Unit-5

Calibration & Validation :

Calibration -

"Calibration of an instrument is the process of determining its accuracy. The process involves obtaining a reading from the instrument & measuring its variation from the reading obtained from a standard instrument."

(Or)

"Calibration is defined as the process of issuing data including a report or certificate of calibration that ensures an end user of a product's conformance with its specification."

- It is important for justifying the processes of Qualification & validation.

- Calibration achieves & objectives -
  (i) It checks the accuracy of an instrument.
  (iii) It determines the traceabilities of the measurement.

Scope / purpose of calibration -

Calibration is primarily done to achieve 5 main purposes which are :

(a) To make sure that the reading of equipment or instrument are consistent with other measurement & display the correct reading every single time.

(b) To determine the accuracy, precision, reliability & deviation of the measurement produced by all the instrument.

(c) To establish the reliability of the instrument being used & whether it can be trusted to deliver repeatable results each time.

(d) To map the 'drift' as documented. Instruments have a tendency to produce inaccurate measurements over a period of time, following repeated use.

(e) Ensuring that the industry Standards, Q.A. benchmarks such as eCGMP & government regulation are adhered to.

Instrument Calibration -

"Instrument Calibration can be defined as the process of comparing the measurements made by the instruments to be calibrated against a known measurement of either standards or an instrument known to be making measurements that exceed the acceptable limits of accuracy & precision."

Usually, Calibration labs prefer a standard with 10 times the accuracy however most regulating authorization & authorities also accept a 3:1 accuracy ratio.

Frequency of Calibration -
How often you conduct instrument calibration mainly depends upon its tendency to drift from the true measurement & how it impacts the quality of the end product. Examine each instrument being used & study as a behaviour. Based on this information, you can design a calibration schedule for each instrument.
The interval between calibration may vary as:
(a) weekly
(b) Monthly or Bi-monthly.
(c) Quaterly, semi-annually or annually.
(d) After every heavy usage of the instrument.

Commonly used Calibration Methods & Procedure -
There are different ways that are used to calibrate an instrument:

(i) Standard Calibration : This method is mostly preferred for calibrating instruments that are non-critical to quality or as not required for accreditation & license purpose. Use traceable Standards & documents its performance.

(ii) Calibration with data : Procedures for calibration with data are similar to that of accredited calibration. The only exception being that these procedures are not accredited to the ISO Standards.

(iii) ISO 17025 Accredited Calibration : This has to be the strictest method of calibration. Generally, it requires a measurement report which has the details of the measurements that are made against a standard of 'as found' (Before calibration is started) & 'as left' (once the calibration is completed). If the calibration is done by a calibration service provider, they must issue a certificate of the same.

Importance of Regular Calibration -

- Calibration is responsible for defining the accuracy of any measurement & its quality that is recorded by an instrument.
- When you regularly calibrate your equipment, you can eliminate the drift at its budding stage instead of allowing it to grow till it affects the measurement in significants ways.
- Calibration helps in quantifying & controlling errors & uncertainties within various measurements processes to an acceptable level.
- It helps in improving the accuracy of the measuring device, which in turns improves the quality of the end product.
- In short, regular calibration allows pharmaceutical companies to have confidence in their results which they can record, monitor, control.

Qualification -

It is the action of proving & documenting that equipments or ancillary systems are properly installed, work correctly & actually lead to the expected results.

Qualification is a part of validation, but the individual qualification steps alone cannot constitute process validation.

Qualification of instruments is not single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into 4 phases of qualification, they are:

(i) Design Qualification:

Design qualification (DQ) is the specifications a manufacturer uses to describe a device or equipment.

In other words, "How it been designed & selected correctly".

DQ checks for:-

- Cgmp & regulatory requirements.
- Performance criteria
- Reliability & efficiency
- Commissioning requirements.
- Construction & installation of equipment.

- Safety & environment impact.
- Description of the intended use of the equipment.
- Preliminary selection of the supplier.
- Final selection of equipment.

(ii) Instalation Qualification (IQ):
IQ is a documented collection of activities required for installing an instrument in the user's environment.

