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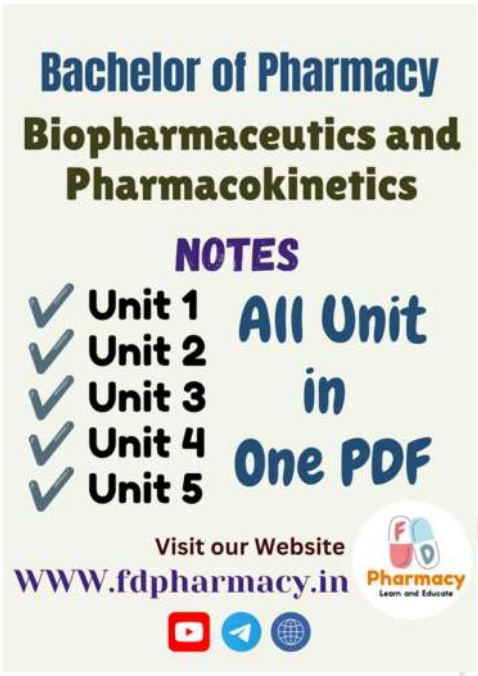
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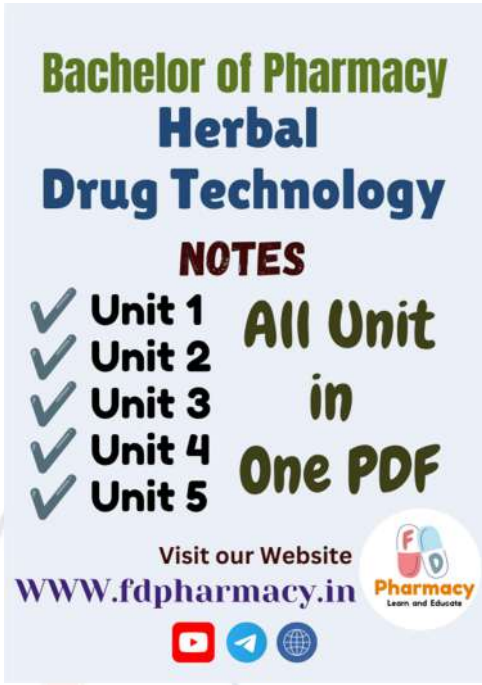
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Unit 1
Unit 2
Unit 3
Unit 4
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NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
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Unit 2
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PHARMACEUTICAL QUALITY ASSURANCE

UNIT 5

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.

Calibration, Validation, Qualification & UV-Visible Spectrophotometer

Calibration

→ Calibration is the process of checking and adjusting an instrument by comparing its readings with a known standard reference to ensure accurate and reliable measurements.
→ In simple words, calibration means verifying whether an instrument gives the correct value.

Principle of Calibration

➢ The principle of calibration is based on comparison with a standard.

Steps:

1. Compare instrument reading with a standard value.
2. Determine the error or deviation.
3. Adjust the instrument if required.
4. Verify that the instrument gives accurate results.

Need of Calibration

- Ensures accurate measurements.
- Maintains consistency in production.
- Prevents defective products.
- Reduces manufacturing errors.
- Ensures proper functioning of instruments.
- Meets GMP and GLP requirements.
- Improves product quality and safety.

Scope of Calibration

Calibration is required for instruments used in:

Production Department

- Temperature indicators
- Pressure gauges
- Weighing balances

Quality Control Laboratory

- pH meters
- HPLC systems
- UV Spectrophotometers

Quality Assurance Department

- Monitoring devices
- Validation instruments

Warehousing

- Temperature monitoring systems
- Humidity monitoring systems

Research & Development

- Analytical instruments
- Experimental equipment

Calibration Procedure

Step 1: Identification

- Identify the instrument to be calibrated.

Step 2: Standard Selection

- Use a certified reference standard.

Step 3: Measurement

- Take readings using the instrument.

Step 4: Comparison

- Compare readings with standard values.

Step 5: Deviation Calculation

- Calculate the difference between observed and standard values.

Step 6: Adjustment

- Adjust instrument if necessary.

Step 7: Documentation

- Record calibration results.

Step 8: Labeling

- Attach calibration label indicating:
  - Calibration date
  - Due date
  - Status

Importance of Calibration

- Ensures reliable measurements.
- Maintains pharmaceutical product quality.
- Supports GMP and GLP compliance.
- Reduces batch rejection.
- Improves patient safety.
- Prevents financial losses.

