Calibration and Validation in Pharmaceuticals

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Calibration

- **Definition:**

  A set of operations to establish the relationship between values of quantities indicated by measuring instruments and systems under specified conditions.

Calibration

- Calibration of instruments is absolutely **essential for correct operations** and for **checking their performances** against known standards.
- It is a process that **assigns values to the response of an instrument relative to reference standards** or to a designated measurement process.
- Calibration aims **to eliminate or reduce bias in the measurement system** relative to the reference base in accordance to a specific algorithm.

Purpose of calibration

- To make sure that **the readings of equipment or instruments are consistent with other measurements and display the correct readings every single time**
- To determine the **accuracy, precision, reliability and deviation of the measurements** produced by all the instruments
- To establish the reliability of the instrument being used and whether it can be trusted to deliver repeatable results each time
- Ensuring that the industry standards, quality assurance benchmarks such as current good manufacturing practice (cGMP) and government regulations are adhered to.

BENEFITS OF CALIBRATION

- Calibration is a process of **testing and comparing the errors of measurement instruments** and **processes with accepted standards** in order to detect and correct variations in performance.
- It determines whether measurements made before the calibration were valid.
- It gives confidence that the future measurements will be accurate.
- It assures consistency and compatibility with those made elsewhere.
- It leads to repeatability and reproducibility assessments of the instruments and processes.

BENEFITS OF CALIBRATION

- Without calibration, the product quality may be poor, thus opening up legal challenges and high failure rates of the products, thus increasing costs.
- It **increases efficiency** by ensuring that measurements are correct.
- In the process industry, calibration of devices **assures that the processes are well controlled and that the products meet expected specifications.**
- It leads to documentation of performance of instruments and processes to meet quality standards such as ISO 9000, ISO 1400, and QS-9000.

BENEFITS OF CALIBRATION

- Frequent calibrations can provide a **graphical view of the equipment uncertainty over time, thus leading to reliability of performance**. This gives in-service life analysis; hence, depreciation and replacements can be predicted in an informed manner.

- **Measurements made within international standards promotes global acceptance, thus increasing competitiveness.**

- It helps convenient implementation of related regulations and legislation that govern the use of equipment in a particular application

Objectives of calibration

- **Objectives —**

a) It checks the **accuracy of an instrument**

b) It determines the **traceability of the measurement**

Steps of successful calibration procedure

- Selection of an appropriate **reference standard** with known values covering the range of interest.
- Application of the instrument or the reference standard
- Conducting **calibration curves** (i.e. least-squares fit) to establish the relationship between the measured and known values of the reference standard.
- **Correction of measurements** using calibration curves.
- Preparation of the **appropriate documentation** of the calibration procedure, results, analysis, and interpretation of results for the client.

LABELS USED IN CALIBRATION

- All measurement equipments shall be securely and durably labeled.
- The labels should clearly indicate the name of the calibration laboratory, date of calibration, due date, usage equivalent, and the authorized officer.
- Information on the label must be clear and durable under reasonable use and storage conditions.
- When it is impractical to affix a label directly on an item, the label may be affixed to the instrument container.
- Temperature-resistant seals may be used when necessary.
- Functional labels should contain reference standards.

