Name of Unit	Calibration and validation, good warehousing and material management
Subject/Course name	Quality Assurance
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Learning Outcome of Unit-5

LO	Learning Outcome (LO)	Course Outcome Code
LO1	Students will able to know about elaborate the calibration, validation procedures.	BP606.6
LO2	To Understand the scope of good warehousing practices	BP606.6
LO3	Students will able to understand the cGMP aspects in a pharmaceutical industry	BP606.6

Module Content Table

Topic
• Calibration and Validation: • Introduction • definition and general principles of calibration • qualification and validation, Importance and scope of validation • types of validation • validation master plan • Calibration of pH meter Qualification of UV-Visible spectrophotometer • General principles of Analytical method Validation. • Warehousing: • Good warehousing practice • Materials management

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.

- Calibration of an instrument also involves adjusting its precision and accuracy so that its readings come in accordance with the established standard.
- This is important for justifying the processes of Qualification and Validation.
- The instrument or equipment with the known accuracy is known as standards. All the other instruments are measured against this standard. It is important to know that the standards vary from one country to the other depending upon the type of industry.
- Calibration Achieves 2 Main Objectives —
  a. It checks the accuracy of an instrument
  b. It determines the traceability of the measurement

Scope/Purpose of Calibration

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

1. To make sure that the readings of equipment or instruments are consistent with other measurements and display the correct readings every single time
2. To determine the accuracy, precision, reliability and deviation of the measurements produced by all the instruments.
3. To establish the reliability of the instrument being used and whether it can be trusted to deliver repeatable results each time.
4. To map the ‘drift’ as documented. Instruments have a tendency to produce inaccurate measurements over a period of time, following repeated use.
5. Ensuring that the industry standards, quality assurance benchmarks such as current good manufacturing practice (cGMP) and government regulations are adhered to.

What Is Instrument Calibration?

Instrument calibration can be defined as the process of comparing the measurements made by the instrument 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 and precision.

Usually, calibration labs prefer a standard with 10 times the accuracy; however, most regulating organizations and authorities also accept a 3:1 accuracy ratio.

Frequency of Instrument Calibration

How often you conduct instrument calibration mainly depends upon its tendency to drift from the true measurement and how it impacts the quality of the end product. Examine each instrument being used and study its behavior. Based on this information, you can design a calibration schedule for each instrument.

The interval between calibrations can vary as:

- Weekly
- Monthly or bi-monthly
- Quarterly, semi-annually or annually
- After every heavy usage of the instrument

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 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

Commonly Used Calibration Methods and Procedures:

There are different ways that are used to calibrate an instrument. These methods are chosen based on the desired results of the calibration and regulatory authorities' requirements, like FDA guidelines. Let us look at three such procedures:

Standard Calibration: This method is mostly preferred for calibrating instruments that are non-critical to quality or are not required for accreditation and license purposes. Use traceable standards and document its performance.

Calibration with Data: Procedures for calibrations with data are similar to that of accredited calibration. The only exception being that these procedures are not accredited to the ISO standard. Moreover, they are not accompanied by data on measurement uncertainties.

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) and '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 and its quality that is recorded by any instrument. When you start working with any instrument, it must be calibrated well, thus assuring you of accurate results. However, over a period of time you will start observing a 'drift'. Calibration minimizes such uncertainties by assuring the accuracy of the test equipment.

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 measurements in significant ways.

Calibration helps in quantifying and controlling errors and uncertainties within various measurement processes to an acceptable level.

Further, it helps in improving the accuracy of the measuring device, which in turn 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 and control.

QUALIFICATION

- 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 is part of validation, but the individual qualification steps alone do not constitute process validation.
- Qualification of analytical instrumentation 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 described below:
    1. Design Qualification (DQ)
    2. Installation Qualification (IQ)
    3. Operational Qualification (OQ)
    4. 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?"

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.
- ➢ The purpose of IQ 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 I.Q, connect each unit (Electrical system, Flow line system) and confirm that the connections are correct.

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

IQ checks items:

- ✓ Equipment design features (i.e. material of construction cleanability, etc.)
- ✓ Installation conditions (wiring, utility, functionality, etc.)
- ✓ Calibration, preventative maintenance, cleaning schedules.
- ✓ Safety features.
- ✓ Supplier documentation, prints, drawings and manuals.
- ✓ Software documented.
- ✓ Spare parts list.
- ✓ 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 predetermined 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.

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.
- ✓ 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:

- 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.
- 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. 20

- 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;

1. Definition of performance criteria and test procedures.
2. Selection of critical parameters, with predefined specifications.
3. 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.