Calibration of pH Meter

→ Calibration of a pH meter is the process of adjusting the instrument using standard buffer solutions so that it gives accurate pH readings.

Principle

The pH meter is calibrated by comparing its readings with standard buffer solutions of known pH values.

Common buffers used:

- pH 4.0
- pH 7.0
- pH 9.2 or pH 10.0

Materials Required

- pH Meter
- Buffer Solution pH 4.0
- Buffer Solution pH 7.0
- Buffer Solution pH 9.2 or 10.0
- Distilled Water
- Tissue Paper

Procedure

1. Preparation of Instrument

- Switch on the pH meter.
- Allow stabilization.
- Clean the electrode.
- Rinse with distilled water.
- Gently dry using tissue paper.

2. Calibration with pH 7 Buffer

- Immerse electrode in pH 7 buffer.
- Allow reading to stabilize.
- Adjust meter to show exactly pH 7.

3. Calibration with pH 4 Buffer

- Rinse electrode.
- Place in pH 4 buffer.
- Adjust reading if necessary.

4. Calibration with pH 9.2/10 Buffer

- Rinse electrode again.
- Immerse in alkaline buffer.
- Adjust meter accordingly.

5. Final Verification

- Recheck all buffer solutions.
- Confirm correct readings.
- The pH meter is now ready for use.

Validation

→ Validation is the process of establishing documented evidence that a process, method, equipment or system consistently performs according to predetermined specifications.
→ In simple words, validation proves that a process works correctly every time.

Principle of Validation

➢ Validation is based on the principle that:
➢ A process which consistently produces products meeting predetermined specifications is considered validated.

It includes:

- Documented evidence
- Consistency
- Reproducibility
- Scientific approach
- Predefined acceptance criteria
- Control of variation

Purpose of Validation

- Ensures consistent product quality.
- Meets GMP and GLP requirements.
- Reduces risks and errors.
- Improves process reliability.
- Ensures safety and efficacy of medicines.
- Increases confidence in manufacturing processes.

Types of Validation

1. Prospective Validation

→ Performed before routine production starts.

Features

- Conducted during development stage.
- Demonstrates process capability.
- Used for new products.

Example

- Validation of a new tablet manufacturing process before commercialization.

2. Concurrent Validation

→ Performed during actual production.

Features

- Data collected during manufacturing.
- Used when prospective validation is not possible.

Example

Monitoring the first few production batches.

3. Retrospective Validation

→ Performed using historical production data.

Features

- Based on past batch records.
- Suitable for established processes.

Example

Reviewing previous batch records to verify consistency.

4. Revalidation

→ Performed when significant changes occur.

Reasons

- Change in equipment
- Change in formulation
- Change in process
- Change in facility

Example

Replacement of tablet compression machine.

Scope of Validation

Process Validation

- Validation of manufacturing process.

Equipment Validation

- Validation of machines and instruments.

Analytical Method Validation

- Validation of testing methods.

Cleaning Validation

- Validation of cleaning procedures.

Utility Validation

- Validation of water, steam, compressed air and HVAC systems.

Computer System Validation

- Validation of computerized systems.

Importance of Validation

- Ensures product quality.
- Reduces batch failures.
- Improves efficiency.
- Meets regulatory requirements.
- Builds confidence in manufacturing systems.
- Supports regulatory approvals.

Qualification

→ Qualification is the process of proving and documenting that equipment, systems or facilities are properly installed, operate correctly and are suitable for intended use.

→ Qualification mainly applies to equipment and systems.

Purpose of Qualification

- Ensures equipment works properly.
- Maintains product quality.
- Supports GMP compliance.
- Prevents manufacturing errors.
- Ensures consistent performance.

Types of Qualification

1. Design Qualification (DQ)

→ Documented verification that the proposed design is suitable for its intended purpose.

Example

- Checking machine specifications before purchase.

Objectives

- Verify design suitability.
- Ensure compliance with requirements.
- Confirm adequate capacity.

2. Installation Qualification (IQ)

→ Documented verification that equipment has been installed correctly according to manufacturer specifications.

Checks

- Components installed properly
- Utilities connected
- Documentation available
- Safety features installed

Example

- Verifying installation of a tablet compression machine.

3. Operational Qualification (OQ)

→ Documented verification that equipment operates properly within specified limits.

