UNIT-5

Calibration and Validation

Analytical instruments are used for a specific analysis of drugs and pharmaceuticals. So, regular verification of their performance is made to ensure that the instruments are properly validated and calibrated.

Calibration

→ calibration of an instrument is the process of determining its accuracy. The process involves obtaining a reading from the instrument and measuring its variation from the reading obtained from a standard instrument.

→ It also involves adjusting its precision and accuracy, so that its reading comes in accordance with the established standard.

→ The instrument with known accuracy is known as standards. All the other instruments are measured against this standard.

→ The standards vary from one country to the other depending upon the type of industry.

→ Ted Byers and Bud Loftus first introduced the validation concept in mid 1970s.

→ Frequency of calibration depends on how well the equipments perform. However, re-calibration should be performed once a year, and the frequency will be much greater in more critical applications.

<u>When should instruments be calibrated ?</u>

The following is a guide outlining when instruments need to be calibrated as a part of GMP.

1) As soon as you bring in a new instrument, you should calibrate it before you test you out.
2) Before and after you take critical measurements.
3) After any instance of electrical or mechanical shock or a similar event that includes a fall, bump, etc.

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

Qualification

Qualification is a process of assurance that the specific system, premises or equipment are able to achieve the predetermined specifications and give the desired results.

→ Qualification can be considered to be a part of the validation process.

→ Qualification of instruments is not a single, continuous process; rather it results from many discrete activities, which have been grouped into the following four phases of qualification:

1) Design qualification
2) Installation qualification
3) Operational qualification
4) Performance qualification.

1) Design Qualification :- It is documented evidence that proposed design of the facilities, system and equipment is suitable for intended use.

Its purpose is to ensure that all the requirements for the final system have been clearly defined at the start.

2) Installation Qualification :- It is documented evidence that the premises, supporting utilities, the equipment have been built and installed in compliance with design specifications

Its purpose is to check the installation site/ environment and verifies the condition of installed equipment. Also to ensure that all aspect of equipment installed correctly and complies with the

original design.

3) Operational Qualification (OQ) :- It is the process of demonstrating that an instrument will function according to its operational specification in the selected environment.
Its purpose is to ensure that all the dynamic attributes comply with original design.

4) Performance Qualification (PQ) :- It is the process that ensure the process under anticipated conditions, consistently produces a product which meets all pre-determined requirements.
Its purpose is to ensure that the instrument is performing within specified limits.

Validation

Validation is "Establishing documented evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality standards.

→ Validation is a systematic approach where it is confirmed that any process in a pharmaceutical facility will operate within the specified parameters as per the requirement.

→ Validation assures that the processes will produce reliable and repeatable results within the pre-determined specifications.

→ Validation verifies whether or not a product in every pharmaceutical facility is conforming to the quality standards.

→ Validation also establishes that the facility is following the cGMP guidelines set for the industry by the authorised regulatory bodies.

Types of Validation

1) Prospective Validation :- It is establishment of documented evidence of what a system does or what it is intended to do based upon a plan. This validation is conducted prior the distribution of new product.

2) Retrospective Validation :- It is establishment of documented evidence of what a system does or what it is intended to do based upon the review and analysis of the existing information. This is conducted in a product already distributed based on accumulated data of production, testing and control.

3) Concurrent Validation :- It is establishment of documented evidence of what a system does or what it is intended to do, based upon the information generated during implemented of the system.

4) Revalidation :- Whenever there are changes in packaging, formulation, equipment or prousses which could have an impact on product effectiveness or product characteristics, there should be revalidation of the validated process.

Validation Master Plan

A Validation Master Plan (VMP) is a comprehensive document describing the applicable validation requirements for the facilility and providing a plan for meeting those requirements.

→ The VMP should be a summary document, which should be brief, concise and clear.

→ VMP is not a requirement of the FDA, but it has becomes almost an industry standard.

→ It is important to include such a document, as it sets the overall goals and limits that will be followed during validation, and can be referred to throughout the project.

→ As a reference document, the plan permits the reviewer immediately to understand the scope of the validation and so avoid misconceptions.

Calibration of pH Meter

A pH meter is an instrument used for measuring the pH, i.e., acidity or alkalinity of a solution.

→ A typical pH meter consists of special measuring probes (a glass electrode and a reference electrode) connected to an electronic meter that measures and displays the pH reading.

Procedure

1) You need a pH meter, distilled water, and special liquids called buffer solutions that have known pH values (usually pH 4, 7 and 10).
2) Start by rinsing the pH meter's probe (the part that goes into the liquid) with distilled water to clean it.
3) Dip the probe into the pH 7 buffer solution. Adjust the meter until it reads exactly 7.
4) Clean the probe and rinse it with distilled water again to avoid mixing the solutions.
5) Now, dip the probe into another buffer solution (either pH 4 or 10). Adjust the meter to match the pH of this buffer.
6) If your meter requires it, you might use a third buffer solution for even more accuracy.