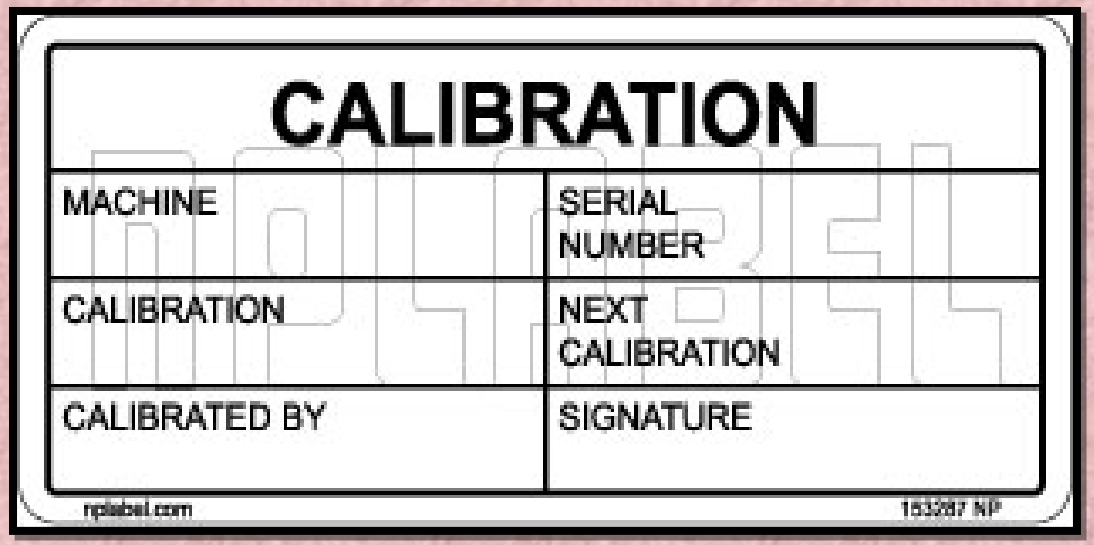
LABELS USED IN CALIBRATION

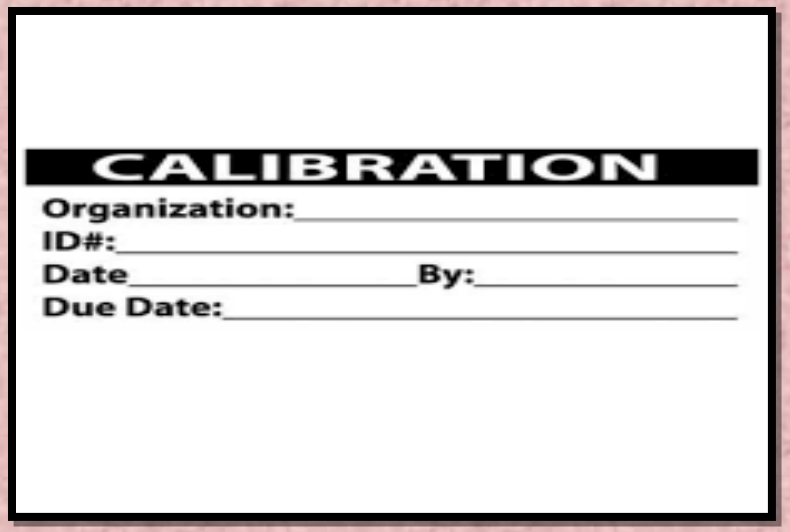
- **Information on the label must contain-**
- Date- last calibrated and next calibration date
- Probe or sensor type
- Information on organization and personnel who conducted the calibration
- Range of measurement and correction factors for each range
- Efficiency of the instrument, and so on.

LABELS USED IN CALIBRATION

- **In addition, the label must contain clear idea about calibration status-**
- calibrate before use
- not calibrated
- obsolete
- do not use
- does not conform
- out of calibration
- reference only
- uncalibrated instrument
- user-calibrated instrument, and so on.

LABELS USED IN CALIBRATION





When should the measuring instruments be calibrated?

- The frequency of calibrating the measuring instruments depends on a number of different factors. The following is a guide outlining when instruments need to be calibrated as a part of GMP:
- As soon as you bring in a new instrument, you should calibrate it before you test it out.
- Before and after you take critical measurements
- After any instance of electrical or mechanical shock or a similar event that includes a fall, bump, etc.

When should the measuring instruments be calibrated?

- When you suspect that the **accuracy of measurements being produced is questionable**
- If there were **any repairs or re-qualifications** of the instrument
- As per included as part of a **calibration schedule**
- Depending on the **task and processes as some require calibration to be conducted** before the work starts
- According to the **manufacturer's recommendation**

Validation

- Validation is an integral part of quality assurance; it involves the **systematic study of systems, facilities and processes** aimed at **determining whether they perform their intended functions adequately and consistently as specified**.
- A validated process is one which has been demonstrated to provide a **high degree of assurance that uniform batches will be produced that meet the required specifications** and has therefore been formally approved.
- Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control.