Checks

- Controls
- Alarms
- Safety systems
- Operating parameters

Example

- Testing machine performance at different operating conditions.

4. Performance Qualification (PQ)

→ Documented verification that equipment consistently performs under routine production conditions.

Example

- Producing several batches and confirming product quality.

Checks

- Consistency
- Reliability
- Reproducibility

Importance of Qualification

- Confirms equipment fitness.
- Reduces equipment failures.
- Ensures reliable production.
- Supports GMP compliance.
- Required during regulatory inspections.

UV-Visible Spectrophotometer

→ UV-Visible Spectrophotometer is an analytical instrument used to measure absorption of ultraviolet (200–400 nm) and visible (400–800 nm) light by a substance.

Principle

The principle is based on absorption of UV or visible light by a substance. The amount of light absorbed is directly proportional to the concentration of the absorbing substance according to:

$A=\varepsilon bc$

Where:

- A = Absorbance
- ε = Molar absorptivity
- b = Path length
- c = Concentration

Instrumentation

1. Light Source

- Provides UV and visible radiation.
  Examples:
  - Deuterium Lamp (UV region)
  - Tungsten Lamp (Visible region)

2. Monochromator

- Selects a specific wavelength.

3. Sample Holder

- Holds the sample cuvette.

4. Detector

- Measures transmitted light.

5. Recorder/Display

- Displays absorbance or transmittance.

Qualification Of UV-Visible Spectrophotometer

→ Qualification of UV-Visible Spectrophotometer ensures that the instrument is properly installed, operates correctly and produces accurate results.

Stages of Qualification

1. Design Qualification (DQ)

➢ Confirms that instrument specifications meet analytical requirements.

Checks

- Wavelength range (200–800 nm)
- Accuracy
- Resolution
- Software features

2. Installation Qualification (IQ)

➢ Verifies proper installation.

Checks

- Instrument components
- Power supply
- Manuals and documentation
- Environmental conditions

3. Operational Qualification (OQ)

➢ Verifies operation within specified limits.

Tests

- Wavelength accuracy
- Photometric accuracy
- Stray light test
- Resolution test

4. Performance Qualification (PQ)

➢ Confirms routine performance.

Activities

- Analysis of standard samples
- Reproducibility studies
- Accuracy verification

Analytical Method Validation (AMV)

→ Analytical Method Validation is the process of proving that an analytical method is accurate, precise, reliable and suitable for its intended purpose.

Purpose

- Ensures reliable results.
- Confirms fitness for intended use.
- Meets GMP and ICH requirements.
- Supports quality control activities.

Parameters of Analytical Method Validation

1. Accuracy

- Closeness of measured value to true value.

2. Precision

- Ability to obtain similar results repeatedly.

3. Specificity

- Ability to measure analyte without interference.

4. Linearity

- Ability to obtain results proportional to concentration.

5. Range

- Concentration interval over which method is accurate and precise.

6. Limit of Detection (LOD)

- Lowest amount that can be detected but not accurately quantified.

7. Limit of Quantitation (LOQ)

- Lowest amount that can be accurately measured.

8. Robustness

- Ability to remain unaffected by small method changes.

Validation Master Plan (VMP)

- Validation Master Plan (VMP) is a document that describes the overall validation strategy, policy and approach for all validation activities in a pharmaceutical organization.
- It acts as a roadmap for validation.

Purpose of VMP

- Defines validation strategy.
- Ensures systematic validation.
- Supports GMP compliance.
- Assigns responsibilities.
- Controls documentation.

Guidelines for VMP

- Must be well structured.
- Approved by QA.
- Follow GMP requirements.
- Clearly define responsibilities.
- Periodically reviewed and updated.

Contents of VMP

1. Introduction

- Title
- Document number
- Revision details

2. Scope

- Process validation
- Equipment validation
- Cleaning validation
- Utility validation

3. Responsibilities

- QA Department
- QC Department
- Production Department
- Engineering Department

4. Validation Policy

- Overall validation approach.

5. List of Equipment and Systems

- Items requiring validation.

6. Documentation

- Protocols
- Reports
- Records

7. Change Control

- Procedure for handling changes.

Importance of VMP

- Guides validation activities.
- Improves planning and execution.
- Facilitates regulatory inspections.
- Enhances quality assurance systems.
- Ensures compliance with GMP requirements.