4. 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.

Scope of Performance Qualification.

- According to regulatory documents, like FDA guidelines, the scope of PQ is somewhat limited. While equipment validation tests the ability individually for each piece of equipment, PQ verifies the performance of equipment, systems and facilities as a whole.
- It represents the final qualification, including any requalification of the system and equipment that you use in your business.
- Typically, the scope of PQ extends to include the following scenarios:
  - ✓ New systems being delivered and operated for the first time
  - ✓ Existing systems in use (as part of a regular maintenance schedule)
  - ✓ Systems that have been modified to any degree
  - ✓ Equipment/systems which have been used more than they normally would be
  - ✓ After a system has been expanded in order to increase its capacity

VALIDATION

Validation is an essential part of good manufacturing practices (GMP). It is,therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. These principles are as follows:

- Quality, safety and efficacy must be designed and built into the product.
- Quality cannot be inspected or tested into the product.
- Each critical step of the manufacturing process must be validated. Other steps in the process must be under control to maximize the probability that the finished product consistently and predictably meets all quality and design specifications.

Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications.

Documentation associated with validation includes:

- standard operating procedures (SOPs)
- specifications
- validation master plan (VMP)
- qualification protocols and reports
- Validation protocols and reports.

The implementation of validation work requires considerable resources such as:

1. ***Time:*** generally validation work is subject to rigorous time schedules.
2. ***Financial:*** validation often requires the time of specialized personnel and expensive technology.
3. ***Human:*** validation requires the collaboration of experts from various disciplines (e.g. a multidisciplinary team, comprising quality assurance, engineering, manufacturing and other disciplines, depending on the product and process to be validated).

These guidelines aim to give guidance to inspectors of pharmaceutical manufacturing facilities and manufacturers of pharmaceutical products on the requirements for validation. The main part covers the general principles of validation and qualification. In addition to the main part, appendices on validation and qualification (e.g. cleaning, computer and computerized systems, equipment, utilities and systems, and analytical methods) are included.

DEFINITIONS:

According to ISO:

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

According to the US Food and Drug Administration (FDA),

"The goal of validation is to: "Establish documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."

According t European commission:

"Action providing in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually lead to the expected results."

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Cleaning validation

Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, and toxicology and equipment size.

Commissioning

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

Computer validation

Documented evidence which provides a high degree of assurance that a computerized system analyses, controls and records data correctly and that data processing complies with predetermined specifications.

Qualification

Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

Standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master batch production documentation.

Validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

Validation master plan (VMP)

The VMP is a high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

Validation protocol (or plan) (VP)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process—or a part thereof—for routine use.

Validation report (VR)

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment.

Verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the GMP principles.

Worst case

A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within SOPs, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily include product or process failure.

Relationship between validation and qualification

Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. In this sense, qualification is part of 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 should be performed: –
    - for new premises, equipment, utilities and systems, and processes and procedures
    - at periodic intervals
    - 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

IMPORTANCE OF VALIDATION

1. Assurance of quality
2. Time bound
3. Process optimization
4. Reduction of quality cost.
5. Minimal batch failures, improved efficiently and productivity.
6. Reduction in rejections.

7. Increased output.
8. Fewer complaints about process related failures.
9. Reduced testing in process and in finished goods.
10. More rapid and reliable start-up of new equipment
11. Easier maintenance of equipment.
12. Improved employee awareness of processes.
13. More rapid automation.
14. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)

TYPES OF VALIDATION

Prospective validation

- It is defined as the established documented evidence that a system does what it purports to do based on a pre-planned protocol.
- This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process.
- Performed on at least three successive production-size (Consecutive batches).
- The objective of the prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot production trials. Prospective validation should normally be completed prior to the distribution and sale of the medicinal product.
- In Prospective Validation, the validation protocol is executed before the process is put into commercial use.

Concurrent validation

- It is a process where current production batches are used to monitor processing parameters.
- Concurrent Validation means establishing documented evidence a process does what it is supposed to based on data generated during actual implementation of the process.
- It is important in these cases when the systems and equipment to be used have been fully validated previously.
- It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

- This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

Retrospective validation

- It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information. This type of validation of a process is for a product already in distribution.
- Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
- Validation of such processes should be based on historical data.
- For retrospective validation, generally data from ten to thirty consecutive batches should be examined to access process consistency, but fewer batches may be examined if justified.