Validation

- **Definition as per USFDA:** The process validation is the establishment of evidence to ensure a high degree of certainty for a specified process to consistently produce a product that meets its predefined specifications and documented quality characteristic.
- **Definition as per ICH:** Process validation represents the means of ensuring and providing supporting documents specifying their design parameters by whom they are capable repeatedly and reliably produce a finished product of the required quality.

Validation

- **Scope of validation:**
- Validation requires an appropriate and sufficient infrastructure including: –
- Organization, documentation, personnel and finances
- Involvement of management and quality assurance personnel
- Personnel with appropriate qualifications and experience
- Extensive preparation and planning before validation is performed

Validation

- **Validation should be performed:** for new premises, equipment, utilities and systems, and processes and procedures; – at periodic intervals; and – when major changes have been made.
- Validation in accordance with written protocols.
- Validation over a period of time, e.g. at least three consecutive batches (full production scale) to demonstrate consistency. (Worst case situations should be considered.)
- Significant changes (facilities, equipment, processes) - should be validated
- Risk assessment approach used to determine the scope and extent of validation needed

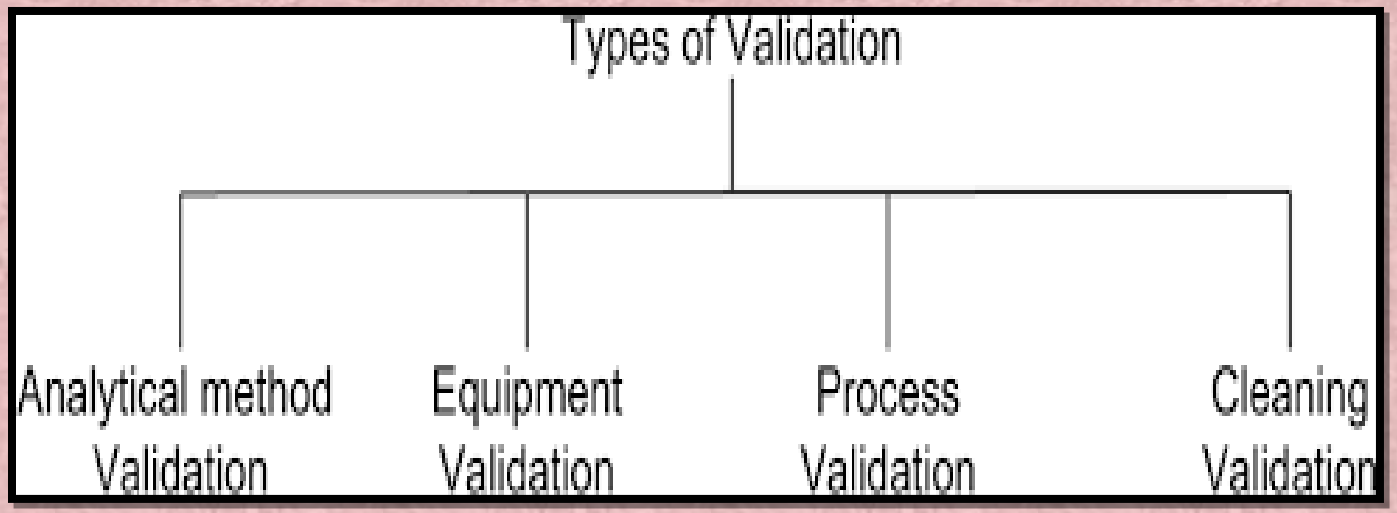
Validation

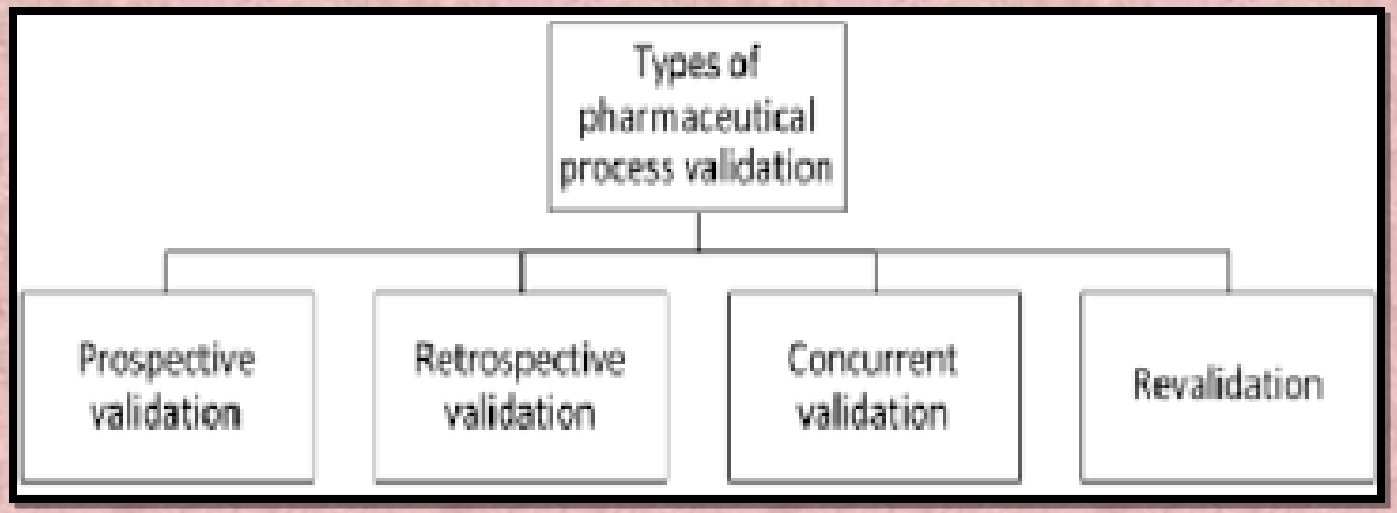
- **Importance of Validation :**
- Assurance of quality
- Time bound
- Process optimization
- Reduction of quality cost.
- Minimal batch failures, improved efficiently and productivity.
- Reduction in rejections.
- Increased output.

Validation

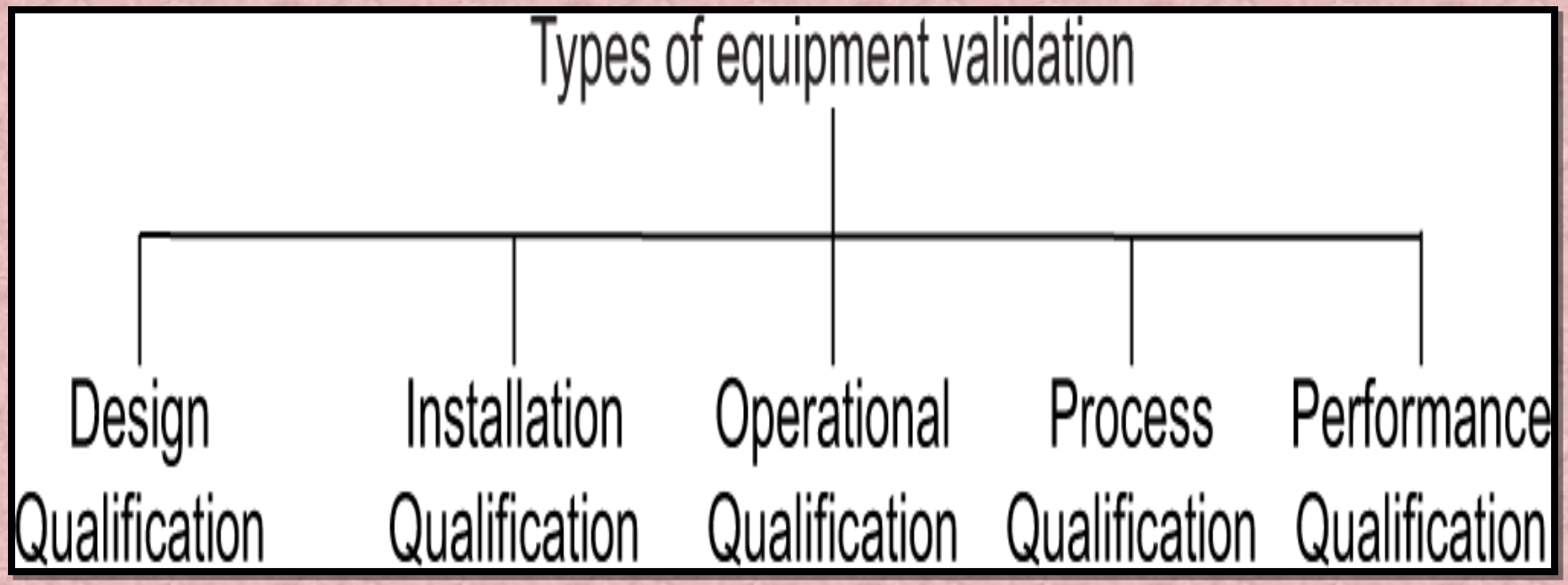
- **Importance of Validation :**
- Fewer complaints about process related failures.
- Reduced testing in process and in finished goods.
- More rapid and reliable start-up of new equipments
- Easier maintenance of equipment.
- Improved employee awareness of processes.
- More rapid automation.
- Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