Qualification of UV-Visible Spectrophotometer

UV-Visible Spectroscopy is an analytical method that measures the absorbance of ultra-violet or visible radiation through an analyte (solution).

The molecular absorption of the analyte causes the excitation of valence electrons as well as the excitation of electrons in different atomic orbitals. The technique of UV-Vis Spectroscopy is effectively used for qualitative and quantitative analysis of organic and inorganic compounds.

Here are the key steps involved in the qualification process:

1) Installation Qualification (IQ)

→ Verify that the spectrophotometer is installed correctly according to manufacturer's recommendations and specifications.

→ Check the power supply, connections, and proper grounding of the instrument.

→ Ensure that all required accessories and peripherals are installed and functioning properly.

→ Document the installation process, including photographs, equipment specifications, and the environment in which the instrument is placed.

2) Operational Qualification (OQ)

→ Verify the functionality and performance of the spectrophotometer under normal operating conditions.

→ Perform a range of predefined tests using standard reference materials and known samples to ensure the instrument meets its operational specifications.

→ Verify the instrument's software functionalities, including data acquisition, data processing and instrument control.

→ Document the test procedures, results and any deviations encountered during the operational qualification process.

3) Performance Qualification (PQ)

→ Validate the spectrophotometer's performance by testing it with a set of pre-established protocols, which are based on the intended use and the requirements of the application or industry.

→ Perform measurements on a range of known and validated samples with pre-determined specifications, concentrations, or absorbance values.

→ Compare the spectrophotometer's measurements with reference methods or instruments to confirm the accuracy and reliability of the results.

→ Evaluate parameters such as precision, accuracy, linearity, limit of detection, limit of qualification, and robustness for specific analytical applications.

→ Document the test protocols, results, and any discrepancies or deviations encountered during the performance qualification process.

4) Calibration and Verification

→ Regularly calibrate the spectrophotometer using certified reference materials to ensure accurate measurements.

→ Verify the instrument's performance at defined intervals or after major maintenance activities using traceable reference standards or calibration standards.

→ Document calibration and verification activities, including the dates, results, reference standards used and any adjustments made.

5) Maintenance and Change Control

→ Implement a preventive maintenance program to ensure the spectrophotometer's proper functioning and reliability.

→ Document maintenance activities, including cleaning procedures, replacement of consumables and routine checks on critical components.

→ Establish a change control process to manage any modifications or upgrades to the instrument, ensuring that they are properly documented, evaluated and validated.

6) Training and Documentation

→ Provide adequate training to the personnel responsible for operating and maintaining the spectrophotometer.

→ Maintain comprehensive documentation of the qualification activities, including protocols, test results, calibration records, maintenance logs, and any deviations or corrective actions taken.

→ Retain all qualification and calibration records as per regulatory requirements and internal quality management systems.

By following these steps, organisations can ensure that their UV-Visible spectrophotometers are quality, calibrated and operating within specified parameters.

General Principals of Analytical Method of Validation

The analytical methods which are used for analysing clinical samples should be validated.
Validation is the process of establishing documented evidence demonstrating that a procedure, process or an activity carried out in testing and then production maintain the required standards at all stages.

→ Validation is a process of planned and systematic study to confirm that it is suitable for intended use.
→ Analytical methods are used to test and ensure the quality, purity, and potency of drug substance.

Need to validate an Analytical Method

→ For assuring the quality of system
→ For achieving the acceptance of the product (safe for human use)
→ Mandatory requirement for registration of any pharmaceutical product.
→ Mandatory requirement for accreditation as per ISO guidelines.
→ Mandatory for regulatory requirements.

Types of analytical procedures to be validated

1) Indentification tests (it ensure the identity of analyte in sample by comparing property of sample with standard.
2) Quantitative test for impurity content
3) Limit test for control of impurity.
4) Quantitative tests of the active moeity in samples of drug substances and products.

Analytical Methods should be validated, verified or revalidated:

1) Before initial use in routine testing
2) when transferred to another laboratory.
3) when the conditions or parameters change beyond the original scope of the method.

Revalidation of analytical methods may also be required:

1) When the synthesis of the drug substance changes
2) When the composition of the finished product changes, or
3) When the analytical procedure changes.

Validation characteristics

The typical validation characteristics which should be considered are:

1) Specificity
2) Linearity
3) Range
4) Accuracy
5) Precision
6) Detection limit
7) Quantitation limit
8) Robustness
9) System suitability testing

1) Specificity :- It is the ability to measure unequivocally the desired analyte in presence of components such as excipient and impurities that may also be expected to be present.

It should be conducted during the validation of identification tests, determination of impurities.

2) Linearity :- It indicates the ability to produce results that are directly proportional to the concentration of the analyte in sample.