Revalidation

- Re-validation provides the evidence that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.
- Re-validation becomes necessary in certain situations. Some of the changes that require validation are as follows:
    - ✓ Changes in raw materials (physical properties such as density, viscosity, particle size distribution etc. that may affect the process or product).
    - ✓ Changes in the source of active raw material manufacturer.
    - ✓ Changes in packaging material (primary container/closure system)
    - ✓ Changes in the process (e.g., mixing time, drying temperatures and batch size
    - ✓ Changes in the equipment (e.g., addition of automatic detection system).
    - ✓ Changes in the plant/facility.

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	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.	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.
In calibration performance of an instrument or device is comparing against a reference standard.	No such reference standards are using in validation program
Calibration ensures that instrument or measuring devices producing accurate results.	Validation provides documented evidence that a process, equipment, method or system produces consistent results (in other words, it ensures that uniforms batches are produced).
Shall be performed periodically, to identify the 'drift' of the measuring device or equipment and make them accurate.	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 calibration SOP	Shall be performed as per validation protocol

VALIDATION MASTER PLAN

- The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning.
- The main elements of it being them list/inventory of the items to be validated and the planning schedule.
- All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as revalidation.
- The Validation Master Plan should be a summary document and should therefore be brief, concise and clear.
- It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and reports.
- The format and content should include:
    - ✓ Introduction: validation policy, scope, location and schedule.
    - ✓ Organizational structure: personnel responsibilities.
    - ✓ Plant/process/product description: rational for inclusions or exclusions and extent of validation.
    - ✓ Specific process considerations that are critical and those requiring extra attention.
    - ✓ Key acceptance criteria.
    - ✓ Documentation format.
    - ✓ Reference to the required SOPs.
    - ✓ Time plans of each validation project and sub-project.
    - ✓ List of products/ processes/ systems to be validated, summarized in a matrix format, validation approach.
    - ✓ Re-validation activities, actual status and future planning

CALIBRATION OF PH METER

What is a pH meter?

A pH meter measures the acidity of an aqueous solution. It is in fact the measurement of the amount of H-ions in aqueous solutions. With a pH meter, each aqueous solution can be measured to determine the pH.

How often should you calibrate a pH meter?

The frequency of calibrating a pH meter depends on usage and possible contamination. The higher the usage and the amount of contamination, the more often you need to calibrate your pHmeter. Ensure a pH meter calibration twice a month to avoid measuring errors. It is also advisable to calibrate the pH meter in the following cases:

- When you use a new electrode
- Whe the electrode hasn't been used for a long time.
- After the electrode has been cleaned.
- After measuring a strong solution
- When it is really important to get a very accurate measurement.

Soak an electrode newly taken from the package, or an electrode that has been dry, for a minimum of 4 hours in a cup with additive fluid. Soak a regularly used electrode in a cup with tap water for 15 minutes.

Preparing for Calibration

1. **Turn on your pH meter.** Before you begin to calibrate and use your pH meter you will first need to turn it on and allow adequate time for the meter to warm up. This should generally take around 30 minutes, but check your pH meter's operating manual for exact times.
2. **Clean your electrode.** Take the electrode out of its storage solution and rinse it with distilled water under an empty waste beaker. Once rinsed, blot dry with Kimwipes or Shurwipes, which are available at most office supply stores.
   - Be sure to rinse your electrode in a waste beaker that is different from the beaker you will be calibrating in.
   - Avoid rubbing the electrode as it has a sensitive membrane around it.
   - If you find the electrode to be particularly dirty consult your operating manual for recommended cleaning solutions.
3. **Prepare your buffers.** You will generally need more than one buffer for calibrating a pH meter. The first will be a "neutral" buffer with a pH of 7, and the second should be near the expected sample pH, either a pH of 4 or 9.21. Buffers with a higher pH (9.21) are best for measuring bases, whereas buffers with a low pH (4) are best for measuring acidic samples. Once you have chosen your buffers allow them to reach the same temperature as the pH

meter because pH readings are temperature dependent. Pour your buffers into individual beakers for calibration.

- Check with your pH meter manufacturer, or current educational or professional institution, about acquiring pH buffer solutions.
- Buffers should be kept in a beaker for no longer than two hours.
- Discard the buffer when you are finished. Do not return it to its original container.