Validation


Types of Validation
Analytical method Validation
Equipment Validation
Process Validation
Cleaning Validation


Types of pharmaceutical process validation
Prospective validation
Retrospective validation
Concurrent validation
Revalidation

Validation


Types of equipment validation
Design Qualification
Installation Qualification
Operational Qualification
Process Qualification
Performance Qualification

Qualification (Validation of Equipments)

- It refers to **activities undertaken to demonstrate that utilities and equipment are suitable** for their intended use and perform properly.
- It is the action of proving that any equipment or process **works correctly and consistently** and produces the expected results.
- It is the action of proving and documenting that equipment or ancillary systems are **properly installed, work correctly, and actually lead to the expected results**.

Qualification

- Qualification of analytical instrument is essential for **accurate and precise measurement of analytical data.** If the instrumentation is not qualified, ensuring that the results indicated are trustworthy, all other work based upon the use of that instrumentation is suspect.
- Qualification of instruments is not a single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into 4 phases of qualification.
- These phases are - Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ)

Design Qualification (DQ)

- It is the documented verification that the proposed **design** of the facilities, systems and equipment is **suitable for the intended purpose.**
- DQ should be performed when new equipment is being purchased, or when existing equipment is being used for a new application.
- DQ serves as the precursor to defining the equipment Installation Qualification (IQ) and OQ protocols.
- The purpose is to ensure that all the requirements for the final systems have been clearly defined at the start.
- In other words, “Has it been designed and selected correctly?”

Design Qualification (DQ)

- **DQ check items:**
- GMPs and regulatory requirements
- Performance criteria
- Reliability and efficiency
- Commissioning requirements
- Construct ability and installation of equipment
- Safety and environment impact
- Description of the intended use of the equipment
- Preliminary selection of the supplier
- Final selection of the equipment

Installation Qualification (IQ)

- It is documented evidence that the premises, supporting utilities, the equipment have been **built and installed in compliance with design specifications**
- It verifies that the equipment has been installed in accordance with manufacturers recommendation in a proper manner and placed in an environment suitable for its intended purpose.
- It involves the co-ordinate efforts of the vendor, the operating department and the project team.