3) Range :- It is the interval between the upper and lower concentration of analyte in the sample for which it has been demonstrated that the analytical procedure has been suitable level of precision, accuracy and linearity.

The range is derived from the linearity studies and depend on intended application of procedure.

4) Accuracy :- It is analytical method is the closeness of test results obtained by that method to the true value.

→ Accuracy should be established across the specified range of the analytical procedure.
→ Assay (drug substance, drug products)
→ Impurities (Qualitative)

5) Precision :- Precision of an analytical procedure expresses the closeness of agreement b/w a series of measurements obtained from multiple sampling of same homogenous sample under prescribed conditions.

6) Robustness :- Robustness should be evaluated during the development phase and the evaluation process depends on the type of procedure being studied.

7) Detection Limit :- It is the smallest quantity of an analyte that can be detected.

8) Quantitation Limit :- It is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision.

9) System Suitability Testing :- system suitability testing is an integral part of many analytical procedures. The tests rely on the concept that the equipment, electronics, analytical procedures/operations and samples to be analysed form an integral system that can be evaluated.
→ System suitability testing depends on the type of procedures being evaluated.

Warehousing

Warehouse → A suitable place which is provided for storing and handling of raw and packaging materials required for manufacturing is known as a warehouse.

Maintaining proper storage conditions for pharmaceutical products is vital to ensure their quality, safety and efficacy. Thus, it is vital to follow Good Warehousing Practices and Good Distribution Practices to ensure the quality of products is maintained.

Various areas of warehousing

1) Receiving area :- include initial inspection, cleaning and weight checking.
2) Sampling area :- with adequate facilities to prevent cross contamination.
3) storage area

4) Rejected materials area
5) Dispensing area

Good Warehousing Practices

Good Warehousing Practices (GWP) includes the following:

1) Personnel

→ There should be sufficient number of personnel, with required qualifications.
→ warehouse staff should include, a responsible pharmacist, warehouse keeper, warehouse worker, cleaner, security guard.
→ staff must be given necessary training on good storage practices, regulations, procedures, etc.
→ They must also be trained on matters of personal hygiene, good sanitation practices, use of working garments and suitable protective clothing.

2) Premises and Facilities

→ Premises should be of suitable size to allow the systematic storage of different categories of materials.
→ There should be proper lightening, ventilation, temperature, sanitation, humidity, space for movement.
→ There must be separate areas for products in quarantine, approved products and products that have been rejected, recalled, etc.
→ Products that are sensitive, dangerous, hazardous, narcotics, etc. with a risk of fire, explosion must be stored in dedicated areas with sufficient security and safety measures.

3) Storage Requirements

→ Entry of unauthorised personnel in the storage areas should be limited or completely prohibited.
→ storage areas of sufficient capacity should be available so that various types of materials and products can be stored properly.
→ The storage areas should be clean, dry and maintained within acceptable temperature limits.
→ A written instruction manual for sanitation should be available.

→ A written instruction manual for pest control should also be available.

4) Returned Goods

→ All returned and recalled goods must be handled according to the approved procedures and related records should be maintained.

→ Returned goods should be kept in quarantine.

→ Goods that pass quality re-evaluation, may be returned to stock approved for sale.

→ Any pharmaceutical products returned by patients to the pharmacy must be destroyed.

5) Packing for Transportation

→ Products should be packed and labelled such that the product identification is not lost.

→ Appropriate measures should be taken against spillage and breakage.

→ Products requiring controlled temperature storage should be stored with insulated packs.

6) Dispatch and Transportation of Goods

→ This should be done in such a way that the prescribed storage conditions are maintained and integrity of the product is not lost.

→ During transportation, devices must be used to monitor temperature conditions.

→ Records for dispatch should contain the following:

1) Dispatch date
2) Customer's name and address
3) Product description, including name, dosage form, strength, batch number, and quantity
4) Transport and storage conditions.

7) Complaints

→ Any complaint regarding product defect should be immediately reported to the supplier.

→ Any complaint related to customer service or shipping errors should be processed as per the established procedure.

→ Records of all the received complaints should be maintained.

Materials Management

The following measures should be followed for the management of materials:

1) Receiving and dispatch areas should be such that the materials and products can be protected from the weather.
2) Only authorised personnel should be allowed to enter the quarantined areas.
3) A separate sampling area should be present in a controlled environment for the starting materials.
4) The rejected, expired, recalled or returned materials or products should be stored after physical separation.
5) A separate area with additional safety and security should be provided for highly active and radioactive materials, narcotics and hazardous materials and pharmaceutical products.
6) Contamination, mix-ups, cross-contamination of the materials and pharmaceutical products should be avoided during their handling and storage.
7) Broken or damaged items should not be present in the usable stock.
8) All stocks should be checked at regular intervals to detect the out-dated and obsolete materials and pharmaceutical products. Necessary measures should be taken to prevent the issue of such materials and pharmaceutical products.