Calibrating Your pH Meter

1. **Place your electrode in the buffer with a pH value of 7 and begin reading.** Press the "measure" or calibrate button to begin reading the pH once your electrode is placed in the buffer.
   - Allow the pH reading to stabilize before letting it sit for approximately 1-2 minutes.
2. **Set the pH.** Once you have a stable reading, set the pH meter to the value of the buffer's pH by pressing the measure button a second time. Setting the pH meter once the reading has stabilized will allow for more accurate and tuned readings.
   - Although not necessary, if you stir your buffer before measuring be sure to stir all other buffers and samples in the same way.
3. **Rinse your electrode with distilled water.** Rinse and pat dry with a lint-free tissue, like Kimwipes or Shurwipes, in between buffers.
4. **Place your electrode in the appropriate buffer for your sample and begin reading.** Press the measure button to begin reading the pH once your electrode is placed in the buffer.
5. **Set the pH a second time.** Once your reading has stabilized, set the pH meter to the value of the buffer's pH by pressing the measure button.
6. **Rinse your electrode.** You can use distilled water to rinse. Use a lint-free tissue, like Kimwipes or Shurwipes, in between buffers to dry the electrode.

Using Your pH Meter

1. **Place your electrode in your sample and begin reading.** Once your electrode is placed in your sample, press the measure button and leave the electrode in your sample for approximately 1-2 minutes.
2. **Set your pH level.** Once the reading has stabilized, press the measure button. This is the pH level of your sample

3. **Clean your electrode after use.** Rinse your electrode with distilled water and blot or dab dry with a lint-free tissue. You may store your pH meter once clean and dry.
   - Consult your operation manual for optimal storage practices for your specific pH meter.

CALIBRATION OF UV VISIBLE SPECTROPHOTOMETER

Calibration of UV spectrophotometer (UV-VIS Spectrophotometer) for all parameters as per IP, BP and USP pharmacopoeia like, Internal Calibration, Match pairing of UV cell / cuvette, Control of wavelength, control of Absorbance, Limit of Stray light, Resolution and Resolution Power, Linearity Study and 2nd derivatives.

General Procedure for UV Spectrophotometer:

- All calibration standards used for the calibration should prepared as per template / SOP.
- Only use calibration standard which is procured from authentic source with certification and it should.
  - NIST traceable or
  - Pharmacopoeial reference standards or
  - From instrument manufacturer.
- Alternatively suitable commercial certified filters (NIST traceable) may be used.
- If the commercially available filters being used, Refer the values provided by the manufacturer in the certificate for comparison.

Internal Calibration of UV Spectrophotometer :

- Internal calibration should perform for the parameters mentioned in Attachment for Internal calibration observation sheet.
- Perform the internal Calibration as per manufacturer's instruction.
- After completion of internal calibration the results obtained shall fill in Attachment -Internal calibration observation sheet, the format may differ base on manufacturer's internal calibration requirement) for further evaluation and conclusion.

Match Pairing of Cells (Cuvette Qualification):

- Clean the cell with methanol
- Remove any spot if any.
- Then rinse and fill the cell with distilled water.

- Measure its apparent absorbance against air at 240 nm for quartz cells and 650 nm for glass cells.
- The apparent absorbance should not be greater than 0.093 for 1 cm quartz cells (UV region) and 0.035 for 1 cm glass cells (Visible region).
- After that measure the apparent absorbance after Rotate the cell in its holder (180°) again
- Check the absorbance, Rotating the cells should give the absorbance difference not greater than 0.005 from initial.
- Record the observations and attach the printout of UV graphs with calibration template.

Sr. No.	Wavelength	The apparent absorbance should not be greater than 0.093 for 1 cm quartz cells (UV region) and 0.035 for 1 cm glass cells (Visible region)		Absorbance difference not greater than 0.005 from initial
		Cuvette 1	Cuvette 2	
1.	240nm			
2.	650nm			

Control of Wavelength:

- **Reagent Preparation**
  - **4M PerchloricAcid :** 5.74 ml of Perchloric Acid (AR grade, 11.6M) shall take in a clean and dried 50 ml of volumetric flask and volume shall make up to to 50 ml with distilled water and mix well.
  - **Preparation of 4% w/v solution of Holmium oxide:**
    - 0.4 gm of Holmium oxide (HO) (AR grade) shall be taken in a clean and dried 10 ml of Volumetric Flask.
    - Then add 8 ml 1.4 M Perchloric acid.
    - After that heat and sonicate the Flask till dissolve.
    - Then make up volume with 1.4 M Perchloric acid and filter the solution through Whatman no.41 paper or Use certified standard solution of 4.0% w/v Holmium oxide.
- **Calibration Procedure :**
  - Take the UV spectrum of 4%w/v Holmium oxide in 1.4 M Perchloric acid solution from 200 nm to 600 nm against the 1.4 M Perchloric acid as a blank.