In other words, "Has it been built or installed correctly".

IQ check items:
- Equipment design features.
- Installation conditions.
- Calibration, preventive maintenance, cleaning schedules
- Safety features.
- Supplier documentation, prints, drawing & manuals.
- Software documented.
- Spare parts list.
- Environmental condition.
- Any problems identified in IQ must be investigated & appropriate action must be taken.

(iii) Operational Qualification (OQ):
OQ is the process of demonstrating that an instrument will function according to its operational specification in the selected environment

In other words, "Does it work correctly".

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OQ check items :-

- Process control limits.
- Software parameters.
- Raw material specifications.
- Process operating procedures.
- Material handling requirement.
- Process change control.
- Training.
- Potential failure modes, action levels & worst-case condition
- Any problems identified in OQ must be investigated & appropriate actions must be taken. All such actions must be documented & approved by higher authority.

(iii) Performance Qualification :-

PQ testing is conducted after performing the IQ & OQ test under the actual running condition across the expected working range.

PQ should always be performed under conditions that are similar to routine sample analysis.
PQ should be performed on a daily basis.

PQ consideration include :-

- Actual product & process parameters & procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability.
- The objective of OQ is to ensure that the instrument is performing within specified limits. The PQ represents the final qualification of equipment.

It is used to establish or confirm :-

- Definition of performance criteria & test procedure.
- Selection of critical parameters, with predefined specification.
- Determination of the test interval.

eg - (a) Everyday
(b) Every time the system is used.
(c) Before, between & after a series of runs.

- Define corrective actions on what to do if the system does not meet the established criteria.

Validation -

According to ISO,

"validation is the confirmation by examination & the provision of objective evidence that the particular requirements for a specific intended use are fulfilled."

According to US FDA,

"validation is the establishment of documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification & quality attributes".

Principles -

(1) Execution of validation should be compliance with regulatory expectation.
(2) Quality cannot be inspected or tested into the

product.

(3) Quality, safety, efficacy should be designed & built into the product.

(4) Quality risk management principles should be applied in determining the need, scope & extent of validation.

(5) On-going review should be ensure that the validated state is maintained & opportunities for continuing improvement are identified.

Scope -

- Validation requires an appropriate & sufficient infrastructure including organization, documentation, personnel & finances.
- Involvement of management & quality assurance personnel.
- Personnel with appropriate qualification & experience.
- Extensive prep" & planning before validation is performed.
- Validation should be performed:
  → for new premises, equipment, utilities & system & processes & procedures.
  → At periodic intervals
  → when major changes have been made.
- Validation in accordance with written protocols.
- Validation over a period of time.
- Significant changes should be validated.
- Risk assessment approach used to determined the scope & extent of validation needed.

Importance -

- Assurance of quality.
- Time band.
- Process optimization.
- Reduction of quality cost.
- Minimal batches failures, improved efficiently & productivity.
- Reduction in rejection.
- Increased output.
- Fewer complaints about process related fa[illegible].
- Reduced testing in process & in finished goods
- More rapid & reliable start-up of new equipment's.
- Easier maintenance of equipment.
- Improved employee awareness of processes.
- More rapid automation.
- Government regulation.

Types of validation -

(i) Prospective validation :

This validation is conducted before distribution of the new product & involves establishing a documented evidence of what a system does or what it is to be intended, based upon a plan.

(ii) Retrospective validation :

This validation is conducted in an already distributed product, based on the data collected on production, testing & control.

It involves establishing a documented evidence of what a system does or what is intended to do based upon the review & analysis of the historical information.

(iii) Concurrent Validation :
This validation involves establishing a documented evidence of what a system does or what it is intended to do, based upon the information generated during implementation of the system.

(iv) Re-validation :
A validated process should be re-validated whenever there are changes in packaging, formulation, equipments or processes which could adversely affect the product effectiveness.

Validation Master Plan -
- The validation master plan should provide an overview of the entire validation operation, its organizational structure & its content & planning.
- The main elements of it being them list / inventory of the item to be validated & the planning schedule.
- All validation activities relating to critical technical operation, relevant to product & process controls with in a firm should be included in the validation master plan.