Installation Qualification (IQ)

- The purpose of I.Q is to check the installation site/environment, confirms equipment specifications and verifies the condition of installed equipment; and also to ensure that all aspects (static attributes) of the facility or equipment are installed correctly and comply with the original design. In other words, “Has it been **built or installed correctly?”**
- In I.Q, connect each unit (Electrical system, Flow line system) and confirm that the **connections are correct.**

Installation Qualification (IQ)

- **IQ check items:**
- Equipment design features (i.e. material of construction cleanability, etc.)
- Installation conditions (wiring, utility, functionality, etc.)
- Calibration, preventative maintenance, cleaning schedules.
- Supplier documentation, prints, drawings and manuals.
- Software documented, Spare parts list, Safety features.
- Environmental conditions (such as clean room requirements, temperature, and humidity).
- Any problems identified in I.Q must be investigated and appropriate actions must be taken. All such actions must be documented and approved by higher authority.

Operational Qualification (OQ)

- It refers to establishing by objective evidence process control limits and action levels which result in product that all pre-determined requirements.
- OQ is the process of demonstrating that an instrument will function according to its operational specification in the selected environment.
- The purpose is to ensure that all the dynamic attributes comply with the original design. In other words, “Does it work correctly?”
- Prior to implementing O.Q, check the system configuration, determine the items to be evaluated and record them in O.Q record and have them approved.

Operational Qualification (OQ)

- **OQ check items:**
- Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- Software parameters, Raw material specifications
- Process operating procedures, Material handling requirements.
- Process change control.
- Training.

Operational Qualification (OQ)

- **OQ check items:**
- Potential failure modes, action levels and worst-case conditions.
- The use of statistically valid techniques such as screening experiments to optimize the process can be used during this phase.
- Any problems identified in O.Q must be investigated and appropriate actions must be taken.
- All such actions must be documented and approved by higher authority.

Performance qualification (PQ)

- After the IQ and OQ have been performed, the instrument's continued suitability for its intended use is proved through performance qualification.
- It refers to establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.
- PQ should always be performed under conditions that are similar to routine sample analysis. PQ should be performed on a daily basis or whenever the equipment is being used.

Performance qualification (PQ)

- **PQ considerations include:**
- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability.

Performance qualification (PQ)

- The objective is to ensure that the **instrument is performing within specified limits.** The PQ represents the final qualification of equipment or system.
- It is used to establish and or confirm;-
- Definition of performance criteria and test procedures.
- Selection of critical parameters, with pre-defined specifications.
- Determination of the test intervals, e.g., (a) - Everyday. (b) - Every time the system is used. (c) - Before, between and after a series of runs.
- Define corrective actions on what to do if the system does not meet the established criteria.

Re – Qualification

- **Modification to, or relocation of equipment** should follow satisfactory review and authorization of the documented change proposal through the change control procedure.
- This formal review should include consideration of re-qualification of the equipment.
- Minor changes or changes having no direct impact on final or in- process product quality should be handled through the documentation system of the preventive maintenance program.

CALIBRATION v/s VALIDATION

- Calibration and validation are two processes in manufacturing to guarantee **the quality of the product** or related apparatus.

- With the calibration, the **measurements are compared with an accepted reference measurement**, to assure the considered measurements comply with the requirements.

- With the validation, the **performance, quality, and other operating parameters of a system are tested to verify that they comply with the requirements.**

CALIBRATION v/s VALIDATION

- Calibration is a demonstration that, a particular Instrument or device produces results within specified limits by comparisons with those produced by a reference or traceable standard over an appropriate range of measurements.
- In calibration performance of an instrument or device is comparing against a reference standard.

- Validation is a documented program that provides high degree of assurance that a specific process, equipment, method or system consistently produces a result meeting pre-determined acceptance criteria.
- No such reference standards are using in validation program.

CALIBRATION v/s VALIDATION

- Calibration ensures that instrument or measuring devices producing accurate results.
- Shall be performed periodically, to identify the ‘drift’ of the measuring device or equipment and make them accurate.
- Shall be performed as per calibration SOP.

- Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced).
- No such requirements. Shall be performed when changes or modifications happen to the existing system or once revalidation period is reached.
- Shall be performed as per validation protocol.

Thank you..