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Review Article

A Review on Life Cycle Management Approach on Asset Qualification

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ABSTRACT

All equipment's used in the production of products shall be properly Validated, Qualified and Calibrated to demonstrate that it is suitable for its intended purpose. Qualification is an important aspect of the pharmaceutical quality system. When the equipment is properly qualified, verified and maintained, there is the possibility of Consistent performance of the equipment. A well designed qualification program saves valuable time and cost. Qualification is called a cyclic process because it is a never ending process. Appropriate documentation of the qualification program is very important as lack of the documented evidence does not give any meaning to qualification (Not documented it means not done). The current programs and procedures of equipment qualification used within any pharmaceutical and bioscience industry are based on 'regulatory requirements', 'voluntary standards', 'vendor practices', and 'industry practices'. The output is considerable variation in the way any pharmaceutical and biotechnological companies approach for the laboratory equipment. The lifecycle management approach of equipment qualification covers entire life cycle for the specification, design, manufacturing, installation, commissioning, qualification (4Qs Model DQ, IQ, OQ, PQ), operation & maintenance of equipment in a risk based life cycle management approach. The goal of any regulated pharmaceutical and bioscience company is to provide reliable and valid data suitable for its intended purpose. Main goal of equipment qualification is to form the basis for written procedures for production and process control which are designed to assure that the drug products have the SISQP (Safety, Identity, Strength, Purity and Quality)

Keywords: Validation, Calibration, Life cycle management approach, Qualification (4Qs Model- DQ, IQ, OQ & PQ), SISQP (Safety, Identity, Strength, Purity and Quality)

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Introduction:

Equipment Qualification: It is the action of proving documented evidence demonstrating that equipment is designed/selected adequately, installed and operates/performs properly for its intended purpose. These activities have been divided into main four phases of qualification.¹ These are listed as: Design, Installation, Operational and Performance qualifications.

Objectives of Equipment Qualification:

1) To review the requirements of equipment

- Selection
- Design
- Use
- Maintenance

2) To discuss the equipment qualification principles, specifically focusing on:

- The different stages of qualification
 - Requalification
 - Qualification of "in use equipment"
- 3) To form the basis for written procedures for production and process control which are designed to assure that the drug products have the SISQP(Safety, Identity, Strength, Purity and Quality)
- 4) To improve and control overall production reliability and availability
- 5) To ensure safety of products

Schedule M states proper concepts about the qualification of the equipment.² Qualification requirements of established equipment are decided on the basis of available historical data of that equipment. ³ As per good laboratory practice rules and regulations impose similar requirements, asset used for the generation, measurement, or assessment of data

shall be adequately tested, calibrated and/or standardized.⁴⁻⁵

➤ **Documentation:**

This section provides guidelines on those requirements relating to documentation covering the EQ process.

Appropriate documentation of the qualification program is very important as lack of the documented evidence does not give any meaning to qualification (Not documented it means not done). It should not be intended to cover other documentation reports relating to operation or servicing (e.g. manuals) of the instrument.⁶