- It should comprises all prospective, concurrent & retrospective validation as well as re-validation.
- The validation master plan should be a summary document & should therefore be brief, concise & clear.
- It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's & validation protocols & reports.

The format & content should include:

- Introduction: validation policy, scope, location & schedule.
- Organizational structure: Personnel responsibilities.
- Plant/Process/product description: Rational for inclusion or exclusion & extent of validation.
- Specific process considerations that are critical & those requiring extra attention.
- Key acceptance criteria.
- Documentation format.
- Reference to the required SOPs.
- Time points of each validation project & sub-project.
- List of products/processes/system to be validated, summarized in a matrix format, validation approach.
- Re-validation activities, actual status & future planning.

Calibration of pH Meter -

pH Meter -

An instrument that measures the H^+ ion conc^n (pH) of a sol^n using an ion sensitive electrode which will ideally respond to one specific ion in this case (H^+)."

"The pH of a sol^n is the negative logarithm of the H^+ ion conc^n".

A typical modern pH meter has a glass & reference electrode in one tube.

How does a pH meter measure H^+ conc^n -

The pH meter has two electrodes in one tube, glass & reference electrode. A saturated KCl & HCl sol^n is contained in a tube which is inside of an outer tube that will have contact with the sol^n to be measured. The outer tube has a double glass bulb with NA^+ which makes an ion specific electrode. When measuring the pH of a sol^n, a salt bridge forms. The NA^+ ion, not H^+, crosses the glass membrane of the pH electrode & allows for a change in free energy which is measured by the pH meter as the conc^n of H^+.

Calibrating a pH meter -

- Make sure the meter is in pH mode.
- For a 3 point calibration, use high pH (basic) gives negative mV value, pH 7.0 (neutral) give 0 mV value., low pH (acidic) gives greater mV value.
- Before calibration, rinse probe thoroughly with de-ionized water or a rinse sol^{n}.
- Immerse the end of the probe completely in the calibration sol^{n}.
- Stir the probe gently to create a homogenous sample.

Measuring the pH of a sol^{n} -

- Always rinse electrodes with de-ionized water prior to placing in a sol^{n} for pH measurement.
- Allow meter to stabilize for 30 seconds or mins, then read.
- Remove electrodes & rinse with de-ionized water.
- The pH bulb should always be stored wet preferably in pH 4.0 buffer with 1/100 KCl.
- other buffers or tap water can be used for storage.

Qualification of U.V - visible spectrophotometer -

UV - visible Spectrophotometer -

Uv visible Spectroscopy is concerned with ultra-violet & visible regions which ranges from 200 - 780 nm.

Instauation procedure -

While the Uv instrument was shipped after the precise adjustment & inspection at the factory, it is recommended to install according to the following procedures so as to provide its optimum performance & to meet the user's demand.

Installation site -

- Room temperature during use of 15 to 35°C.
- Out of direct sunlight.
- No strong vibration or continuous weak vibration.
- No strong magnetic fields or electromagnetic fields.
- Humidity of 45 to 80 %.
- No corrosive gases or organic or inorganic gases with absorptivity in the UV range.
- Small amount of dust.

Acceptance procedures -

Item to be checked	Specification
Appearance	No Defect
No. of parts	No missing part
Rom check	latest version
Linearity of Absorbance	Bent: ± 0.002 Abs (Shock noise: ± 0.004 Abs)
Noise level	Noise width: ± 0.002 Abs (Shock noise: ± 0.004 Abs)

Accuracy of wavelength	± 0.5 nm
Repeatability of wavelength	± 0.1 nm.

Performance Qualification -

(i) **Wavelength Accuracy:**
It is defined as the deviation of the wavelength reading at an absorption band & emission band from the wavelength of the Band.

Acceptance -
- ± nm in UV range (200-380nm)
- ± nm in visible range (380-800 nm)

Three repeated scan of the same peak should be within ± 0.5 nm.

(ii) **Stray light:**
It is defined as the detected light of any wavelength that is outside the band width of the wavelength selected.