- Wavelength shall be check for the peak detection of Holmium Oxide at 241.15 nm, 287.15 nm, 361.5 nm, 486.0 nm and 536.3 nm.
- The permitted tolerance limit shall be ± 1 nm for the range of 200 nm to 400 nm (UV range) and ± 3 nm for the range of 400 nm to 800 nm.(Visible range)
- Record the observations and attach the printout of UV graphs with calibration report.

Expected wavelength (nm)	Observed wavelength (nm)	Range	Tolerance Limit
241.15		240.15 – 242.15nm	±1nm (For the range of 200nm to 400nm)
287.15		286.15 – 288.15nm	
361.50		360.50 – 362.50nm	
486.00		483.00 – 489.00nm	±3nm (For the range of 400nm to 600nm)
536.30		533.30 – 539.30nm	

Control of Absorbance:

- **Preparation Reagent / Dilution**
  - **0.005 M Sulfuric acid:** 0.54 ml sulfuric acid (AR grade, 18.4 M) shall be taken in a clean and dried 2000 ml volumetric flask containing at least 50 ml of distilled water.
    - Make up final volume cautiously to the mark with distilled water and mix well.
  - **Potassium dichromate solution in 0.005 M Sulfuric acid:** Stock solution for 430 nm (600 ppm):
    - Use potassium dichromate previously dried to constant mass at 130°C and About 60 mg (57 mg-63.0 mg) of potassium dichromate (AR grade) shall take in 100 ml clean and dried volumetric flask,
    - Dissolve and make up the volume with 0.005 M Sulfuric acid and mix well or
    - Use certified standard solution of potassium dichromate(600 ppm).
  - **Final solution (60 ppm):**
    - 10 ml of above stock solution shall taken in 100 ml clean and dried volumetric flask, make up the volume with 0.005 M Sulfuric acid and mix well or
    - Use certified standard solution of potassium dichromate (60 ppm).
- **Calibration Procedure:**

- Take the spectrum of the Potassium dichromate **final solution** between 200 nm to 400 nm using 0.005 M Sulfuric acid as a blank.
- Measure the absorbance of peak detection at 350 nm & 257 nm and Valley detection at 313 nm & 235 nm.
- Absorbance of the Potassium dichromate **stock solution** shall taken at 430 nm using 0.005 M Sulfuric acid as a blank in photo-metric mode. Calculate the specific absorbance ($A_{1\ cm}^{1\%}$) & verify the results.

- **Calculation formula :-**

Control of absorbance = (Absorbance X 10000) / Wt. Taken in mg.

Control of absorbance (for λ 430 nm) = (Absorbance X 1000) / Wt. Taken in mg.

- Record the observations and attach the printout of UV graphs with calibration report.

Sr. No.	Type of Detection	Wavelength(nm)	Observed value		Tolerance Limit
			Absorbance	A(1%,cm)	
1	Peak	350nm			105.6 – 109.0
2	Peak	257nm			142.8 – 146.2
3	Valley	313nm			47.0 - 50.3
4	Valley	235nm			122.9 - 126.2
For Stock Solution:-					
5	NA	430nm			15.7 - 16.1

Limit of Stray Light :

- **Preparation Potassium chloride solution: (12,000 ppm):**
  - 1.2gm of potassium chloride (AR grade) shall take in 100 mL clean and dried volumetric flask.
  - Dissolve and make up the volume with distilled water and mix well or
  - Use certified standard solution of Potassium chloride solution (12,000 ppm).
- **Procedure:**
  - Absorbance of the potassium chloride solution shall be taken against distilled water as a blank between 220 nm and 190 nm in scan mode.

- Check absorbance at 198 nm by keeping cursor.
- Absorbance steeply increases between 220 nm to 200 nm and shall ³ 2.0 at 198 nm.

Wavelength	Absorbance	Limit
_____198nm		NLT 2.0

Linearity Study :

- **Preparation of 0.005 M Sulfuric acid:**
  - 0.54 ml sulfuric acid (AR grade, 18.4 M) shall take in a clean and dried 2000 ml volumetric flask containing at least 50 ml of distilled water.
  - Make up final volume cautiously to the mark with distilled water and mix well.