• **Stages of Equipment Qualification:⁷**

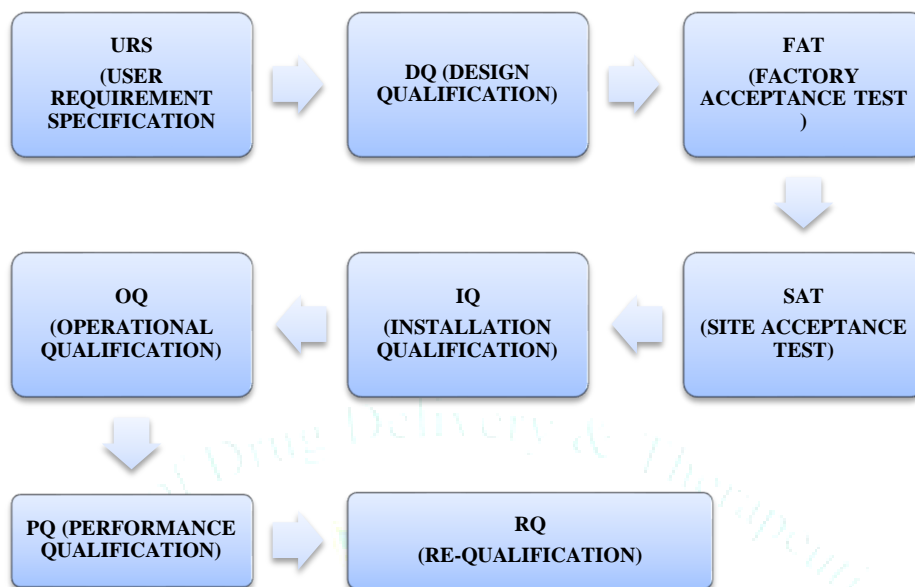


Fig 1: Stages of Equipment Qualification

➤ **Responsibilities:⁸**

1) **URS:**

- User department- to prepare URS
- Engineering department/ Vendor – to verify

2) **DQ:**

- Engineering department/ Vendor: DQ Protocol
- User department: to verify

3) **IQ:**

- Engineering department/ Vendor: IQ Protocol
- User department: to review
- QA department: to approve

4) **OQ:**

- Engineering department/ Vendor: IQ Protocol
- User department: to review
- QA department: to approve

5) **PQ:**

- Engineering department/ Vendor: IQ Protocol
- User department: to review
- QA department: to approve

➤ **Gap analysis:**

The gap analysis contains a short, observes GLP lineament, regulatory requirements, and is convenient for the process

and validation strategy. It has the management of qualification execution plan, and makes a lot of facility maintenance validity.⁹ Gap analysis includes the responsibility of applicable personnel, characteristics of equipment to be evaluated, the model number, serial manufacture number, serial asset number, using purpose, location, document or SOP, number, equipment logs, date of last calibration, personnel training records, a validation certificate, system controls, data storage methods, risk type, the level of the responsible person, and validation specialist (Qualification study director). Gap analysis offers the easy and convenient information for the validation process. The qualification study director wants to cooperate with the manufacture or vendor, and to notify any abnormality of the facility to them. The document for gap analysis is similar to those shown in Table 1.

Table 1: Gap Analysis Record¹⁰

| Sr.no | 1 | 2 | 3 | 4 |
|--|---|---|---|---|
| Equipment-Asset | | | | |
| Make | | | | |
| Model No. | | | | |
| Serial No | | | | |
| Inst.ID. | | | | |
| Software | | | | |
| 21 CFR compliant status | | | | |
| Critical/Non Critical Calibration | | | | |
| IQ/OQ/PQ | | | | |
| SOP No | | | | |
| Document Archival | | | | |
| Location | | | | |
| Remark | | | | |

I. User Requirement Specification

The specification for equipment shall be defined in a URS. The set of owner, user and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system and any GMP risks mitigated to an accepted level. The URS shall be a point of reference throughout the validation life cycle. URS may be considered as the first initial and important step in the qualification "flowchart", which can be shown in the figure above (Fig. 1):

The URS shall cover the specific requirements of the equipment to be procured.

The user department shall prepare the URS for the new equipment, utility and system considering the principles, requirements and precautions that should be followed to safeguard product quality, EHS objectives, GMP and GEP on site.

The contents of URS shall include the following but not limited to;

- Name of Machine
- Purpose of machine
- Size/capacity
- MOC
- Change parts
- Working condition requirements
- Electrical requirements
- Utility requirements
- Control panel
- Display requirements
- Software requirements
- cGMP requirements
- Safety requirements
- Document requirements

II. Design Qualification

The DQ confirms that the design of the equipment is appropriate and meets with the URS. DQ shall be done based on the product/process requirements. The compliance of the design with cGMP shall be demonstrated and documented during design review.¹¹

Design qualification is combination of user requirement specification, design specification, and functional requirement specification

Design Qualification is used when a design that has been developed from the URS is reviewed and commented on by competent persons to ensure that the designed equipment, while built properly, it will satisfy all the detailed specified requirements. It can also be used to review of the shelf item to ensure it will satisfy the URS.

User Requirement Specifications consisting of design and functional specifications for the equipment shall be verified with the actual equipment details (design and functional) offered by the Supplier. This is called Design Qualification and this is a documentation activity and recommended to be completed before the PO is placed (if applicable).

