency and compliance in equipment qualification and maintenance practices. Firstly, it explores the importance of equipment qualification, encompassing installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), as essential steps in validating equipment performance. Next, the focus shifts to maintenance strategies, highlighting preventive maintenance, predictive maintenance, and corrective maintenance approaches to minimize downtime and prevent equipment failures. Furthermore, the article delves into the integration of advanced technologies such as predictive analytics, remote monitoring, and condition-based maintenance, which offer opportunities for proactive equipment management and optimization. Additionally, regulatory considerations and compliance requirements set forth by authorities such as the FDA and EMA are discussed, emphasizing the necessity for adherence to current good manufacturing practices (cGMP). Moreover, the review examines the role of risk-based approaches in prioritizing equipment qualification and maintenance activities based on potential impact to product quality and patient safety. Lastly, it discusses emerging trends and future directions in equipment qualification and maintenance, including

the adoption of industry 4.0 technologies and the increasing emphasis on sustainability and resource efficiency in pharmaceutical manufacturing operations.

KEYWORDS: Equipment Qualification, Maintenance Strategies, Pharmaceutical Manufacturing, Efficiency Compliance, Risk-based Approaches.

1. INTRODUCTION

The equipment qualification in pharmaceutical manufacturing is to ensure that all equipment used in the production process consistently performs according to predefined specifications and regulatory requirements. This process involves validation and documentation whether the equipment is properly installed, operates correctly, and produces the acquired results.

Maintenance of equipment ensures that the medicines produced are of high quality and safe for consumption. Regular maintenance also helps prevent unexpected breakdowns, reducing downtime and ensuring that production runs smoothly.

Efficiency and compliance in pharmaceutical manufacturing can be enhanced through various strategies. These include implementing automated processes to streamline production, conducting regular training for staff to ensure adherence to regulations, and leveraging data analytics to optimize resource allocation and identify areas for improvement. Additionally, fostering a culture of continuous improvement and collaboration across departments can further support efficiency gains while maintaining compliance with industry standards.

2. Types of validation[1]

types of equipment validation commonly used in the pharmaceutical industry are

1. **Installation Qualification (IQ):** Ensures that equipment is installed correctly according to manufacturer specifications and site requirements.
2. **Operational Qualification (OQ):** Verifies that equipment functions as intended within specified operational limits, including testing for performance and functionality.
3. **Performance Qualification (PQ):** Confirms that equipment consistently produces results meeting predetermined specifications and requirements when used in its intended environment.
4. **Process validation:** Extends beyond individual equipment validation to ensure the entire manufacturing process, including equipment, materials, procedures, and personnel, consistently produces products meeting quality standards.

5. **Cleaning validation:** Validates the effectiveness of cleaning procedures to remove residues from equipment surfaces, ensuring product quality and safety.
6. **Computer System Validation (CSV):** Validates computerized systems used in equipment operation, data management, and process control to ensure accuracy, reliability, and compliance with regulatory requirements.
7. **Re-Qualification (RQ):** The documented verification that the systems as connected together, are still performing satisfactorily. Re-qualification is required as an outcome of relocation, major modification and due to ageing.

3. Purpose of validation

Validation can be called for

- ✓ With a new instruments
- ✓ When a specified usage (Operating hours) has passed
- ✓ When a specified time period is passed
- ✓ When an instrument has had a shock or vibration which potentially may have put it out of calibration
- ✓ Sudden change in weather

The status of the instruments is identified by checking the calibration tag of the instruments. Tag consists of information regarding instruments like name of instrument, date of procurement, date of calibration, next calibration date and signature of calibrated person with date. Calibration of instruments is done in two ways internal calibration and external calibration. Internal calibration is done the in-house officials whom have sound knowledge on it. External calibration is done according to the instructions of the manufacturer and should be done in the government approved individual or institution.

4. Qualification of equipments used in laboratories

1. Friability test apparatus[2]

1. Switch on the power supply.
2. Set the RPM to 25 and start the machine simultaneously with the stop watch. Count the actual rotations and not the time required for the same.
3. Similarly set the RPM to 100 and note the time required and actual rotations.
4. Apparatus is in proper working condition if,
5. Time required for 25 rotations is 1 min ± 05 sec.

Time required for 100 rotations is 4 min ± 20 sec.

Record the observation in the calibration record.

6. Affix a "Calibration Status" label on the instrument.
7. In case of any discrepancy, report the observations to QC manager / QA Manager and notify the defect to Engg. Department.
8. Affix an 'UNDER MAINTENANCE" label on the instrument.

Frequency: Once in a month and after each maintenance job.

