Unit-5

Pharmaceutical Quality Assurance

B.Pharma 6th Sem Notes

Unit: 5

- **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 and Validation – Introduction

Calibration, qualification, and validation are essential quality assurance activities in the pharmaceutical industry. They ensure that instruments, equipment, analytical methods, and processes consistently produce **accurate, reliable, and reproducible results**, in compliance with **GMP and regulatory requirements**.

- **Calibration** → Accuracy of instruments
- **Qualification** → Suitability of equipment
- **Validation** → Reliability of processes and methods

Definitions

Calibration

Calibration is the process of **comparing the readings of a measuring instrument with a known standard** to ensure accuracy within specified limits.

Example: Calibration of pH meter using buffer solutions.

Qualification

Qualification is the documented process that proves **equipment or systems are properly installed, operate correctly, and perform consistently**.

Types:

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Qualification: The action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results.

- *Goal:* Equipment readiness ("Is the machine fit for use?").

Validation: The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

- *Goal:* Process consistency ("Does the process work every time?").

Verification, Calibration, Qualification, and Validation: Key Differences

	Verification	Calibration	Qualification	Validation
Definition	Process of confirming tthat a requirement has been fulfilied	Process of adjusting and/or determining the accuracy of a measuring instrument	Process of equipment/system suitability operaternt or systems and perform	Process of establishing documented evidence that a process, method, or system produces consistent results
Scope	Confirm requirements met	Ensure accuracy of measuring devices	Ensure equipment/ system suitability	
Differences	Checking/testing	Adjusting/measuring accuracy	Installation, operation, performance	Processes, methods, systems

Importance and Scope of Validation

Importance:

- **Regulatory Compliance:** Mandatory for GMP (Good Manufacturing Practice), GLP, and ISO certification.
- **Quality Assurance:** Reduces the risk of product failure and recalls.
- **Cost Reduction:** Minimizes re-testing and batch rejections by ensuring "Right First Time."
- **Safety:** Ensures patient safety by guaranteeing drug potency and purity.

Scope:

Validation applies to almost every aspect of production and analysis:

- **Analytical Methods:** Ensuring testing methods are accurate.
- **Equipment:** Ensuring machines function correctly.
- **Computer Systems:** Ensuring software handles data integrity.
- **Cleaning:** Ensuring no cross-contamination between batches.
- **Process:** Ensuring the manufacturing steps are robust.

Types of Validation

There are four primary approaches to validation in the pharmaceutical industry:

1. **Prospective Validation:**
    - Conducted *before* a new product is released to the market.
    - Based on a pre-planned protocol.
    - Typically performed on the first 3 consecutive production batches.
2. **Concurrent Validation:**
    - Conducted *during* routine production of products intended for sale.
    - Used when data from replicate production runs is unavailable (e.g., orphan drugs with low production volume).
3. **Retrospective Validation:**
    - Conducted for established products based on *historical data*.
    - involves analyzing past batch records, control charts, and logbooks to prove consistency. (Note: This is becoming less accepted by regulatory bodies like the FDA).
4. **Re-validation:**
    - Repeated validation to ensure continued compliance.
    - **Triggered by:** Changes in raw materials, equipment, process parameters, or location; or periodically as per schedule.

Validation Master Plan (VMP)

Definition:

The VMP is a high-level document that outlines the overall philosophy, intention, and approach to validation for the entire facility. It serves as a roadmap for the validation program.

Key Components of a VMP:

- **Validation Policy:** The company's commitment to quality.
- **Organizational Structure:** Roles and responsibilities.

- **Facility Description:** Details of the plant, systems, and equipment.
- **Format of Documentation:** Templates for protocols and reports.
- **Validation Schedule:** Timeline for when validation activities will occur.
- **Change Control:** How changes to validated systems are managed.

Calibration of pH Meter

A pH meter measures the potential difference between a reference electrode and a glass electrode to determine acidity or alkalinity.

General Principles:

- Calibrated using **Standard Buffer Solutions** (typically pH 4.0, 7.0, and 9.2/10.0).
- Ideally calibrated daily or before use.
- Slope verification (efficiency) should be between 95% - 105%.

Step-by-Step Procedure:

1. **Inspection:** Check electrode for cracks or air bubbles; check electrolyte level.
2. **Warm-up:** Switch on the meter 15–30 minutes before use.
3. **Cleaning:** Rinse the electrode with distilled water and gently blot dry (do not rub) with tissue paper.
4. **Standardization (pH 7.0):** Dip electrode into pH 7.0 buffer. Adjust the "Calibration" or "Asymmetry" knob until the display reads exactly 7.00.
5. **Slope Adjustment (pH 4.0 or 9.2):**
    - For acidic samples: Use pH 4.0 buffer.
    - For basic samples: Use pH 9.2 buffer.
    - Dip electrode and adjust the "Slope" knob until the reading matches the buffer value.

6. **Verification:** Rinse and check the pH 7.0 buffer again to ensure no drift occurred.

Qualification of UV-Visible Spectrophotometer

Qualification ensures the instrument performs according to pharmacopoeial (USP/BP/IP) standards. It involves four phases:

- **DQ (Design Qualification):** Verifying specs before purchase.
- **IQ (Installation Qualification):** Verifying proper installation and environment.
- **OQ (Operational Qualification):** Verifying buttons/functions work.
- **PQ (Performance Qualification):** Testing the optical performance (Crucial step).