The design qualification protocol shall be given by vendor and in case vendor does not provide the DQ document; engineering department shall prepare the DQ in coordination with user department and manufacturer / supplier in reference with URS. The DQ protocol shall be prepared for each equipment based on the quotation / proposal and technical discussions between supplier and user department.⁷ The DQ protocol must cover all the necessary diagrams, layouts, location suitability and desired special feature of components, equipment components and their specification, desired material of construction (MOC), location of control panel, electrical requirement and utility requirement. The compliance of the design with cGMP and also with the specification must be introduced and documented as per general guidance mentioned in given Qualification protocol.¹²

III. Factory Acceptance Test (FAT)

Equipment, especially if incorporating novel or complex technology, it shall be evaluated at the vendor site prior to delivery. Team from user engineering and QA shall perform the Factory Acceptance Test (FAT) at Vendor's site after fabrication of equipment and before dispatch to company site, to ensure that the equipment is build/fabricated with the required functionality as specified in URS/DQ. The FAT shall be documented in supplier's document and the contents of FAT documents shall include at least the following but limited to;

- 1) **Visual inspection of components:** This includes the verification of Dimensions, Motor, Blower specification, MOC, Valves (Size/No) and safety requirements (Alarm/Interlocks).
- 2) **Critical operational requirements:** This includes the verification of critical operations based on URS.
- 3) **Operational test (If applicable):** The critical operations shall be performed under FAT.

If equipment is identified as critical/sophisticated, FAT shall be performed depending upon the complexity of equipment.

IV. Site Acceptance Test (SAT)

SAT shall be applicable for the major customized machines. Vendor shall provide the SAT documents and if vendor does not provide the SAT protocol, In-House protocol shall be prepared by engineering department in coordination with user. SAT shall be performed by relevant subject matter experts of different functional areas like Engineering, Production, QA & QC at company site, after the receipt of equipment with the following objectives;

- 1) To inspect and ensure that the equipment received at company site is in good state and no components are damaged during transportation.
- 2) To provide documented evidence that the equipment received at company site is in good state and meeting as designed.
 - The main contents of SAT shall include, but is not limited to, the following;
 - 1) Equipment details
 - 2) Receipt of consignment
 - 3) Inspection of equipment consignment
 - 4) Inspection of equipment
 - 5) Inspection of major components

- 6) Accessories/Spare parts
- 7) Master documents- Maintenance/User's manual/Calibration certificate.

V. Installation Qualification

Documented verification that all aspects of a system, facility, utility or equipment that can affect product quality are installed or modified, comply with the approved design and the manufacturer's recommendations.¹³ IQ applies to a new, pre-owned or an existing onsite but not to already existing qualified instrument.¹⁴ The activities and documentation associated to IQ are as follows:

IQ shall be performed on new or modified equipment, for establishing the evidence that all key aspects of the process equipment and ancillary system installation as per the requirements of Company's approved specification and recommendations.

The main contents of IQ include but are not limited to, the following:

- Physical verification of equipment
- Manufacturer specification verification
- Purchase order specifications
- Piping and installation drawing (P&ID)
- Construction and installation
- Component verification
- Test equipment's instrument calibration
- Critical component calibration requirements
- Required spare parts
- Cleaning/Passivation
- Weld inspection
- System installation compliance to cGMP
- Change/Replacement spare parts
- Physical verification of area
- Verification of Material of construction
- Identification of instrument to be calibrated
- Verification of utilities
- Verification of safety features
- Identification/preparation of SOPs for operation, cleaning, calibration and Preventive maintenance.

IQ protocol shall be provided by vendor and shall be reviewed and approved from user and engineering department. After approval, QA department shall authorize the protocol for further execution.

After completion of an execution by vendor, provided documents review of executed protocol, raw data shall be done by user, engineering and QA. After successful completion of the protocol activity, initiate the post approval to close the document.

In case vendor is not providing the installation qualification document, user department shall prepare the in house protocol in coordination with engineering and QA. After successful completion of the protocol activity, all instrument associated with the equipment shall be identified and shall add in the master list of instrument as applicable.

➤ Installation Qualification to be re-qualified in case of:

- Transferring of the equipment from one location to another (excluding portable type).
- In case of major changes or to address the qualification of newly added component

VI. Operational Qualification

After successful completion of the IQ protocol activity, operational qualification shall be performed to verify that the equipment operates in accordance with design specifications, manufacturer recommendations and meeting the operational cGMP requirements.

Documented verification that all angles and functions of a system, facility, utility or equipment that can affect quality of product, operate properly within all anticipated operating ranges as required by the process, capability, procedures and design specification.

The OQ phase focused on following parameters:

All testing equipment shall be identified and calibrated before use. Test methods shall be authorized; implemented and resulting data shall be collected and evaluated. It is important at this stage to assure all operational test data conforms to predetermined acceptance criteria for the studies undertaken.