Linearity Solution Preparation in 0.005 M Sulfuric Acid :

- **100 ppm Solution:**
  - Weigh 100 mg of potassium dichromate (AR grade) (previously dried to constant mass at 130 °C).
  - Transfer in 1000 ml in clean and dried volumetric flask,
  - Dissolve and make up the volume with 0.005 M Sulfuric acid and mix well or
  - Use certified standard solution of Potassium dichromate (100 ppm).
- **80 ppm Solution:**
  - Take 20 ml of 100 mg/lit solution in 25 ml clean and dried volumetric flask and dilute up to mark with 0.005 M Sulphuric acid and Mix well or .
  - Use certified standard solution of Potassium dichromate (80 ppm).
- **60 ppm Solution :**
  - Take 15 ml of 100 mg / lit solution in 25 ml clean and dried volumetric flask and dilute up to mark with 0.005 M Sulfuric acid and mix well or
  - If 60 ppm (conc.) certified standard solution of Potassium dichromate available, same can be used.
- **40 ppm Solution :**
  - 20 ml of 100 mg/lit solution shall be taken in 50 ml clean and dried volumetric flask and dilute up to mark with 0.005 M Sulphuric acid and mix well or

- If certified standard solution of Potassium dichromate (40 ppm) is available. It can be used directly.

- **20 ppm Solution :**
  - 20 ml of 100 mg / lit solution shall be taken in 100 ml clean and dried volumetric flask and dilute up to mark with 0.005 M Sulphuric acid and mix well or
  - Use certified standard solution of Potassium dichromate (20 ppm).
- After preparing the Solution. measure the absorbance of the solutions at 257 nm by using 0.005 M sulfuric acid as a blank.
- Graph shall be plotted between absorbance verses concentration.
- **Acceptance Criteria:**
  - R-square value shall £ 0.999.

Resolution Power:

- **Preparation of Toluene solution in Hexane (0.02%v/v) :**
  - Take 2 ml of Toluene (HPLC grade) in 100 ml clean and dried volumetric flask and diluted up to mark with Hexane (HPLC grade).
  - Then take 1 ml of this solution is in 100 ml clean and dried volumetric flask and diluted up to mark with Hexane and mix well or
  - Use certified standard solution of Toluene in Hexane (0.02%v/v).
  - Take the spectrum of the Toluene solution in the range of 255 nm to 275 nm against Hexane as a blank.
  - The ratio of the absorbance at the maximum at about 269 nm to that the minimum at about 266 nm NMT than 1.5.

Maximum Absorbance at 269nm	Minimum Absorbance at 266nm	Ratio= Max. abs. / Min. abs.	Limit
			Ratio should not less than 1.5

Resolution (2 nd Derivative test):

- **Preparation of Toluene solution in Methanol (0.02%v/v) :**
  - Take 2 ml of Toluene (HPLC grade) in 100 ml clean and dried volumetric flask and diluted up to mark with Methanol (HPLC grade).

- Then further take 1 ml of this solution in 100 ml clean and dried volumetric flask and
- Dilute up to mark with Methanol and mix well or
- Use certified standard solution of Toluene in Methanol (0.02%v/v).

- Take second derivative spectrum of the resulting solution in the range of 255 nm to 275 nm.
- A small negative extremum (or trough) located between two large negative extrema (or troughs) at about 261 nm and 268 nm, should clearly visible, as shown in below figure.
- The ratio A/B (pl. see figure) **is not less than 0.2.**
- Solution for calibration of UV Spectrophotometer shall prepare freshly and shall use within 24 hrs. Record the readings.
- If any part of the instrument is replaced during the maintenance then record the activity in the instrument history card and if required, calibrate the instrument.
- If the readings do not fall within the specified ranges, Contact to service engineer .

Re-Calibration :

- After maintenance (change in critical parts like lamp,filter,mirrors etc.). Re-Calibrate the UV spectrophotometer .
- Upon change in cuvette. Perform Cuvette Qualification..

Out Of Calibration :

- In case failure of UV Calibration in any of the its calibration parameter. Follow SOP on handling out of calibration procedure for laboratory instruments.

Relocation of UV Spectrophotometer :

- If the instrument is shifted for any purpose. Perform the Qualification.
- After following maintenance and for other maintenance. Carryout the UV Calibration ,
- Decide the Calibration requirement case by case basis.

Calibration Parameters:	Satisfactory/Not Satisfactory
Control of wavelength	
Control of absorbance	
Limit of stray light	
Resolution power	
Resolution (2 nd Derivative test)	
Linearity study	

ANALYTICAL METHOD VALIDATION

Principle

1. This appendix presents some information on the characteristics that should be considered during validation of analytical methods. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product.
2. The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.
3. Analytical methods, whether or not they indicate stability, should be validated.
4. The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

General

1. There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.
2. Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non-pharmacopoeial methods") as approved by the national drug regulatory authority may be used.
3. Well-characterized reference materials, with documented purity, should be used in the validation study.
4. The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.
5. The results of analytical procedures should be reliable, accurate and reproducible.
6. Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.
7. The verification or degree of revalidation depends on the nature of the change(s).