2. Hardness tester[3]

1. Take out the force gauge to be calibrated and hold vertically up.
2. Adjust the zero on the force gauge.
3. Standard Weights are then applied to the hook of force gauge and measure the tension of the spring on the force gauge.
4. When 1 kg of standard weight is applied, scale on the force gauge should also show 1 kg tension produced from the initial point where pointer is adjusted.
5. Adjust the zero on the force gauge again.
6. Follow the same procedure for other weights.
7. The test to be carried out for 1.0 kg, 2.0 kg, 5.0 kg, 10.0 kg, 20.0 kg & 30.0 kg standard weights.

Tolerance: ± 0.25 kg / ± 0.1 kg

Frequency: Once in 6 months.

Maintenance / Repair When the instrument does not comply with the requirement specified above; the instrument should be labelled as "Out of Calibration" and should get repaired / serviced. After repairing / servicing the instrument before taking for use, the instrument must be calibrated as per the above-mentioned procedure.

5. Disintegration test apparatus[4]

A. Calibration for number of oscillations per minute

1. Take a pre-calibrated stopwatch. Operate the apparatus as per SOP. Start the apparatus and stopwatch simultaneously and count the number of oscillations per minute.
2. Repeat the same for five times and note down the number of oscillations per minute for each time.
3. The oscillations per minute shall be within the limit of 29 to 32 through a distance of 53 to 57 mm throughout the period of operation. Record the observation.

B. Calibration for temperature

1. Switch on apparatus and press key.
2. Turn on the heater by pressing 'ON' key.
3. Set the bath temperature by pressing scroll keys.
4. Wait till the temperature of beaker A and beaker B attain the set value.
5. Screen shall show the set temperature of bath and the temperature of beaker A and beaker B.
6. Take a pre-calibrated thermometer and check the temperature of beaker A and beaker B.
7. Record the observation.

C. Timer calibration

1. Set the timer for '30 minutes' and start the equipment and stop watch simultaneously. Note down the stop watch reading immediately when the equipment stops and note down the observation.
2. Observed time should not deviate by '± 1 min' of set time.

D. Sieve integrity test

Check the 'integrity' of woven stainless steel cloth (Sieve) attached to the base plate of each basket with a pre-calibrated vernier calliper. The sieve has weaven squares of aperture of 1.8 – 2.2 mm and wire diameter of 0.57 to 0.66 mm. Note the observations.

- Affix the 'CALIBRATION STATUS' tag duly filled and signed on the equipment after completion of calibration.
- If the instrument is out of calibration then affix 'UNDER MAINTENANCE' tag and inform to maintenance department.
- The frequency for calibration of Disintegration Test apparatus shall be after every one month or after every maintenance work.

6. Dissolution test apparatus[5]

Part 'A'

The instrument shall be calibrated for RPM and Temperature.

For temperature calibration

Measure the temperature of the water bath and of each jar with a calibrated thermometer and compare the result against the digital display on the apparatus.

Acceptance Criteria: 37°C ± 0.5°C

For RPM Calibration

Calibrate the apparatus at 50 and 100 RPM. Compare the RPM shown on the digital display of the apparatus with the RPM measured with a stopwatch or Taco meter.

Acceptable criteria: ± 1 RPM – for 50 RPM ± 2 RPM – for 100 RPM

Part 'B' Apparatus suitability test disintegrating type

1. Use USP dissolution calibrator disintegrating type 50 mg prednisone tablets.
2. This USP Dissolution Calibrator is provided for the Apparatus Suitability Test in the general chapter of USP 24 or as per the method specified in the documents received along with the respective lot of the tablet.
3. Do not expose the tablets to excessive humidity. Store in dry, cool place.
4. Dissolution Media: Distilled water 500 ml.
5. Using a membrane filter, with stirring for about 5 minutes.
6. Weigh accurately about 10 mg of prednisone reference standard (already dried on 105°C for 3 hour into a 100 ml volumetric flask and dissolve in 5 ml of ethanol. Make up to volume with distilled water.
7. Dilute 10 ml of the solution to 50 ml with distilled water.
8. Conduct the suitability test at conditions mentioned in the certificate of tablets using apparatus I and II.
9. After completion of the dissolution time withdraw filter and aliquot of the solution.
10. Heat the medium with gentle stirring, to about 45° C, immediately filter under vacuum
11. Discard the first 2 ml of solution and measure the concentration of prednisone at 242 nm against the absorbance of prednisone USP reference standard solution.
12. The apparatus is suitable if each of the individual calculated values for each apparatus at all indicated speeds are within the specified ranges.