OQ protocol shall be provided by the vendor and shall be reviewed and approved from the user and engineering department. After approval QA department shall authorize the protocol for further execution.

After completion of an execution by vendor, provided documents review of executed protocol, raw data shall be done by user, engineering and QA. After successful completion of the protocol activity, initiate the post approval to close the document.

The OQ shall be performed in accordance with the pre-approved written protocol.

➤ The contents of OQ shall include at least the following but not limited to;

- Calibration review of critical instruments/components.
- Calibration review of reference test equipment/instrument.
- Methodology for operational procedure to includes the tests that have been developed from knowledge of processes, systems and equipment to ensure the system is operating as designed.
- Test including the conditions encompassing upper and lower operating limits, and/or "worst condition".
- Testing of safety features and alarm testing
- Power failure verification
- Computer system validation
- Verification of SOP
- Verification of PM
- Testing to concerned persons

OQ shall be performed as a combined Installation/operational qualification i.e. IOQ and IOPQ. If IOPQ needs to be performed same format shall be used for protocol preparation and PQ test shall be incorporated as required.

The completion of a successful OQ shall allow the finalization of SOP & cleaning procedures, operator training and PM requirement.

➤ **Operational Qualification to be re-qualified in case of:**

- Transfer of the equipment from one location to another (excluding portable type).
- In case of major changes or to address the qualification of newly added component, RQ shall be required.

VII. Performance Qualification

After successful completion of the IQ protocol activity, operational qualification shall be performed to verify that the equipment or equipment under anticipated conditions, providing the consistent performance to produces a product, which meets all predetermined requirements.

Documented verification that all aspects of a system, facility, utility or equipment that can affect product quality produce the required output over an extended period under typical operating conditions and interferences.

PQ shall be carried out in accordance with a preapproved written protocol. The specific PQ attributes developed from the finished product specifications, R&D data, cGMP requirements and other specific documentation shall be verified along with the acceptance criteria.

SOP of "operation and cleaning of equipment" and "PM procedure" must be approved prior to start the PQ.

The data generated under PQ shall not be considered for routine production and for human use. It shall be restricted to the qualification purpose only.

The PQ test shall be considered successful if all the test results are meeting the acceptance criteria.

If vendor provided PQ protocol is available then it shall be reviewed and approved from user and engineering department. After approval QA department shall authorized the protocol for further execution.

After completion of the execution of vendor provided documents review of executed protocol, raw data shall be done by user, engineering and QA. After successful completion of the protocol activity, initiate the post approval to close the document.

In case if vendor is not providing the PQ document, user department shall prepare the in house protocol in coordination with engineering department and QA.

PQ must include the following but not limited to;

- Prerequisite for PQ
- Tests, with production materials, qualified substitutes or simulated products that have been developed from knowledge of the process and the equipment.
- Tests including the condition or set of conditions encompassing upper and lower operating limits (worst case).
- Qualification done or documented by the equipment supplier shall be also accepted after reviewing it for adequacy and approving by the responsible personnel from company.
- After successful completion of PQ, QA shall release the equipment for routine operation.

During PQ, equipment shall be qualified for the entire operating range as per DQ. However, PQ can also be performed simultaneously with process validation of product to cover the complete range of product manufactured. For such qualification, summary report of validation activity shall be prepared and it report shall attached with qualification documents.¹⁵

➤ **Performance Qualification to be re-qualified in case of:**

- Replacement/ modifications of existing equipment/ component in the equipment with a new one, which can have a direct impact on the performance of the equipment.
- Any major changes to the existing Equipment/System, which can affect the overall performance of the equipment.
- If system founds malfunctioning during performance qualification.

VIII. Re-Qualification

- Re-Qualification is an activity involving complete or portions of 'elements' of qualification activities, like IQ, OQ and PQ.¹⁶

➤ **Re-Qualification carried out for following reasons:**

- To overcome deficiencies observed in an qualification
- Need for any new additions in qualification tests
- To qualify modifications done in the equipment or a process involving an equipment

Failure

- Findings/Recommendations from Inspections/Audits/PQR, etc.
- Inputs from Preventive Maintenance/Calibration Program
- Equipment Up-gradation
- To testing of the elements impacted by the changes or qualification parameters found to be deficient, all critical components of the equipment verified for functionality during Re-Qualification.