8. There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency").

CHARACTERISTICS OF ANALYTICAL PROCEDURES

Characteristics that should be considered during validation of analytical methods include: —

- Specificity
- Linearity
- Range
- Accuracy
- Precision
- Detection limit
- Quantitation limit
- Robustness

Accuracy is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure.

Note: it is acceptable to use a "spiked" placebo where a known quantity or concentration of a reference material is used.

Precision is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

Repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

Intermediate precision expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

Reproducibility expresses precision between laboratories.

Robustness (or ruggedness) is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate

samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters.

Factors that can have an effect on robustness when performing chromatographic analysis include:—

Stability of test and standard samples and solutions;

Reagents (e.g. different suppliers);

Different columns (e.g. different lots and/or suppliers);

Extraction time;

Variations of pH of a mobile phase;

Variations in mobile phase composition;

Temperature;

Flow rate.

Linearity indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used.

Range is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

Specificity (selectivity) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

Detection limit (limit of detection) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- Visual evaluation;
- Signal to noise ratio;
- Standard deviation of the response and the slope;

- Standard deviation of the blank; and
- Calibration curve.

Quantitation limit(limit of quantitation) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- Visual evaluation;
- Signal to noise ratio;
- Standard deviation of the response and the slope;

GOOD WAREHOUSING PRACTICES

Warehouse management is complex, but done right it can reduce costs, improve customer satisfaction and increase warehouse operational efficiency.

Introduction:

Maintaining proper storage condition for pharmaceutical products and paramedical is vital to ensure their quality, safety and efficacy. Factory stores will invariably be receiving duly approved raw materials materials and packaging packaging materials materials from third party. A suitable space is provided to raw material, handling of raw & packaging materials required for manufacturing, including packaging of pharmaceuticals. This space is known as Warehouse. It is a part of pharmaceutical company.

For what purpose?

To enable the fastest and cheapest transport of drugs and medical equipment from suppliers to beneficiaries.

There are mainly 3 stages:

1. Purchase of pharmaceutical products.
2. Storage of ordered products.
3. Distribution of stocked products.

VARIOUS AREAS OF WARE HOUSING

Receiving area: - includes initial inspection, cleaning & weight checking.

Sampling area: - with adequate facilities to prevent cross contamination.

Storage area: - including specific storage like air

Storage area: - including specific storage like air condition rooms, cold rooms, hazardous chemical storage room.

Rejected materials:-Destroy or retested unsuitable.

Dispensing area:-with adequate facilities to preclude cross contamination during dispensing.

Design:

Principle: Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General:

- The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning. to avoid cross-contamination and facilitate cleaning.
- Premises should be situated in an environment in which the minimum risk of any contamination of materials or products.
- Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not causes any hazard to the quality of products.
- Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.
- Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a standard procedure to prevent from rodent and pest control.
- Premises should be designed to ensure the logical flow of materials and personnel.

General guide lines:-

- Materials received against specific supply devices

- Each such consignment have written documents (delivery Chelan)
- All materials received by responsible persons
- materials to be checked for cleanliness & package integrity
- Damaged container separated & reporting immediately
- Check for proper container labeling

  i.e status of materials UNDER TEST, A Waiting for APPROVAL

GOOD WAREHOUSING PRACTICE:-

1. Factory Stock which should be received with proper documents detailing the names of product ,the batch number ,the number of units of final packs of each batch ,the date of dispatch and the quality control status of the batches.
2. The stock control system must be such that only passed batches of products are issued for distribution. Stocks should be stored, product wise to enable quick identification and control of stock movement .Stocks should therefore be racked and stored in a manner that earlier stocks are more early accessible than the later ones.
3. The picking and 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 and with proper labels which clearly identify the products.
4. Assembled products should be checked for accuracy of quantities and identities of products ordered. Batch details should be recorded in relevant documents.
5. Finished product should be packed in the containers and dispatched for the transportation.
6. The unit product packs should be not contaminated by other products. Vehicles which carry the final packaged stocks of products should be so selected that-
    - They are clear, dry and sufficiently protected from rain and other weather factors.
    - They are free from infestation.
    - They do not give off strong odours which may contaminate the products.
    - They are suitable to withstand the weight of the load they carry.