Table 1: Basket and Basket shaft measurement.

S. No	Name of Element	Usp Limit(Mm)
1.	Diameter of shaft	9.4-10.1
2.	Vent hole	2.0
3.	Clear operating	20.2 ±0.1
4.	Shaft base	5.1 ±0.5
5.	Outer diameter of basket base	26.4 ± 3
6.	Inner diameter of basket base	20.2 ±1
7.	Outer length of basket	36.8 ±3
8.	Inner length of basket	27.0 ± 3
9.	Outer diameter of screen	22.2 ±1

Table 2: Paddle and Paddle shaft measurement.

S. No.	Name of Element	Usp Limit (Mm)
1.	Longer width of paddle	74.0-75.0
2.	Weight of the paddle	19.0 ±0.5
3.	Lower width of paddle	42.0
4.	Width of paddle	04.0 ±1
5.	Diameter of shaft	9.4-10.1

Apparatus Suitability Test Non-disintegration Type

a. Apparatus suitability test for non-disintegrating type Salicylic Acid 30 mg tablets.
b. This USP Dissolution Calibrator is provided for the Apparatus Suitability Test in the general chapter of USP 24 or as per the method specified in the documents received along with the respective lot of the tablet.
c. These tablets are pure salicylic acid with no binders or fillers, because of the physical properties of such tablets, some sticking may occur during storage. Gentle tapping of the bottle may be used to separate the tablets.
d. Do not expose the tablets to excessive humidity. Store in a dry, cool place.
e. Dissolution Medium – 0.05 M phosphate buffer pH 7.4 ± 0.05, 900 ml.
f. Weigh accurately about 27.22 g of monobasic potassium phosphate and dilute to 1000 ml with water. (Solution A)
g. Weigh accurately about 8 g sodium hydroxide and dilute to 1000 ml with water 0.2M Solution (Solution B).
h. Place 500 ml of solution A and 391 ml of solution B and dilute to 2000 ml with water and adjust the pH to 7.4 ± 0.05 with either of the solution A/B.
i. Dry a portion of salicylic acid working standard over silica gel for 3 hours before use.
j. Weigh accurately about 33 mg of salicylic acid working standard into a 100 ml volumetric flask, add 1 ml methanol and dissolve the powder, Dilute to volume with phosphate buffer. Dilute 5 ml to 50 ml with buffer.
k. Place one Salicylic acid Non-disintegrating type tablet in each of the 6 containers and operate the apparatus at each of the speeds indicated in the certificates. Withdraw and filter an aliquot of the solution
l. Discard the first 2 ml of solution. Dilute 5ml of the filtrate to 50 ml with dissolution medium (Phosphate buffer) and measure the concentration of Salicylic acid at 296 nm against the absorbance of Salicylic acid reference standard solution.
m. The apparatus is suitable if each of the individual calculated values for each apparatusat all indicated speed is within the specified ranges.

The frequency for calibration of Dissolution Test apparatus shall be after every three month or after every maintenance work.

7. Tap density tester[6]

- Measure the tapping height (3mm or 14mm) with a ruler
- Obtain calibrated cylinder (250mL or other volume) from qualified supplier
- Measure the length of the cylinder.
- Set the count number and start tapping.
- Count the tapping number using a stopwatch setting to 1 minute, check the allowed tap number error range as per specific international standard.
- Weigh the tapping device including the cylinder

Maintenance in pharmaceutical manufacturing

Pharmaceutical manufacturing hinges on rigorous maintenance practices beyond just preventive measures. A comprehensive program incorporates elements like:

- **Risk-based approach:** Critical equipment gets prioritized for more frequent checkups to minimize potential risks.
- **Predictive maintenance:** Advanced monitoring systems analyze equipment data to predict and address potential failures before they occur.
- **CMMS (Computerized maintenance management systems):** Software helps manage work orders, track maintenance history, and streamline the entire process.
- **Highly skilled technicians:** Proper training ensures staff can effectively maintain complex machinery and adhere to strict GMP regulations.

This multi-faceted approach optimizes equipment performance, safeguards product quality, and keeps production running smoothly.

CONCLUSION

Rigorous equipment qualification and meticulous maintenance are the cornerstones of a robust pharmaceutical manufacturing operation. Qualification ensures equipment meets design specifications and functions as intended. Preventive maintenance programs, with elements like risk assessment, predictive technologies, and skilled technicians, proactively address potential issues before they escalate into costly downtime or product contamination. This integrated approach guarantees consistent production of high-quality pharmaceuticals, safeguarding patient well-being and ensuring compliance with regulatory requirements.

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