➤ **Risk Assessment/ Risk Management:**

Qualification is to accomplish written evidence that processes and equipment work within their specifications to get quality products. Working with processes and equipment, there are always risks that may or may not be acceptable.¹⁷ To ensure about the product quality, a crisis evaluation or quality risk management shall be performed.

- To assess the potential critical and non-critical points of the process or equipment.
- **Critical Equipments:** These are the equipments that comes into direct contact with product which may affect on the SISPQ (Safety, Identity, Strength, Purity & Quality) of products. Critical equipment often impacts safety, regulatory conformity, cost, or operational procedures output.¹⁸

E.g.; Laminar air flow, PH meter, HPLC, PCR, Homogeniser, Fermenter, Downstream chromatographic system (AKTA) etc.

- **Non-critical Equipments:** These are the equipments that do not comes into direct contact with product and

not affecting SISPQ (Safety, Identity, Strength, Purity & Quality) of products.

E.g.; Refrigerator, Centrifuge, Weighing balance, CO₂ incubator, etc.

- Using three dimensional risk factors like severity, probability and detectability, risk shall be quantified. A risk probability number (RPN), is calculated based on these three factors.
- Risk priority number (RPN) assessment is a function, the severity of the effect of failure, the probability of occurrence, and the ease of detection for each failure mode. RPN is calculated as per the formula below,

$$RPN=S \times O \times D$$

Where,

S - the severity of the effect of failure,

O - the probability of occurrence, and

D - the ease of detection.

In the choice of an action against failure modes *RPN* may not have any role, but it will help in indicating the threshold values for determining the areas of greatest concentration. In other words, a failure mode with a high *RPN* number should have the highest priority in the analysis and corrective action.

- Risk Based approach Impact Assessment should be focusing on product impact. Every Equipment need to be classified between Direct impact, Indirect Impact, or No Impact to the product.

➤ Purpose of the equipment impact Risk Assessment

- Determine Equipment criticality based on impact to Product safety.
- Determine level of qualification required for new Direct Impact Equipment.
- Determine level of qualification required when changes are made in qualified Equipment.

➤ Form FDA 483 issuance related to Equipment Qualification:

A Form 483, also called "Inspectional Observations," is a list of conditions or practices that indicate a potential violation of the FDA's requirements.¹⁹ The FDA has authority to inspect factories that manufacture products regulated by the FDA.²⁰ **FDA inspectors can come in to firm and can inspect any given facility at any time**, and they essentially write down their observations on a form called Form FDA 483s. The observations are listed in descending order of importance for the corrections. This is not an all-inclusive list, but more of a snapshot of possible issues noted at the site.²¹⁻²² There are multiple examples of issuance of form 483 related to qualification of equipments. Hence there is a need of robustness and ruggedness in analytical procedure while performing the process of equipment qualification.

There are few examples of observations in form 483 related to equipment qualification:

E.g.; Observation: Form 483 is issued by Cipla Ltd., Salcette Goa, India on the date of 25/01/2018

As per FDA, Assets used in the process of manufacture, processing, packing or holding of drug products is not of

appropriate design to facilitate operating procedure for its intended use.

Specifically, you do not always adequately qualify/requalify equipment used for the manufacturing of drug products such as Capsules in that:

- a) Company not have an approved protocol for equipment requalification of their Encapsulation machine moved from Unit to Unit with acceptance criteria for each critical variable prior to initiation of performance requalification operations.
- b) Company not have data showing their Encapsulation machine which is capable for successful operating procedure over the full range of their acceptance criteria for critical variables.²³

Conclusion:

This article presents an approach to life cycle management of equipment & it's qualification. In a risk based life cycle management approach, it covers the entire life cycle for the various stages of specification, design, manufacture installation, commissioning, qualification, operation and maintenance of the equipment. The success of equipment qualification is mainly depends on the good engineering practices followed in the organization. Appropriate documentation of the qualification program is very important as lack of documented evidence does not give any meaning of qualification. A relationship between user & supplier by building program, the redundancies can be reduced and provide significant advantage for both parties.

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➤ Abbreviations:

- E.g. - Example
- SOP - Standard Operating Procedure
- SYS- System
- URS - User Requirement Specification
- DQ - Design Qualification
- FAT - Factory Acceptance Test
- SAT - Site Acceptance Test
- IQ - Installation Qualification
- OQ - Operational Qualification
- PQ - Performance Qualification
- RQ - Requalification
- SISPQ - Safety, Identity, Strength, purity and Quality
- RPN - Risk Priority Number

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