Rules for warehousing:-

- Systematic storage of the delivered goods.
- Use air circulation & protection against rodents.

- Keeping a space at least 50cm between the rows of pellets walls.
- Providing each products have only one specific place.
- On shelves clear labeling of products should be there.
- Adequate space should be provided for each goods.
- Provide separate stoke card for each products.
- All boxes in stock should be closed.
- Flammable products should store in separate place.

Characters of good warehouse:-

- Properly cleaned.
- Good preservation of drugs &equipments.
- Provide safety for staff & stocked goods.
- Control of air, light, humidity& temperature.
- Products to be purchased according to needs.
- Order the destruction of unsuitable products.
- Promote rational use of pharmaceutical products.

The warehouse staff:-

1. **The responsible pharmacist His duties**
   - Good management of the stock of the warehouse.
   - Good preservation of drugs and equipment's.
   - Safety of stored goods.
2. **The warehouse keeper His duties**
   - Reception of supplies.
   - Storage of stocks of goods.
   - Recording of every IN and OUT movement of the products in the stock card.
   - Issue of products during manufacturing.
3. **The warehouse worker His duties**
   - Handling operations includes the carrying and moving of goods which are intended for storage, shipment and sale.
   - The warehouse staff helps in receives and issue goods and maintain inventory.
4. **The cleaner His duty**
   - Ensure cleanliness of premises and equipment.

5. The security guard His duty

- He is responsible for ensuring supervision and security of the warehouse.

Storage of raw & packaging materials:-

Storage conditions- special storage area with controlled temperature, humidity & stored off from the floor. .

a) STORAGE OF PACKAGING MATERIAL: -

- Bottles, vials, ampoules, tins, tubes should be stored in a manner that they do not contaminated by extraneous matter.
- Printed packaging material also stored properly.
- Printed materials such as labels, printed films / foils /laminates, cartons should kept in storage cupboards.
- Preventing mix up of printed & non printed materials.
- Physical segregation of printed & labeled containers should be made.
- Special precautions are needed for the storage of packaging labeling controlled products. Appropriate storage condition to be provided (air conditioning, aluminum foil)

Handling & issue – raw materials:-

- Attention to be made for -prevent cross contamination ,health of personnel handling materials ,containers should be closed properly ,materials that support microbial growth are handled carefully. Eg.agar.
- Materials issued only against authorized person.
- Personnel protective devices like gloves, facemasks etc. should be used to avoid health hazards.
- Adequate dust extraction system should be provided to suck away fine dust as to prevent cross-contamination.

Handling & issue: packaging Materials: -

- Packaging materials issued to production only against packaging materials order.
- Care should made to check for only right packaging materials to be issued.
- Unlike raw materials , exact quantity of packaging materials to be issued.
- Unused packaging materials returned to the warehouse & will accompanied by authorized documents

Ware housing of finished products:-

For avoiding deterioration, spoillage or breakage

requirements:- safe , orderly & dispatch of all products -cold storage area have temperature monitoring & recording devices -racking & shelving system should have good mechanical strength .

Procedure:-

- Stock received from factory with proper documentation (name, batch number, date of dispatch)
- Finished products which are under test" must be quarantined & segregated from passed stocks”
- Stock should be stored product wise to enable quick identification & controlled stock movement
- Store rotation should be on first in ,first out basis

Ware housing of returned goods:-

- Stocks should be carrying out only consultation with quality controlled manager.
- Returned goods must be isolated on receipt, clearly identified & records regarding reason for the return.
- QC manager should examine whether these goods are reprocessed or destroyed.
- Reprocessing of returned should be done according the instruction of Qc manager

QUESTION BANK

SHORT QUESTIONS(2marks)

1. Define validation.
2. Name the elements of validation protocol.
3. Name the different types of validation in pharmaceutical industry.
4. What is validation protocol?
5. What is the advantage of good warehousing?
6. What is material management?
7. Write the basic needs of material management
8. Define calibration.
9. What are the elements of material management?
10. Why blending is a critical parameter in tablet manufacturing.
11. Define process validation with flow chart.
12. Define Operational qualification.

Long Questions (5marks)

1. What is validation discuss the various types of validation.
2. How analytical equipment can be validated.
3. Difference between validation and calibration.

Very long questions (10 marks)

1. Discuss calibration of pH meter
2. Discuss calibration of UV Visible spectrophotometer
3. Write a detailed note on Good Warehousing practice.
4. Write a note on qualification in detail.