Acceptance - The transmittance of the sol" in a 1cm cell should be less than 0.01 or the absorbance value should be greater than 2.

(iii) **Resolution Power:**
The resolution of the UV - VIS Spectrometer is related to its spectral band width. The smaller the band width the finer the resolution. The SBW depends on the slit width & the dispersive power of the

monochromator.

Acceptance - The ratio of the absorbance at 269 nm & absorbance at 266 nm should be greater than 5.

(iii) Noise:

It is the measurement affects the accuracy at the both end of the absorbance scale. Photon noise from the light source affects the accuracy of the measurement leads to low absorbance.

Acceptance - The R.M.S noise should be less than 0.001 AU.

(v) Baseline flatness:

The flat baseline test demonstrates that the ability of the instrument to normalise the light intensity measurement & the special output at different wavelength throughout the special range.

Acceptance - The measurement is typically less than 0.001AU

(vi) Stability:

The lamp intensity is a function of the lamp age, temperature, fluctuation & wavelength of the measurement. These changes can lead to errors in the value of the measurements, over an extended period of time.

Acceptance - The deflection is less than 0.002 AU/hr.

(vii) Photometric accuracy :
It is determined by comparing the difference between the measured absorbance of the reference material & the established value.

Acceptance - Six replicate measurements of the 0.006 % w/v of the potassium dichromate sol" at 235, 257, 313 & 350 nm should be less than 0.5% RSD.

(viii) Linearity :
The linearity dynamic range of measurement is limited by stray light at high absorbance & by noise at low absorbance. The accuracy of the quantification of the sample depends on the precision & linearity of the measurements.

Acceptance - Correlation Coefficient $R > 0.999$.

Analytical Method Validation -
Validation of an analytical method is the process by which it is established by laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical application.

Need to validate an Analytical Method -
Analytical procedures should be validated due to regulatory requirements, good science & quality control requirement.

According to the Code of Federal Regulation (CFR) 311.165c, "the accuracy, sensitivity, specificity & reproducibility of test methods employed by the firm shall be established & documented".

The management of quality control unit ensures that the analytical methods use to release the products are properly validated for their intended use to prove the products safe for human use.

Revalidation, validated, verified of analytical methods may also be required:

- Changes in the process for synthesis of the drug substance.
- Changes in the composition of the finished product.
- Changes in the analytical procedure
- Changes in major pieces of equipment instrument.
- Extent depends on the nature of the changes.
- Evidence of 'analyst proficiency'.

Principles –

- Guidelines present information on the characteristic to be considered.
- Manufacturers to demonstrate analytical procedure is suitable for its intended purpose.
- Validate analytical methods whether they indicate stability or not.
- Validated by R & D before being transferred to the quality control unit when appropriate.

Validation Protocol -

Validation protocol should contain the following contents at a minimum:

(a) Objective of the protocol.
(b) validation parameters that will be evaluated.
(c) Acceptance criteria for all the validation parameters evaluated.
(d) Details of the experiments to be performed.
(e) Draft analytical procedures.

The data from the method validation data should be analyzed as the data are obtained & processed to ensure a smooth flow of information. If an experimental error is detected, it should be resolved as soon as possible to reduce any impact it may have on later experiments.

Types of Analytical procedures to be validated -

(1) Identification tests.
(2) Quantitative tests for impurities content.
(3) Limit test for the control of impurities.
(4) Quantitative tests of the active moiety of drug substance or drug product or other selected components in the drug product,
(5) Dissolution testing & determination of particle size.

Validation characteristics -

(a) Specificity (b) Linearity (c) Range
(d) Accuracy (e) Precision (f) Detection limit
(g) Quantitation limit (h) Robustness
(i) System suitability testing

Characteristics to Consider During Analytical Validation

Types of Analytical Procedures	Identification	Testing for Impurities	Testing for Impurities	Assay - Dissolution (Measurement only) - Contents / Potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate Precision	–	+	–	+
Specificity	+	+	+	+
Detection test	–	–[b]	+	–
Quantitation test	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

(–) → Characteristics is normally not evaluated.
(+) → Characteristics should normally be evaluated.
b → May be needed in some cases.

Steps in Analytical Method validation –

Method development plan definition
↓
Background information gathering.
↓
Laboratory method development.
↓
Generation of test procedure.
↓
Methods validation protocol definition.
↓
Laboratory methods validation.
↓
Validated test method generation.
↓
Validation report.

Validation Report -

A validation report should be included the following details:

(1) Objective & scope of the method.
(2) Types of compounds & matrix.
(3) Chemicals, reagents, reference standards, control sample preparation.
(4) Procedures for quality checks of standards & chemical used.
(5) Safety consideration
(6) Method parameters.
(7) Critical parameters indicated from robustness testing.
(8) Listing of equipment & its functional & performance requirements.
eg - Cell dimension, Baseline noise & Column temp. range
(9) Details of how the experiments were conducted & samples were prepared.
(10) Statistical procedures & representative calculation.
(11) Procedures for quality control in the routine. (eg - System stability test)
(12) Representative plots. eg - Chromatograms, Spectra, calibration curve
(13) Method acceptance limit performance data.
(14) Expected uncertainty of measurements results.
(15) Criteria for revalidation.
(16) Person who developed & initially validated the method.
(17) Summary & conclusion.

: Warehousing :

Warehouses for storage of pharmaceutical products should be efficiently laid out with all the required storage areas, goods assembly, packing, receiving & dispatch points & office & subsidiary accomodation for effectual operation of the store.

Good Warehousing Practice –

(1) Factory stock which should be received with proper documents detailing the names of product, the batch no., the no. of units of final packs of each batch, the date of dispatch & the quality control status of the batches.

(2) The stock control system must be such that only passed batches of the products are issued for distribution. Stocks should be stored, product-wise to enable quick identification & control of stock movement. Stocks should therefore be racked & stored in a manner that earlier stocks are more easily accessible than the later ones.

(3) The picking & assembling areas should be so arranged as to minimize the distance travelled by warehouse operators. Picking stocks should be located on shelves at convenient heights & with proper labels which clearly identify the products.

(4) Assembled products should be checked for accuracy of quantities & identities of product ordered. Batch details should be recorded in relevant documents.

(5) Finished products should be packed in the containers & dispatched for the transportation.

(6) The unit product should not be contaminated by other products. Vehicles which carry the final packaged Stocks of products should be so selected that:

(a) They are clean, dry & sufficiently protected from rain & other weather factors.

(b) They are free from infestation.

(c) They donot give off strong odours which may contaminate the products.

(d) They are suitable to withstand the weight of the load they carry.

Materials Management - (MM)

Material management is a scientific technique, concerned with planning, organizing & control of flow of materials form their initial purchase to destination.

MM Process -

Planning → Purchasing → Receiving → Quality control

↓

Production department ← Inventory Control ← Warehousing & Storage

↓

Distribution → Consumer.

Function of MM -

(1) Material Planning & Programming.
(2) Material Purpose.
(3) Store Keeping.
(4) Inventory Control.
(5) Quality control & inspection
(6) Material handling.

Principles in MM -

(1) Right Quality.
(2) Right Quantity.
(3) Right Price.
(4) Right Source.
(5) Right Time & place.

Objectives of MM

They are two types of objectives:

(1) Primary (2) Secondary.

→ Primary objectives -

- Reduction in Real Cost.
- Regular supply.
- Procurement of Quality materials.
- Efficient handling of materials.
- Favourable supplier relations.
- Enhancement of firm's good will.

→ Secondary objectives -

- Reciprocal relation.
- New developments.
- Economic make-or-buy.
- Product improvement.
- Inter-departmental harmony.
- Conceptions of future outlook.

Main Departments of MM -

- Material & Production planning & Control.
- Procurement.
- Inventory Control.
- Store / warehouse

Benefits of MM -

(1) Reduced cost - less waste.
(2) Improved employee awareness & efficiency
(3) Enhanced Company image & Competitiveness.
(4) A safer & tider Workplace.
(5) Increased Customer & employee Satisfaction