Performance Tests (PQ Parameters):

1. **Wavelength Accuracy:**
    - *Goal:* Ensure the assigned wavelength is the actual wavelength.
    - *Method:* Scan a **Holmium Oxide** filter or solution.
    - *Acceptance:* Peaks must be detected at standard values (e.g., 241.1 nm, 361.5 nm) within ± 0.5nm (UV) or ±1 nm (Vis).
2. **Stray Light:**
    - *Goal:* Ensure only the selected wavelength passes through the sample.
    - *Method:* Measure absorbance of **1.2% KCl** solution at 200 nm.
    - *Acceptance:* Transmittance should be < 1% (or Absorbance > 2.0).
3. **Resolution Power:**
    - *Goal:* Ability to separate adjacent peaks.
    - *Method:* Scan **0.02% Toluene in Hexane**.

- *Acceptance:* The ratio of absorbance at the maximum (269 nm) to the minimum (266 nm) should be ≥1.5.

4. **Photometric Accuracy:**

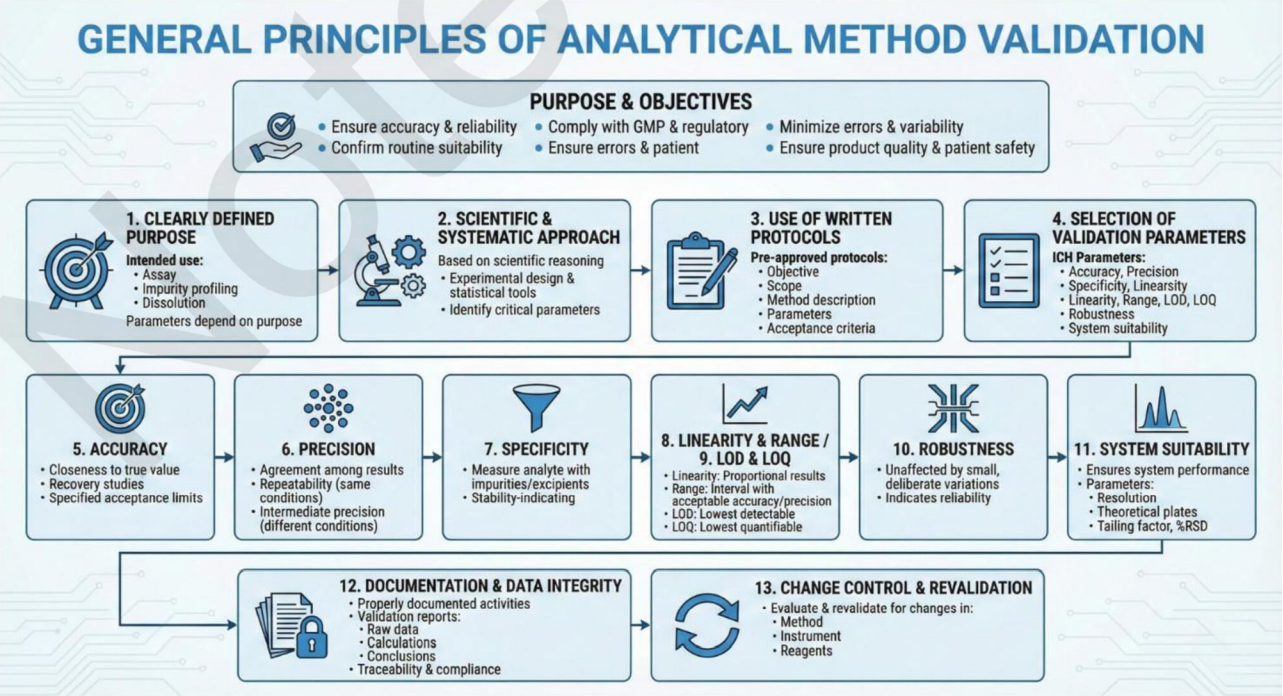
- *Goal:* Ensure absorbance reading is correct.
- *Method:* Measure **Potassium Dichromate** solution.
- *Acceptance:* Absorbance values must match standard values within limits.

General Principles of Analytical Method Validation

Analytical Method Validation is the documented process that demonstrates that an **analytical method is suitable for its intended purpose** and consistently produces **accurate, precise, and reliable results** for the analysis of pharmaceutical substances and products.

Objectives of Analytical Method Validation

- To ensure **accuracy and reliability** of analytical results
- To confirm **suitability of the method** for routine analysis
- To comply with **GMP and regulatory requirements**
- To minimize **analytical errors and variability**
- To ensure **product quality and patient safety**



General Principles

Clearly Defined Purpose

- The method must have a **clearly stated intended use**, such as:
  - Assay of API
  - Impurity profiling
  - Dissolution testing
- Validation parameters depend on the **purpose of the method**.

Scientific and Systematic Approach

- Validation should be based on **scientific reasoning**.
- Use appropriate experimental design and statistical tools.
- Critical method parameters must be identified and controlled.

Use of Written Protocols

- Validation must be performed as per **pre-approved validation protocols**.
- Protocols should include:
  - Objective and scope
  - Method description
  - Validation parameters
  - Acceptance criteria

Selection of Validation Parameters

The following parameters are commonly evaluated (as per ICH):

- **Accuracy**
- **Precision** (repeatability, intermediate precision)
- **Specificity**
- **Linearity**
- **Range**
- **Limit of Detection (LOD)**
- **Limit of Quantification (LOQ)**
- **Robustness**
- **System suitability**

Accuracy

- Measures the **closeness of test results to the true value**.
- Usually evaluated by **recovery studies**.
- Results should fall within specified acceptance limits.

Precision

- Expresses the **degree of agreement among individual results**.

- Types:
  - Repeatability (same analyst, same day)
  - Intermediate precision (different days, analysts, equipment)

Specificity

- Ability of the method to **measure the analyte in the presence of impurities, degradants, or excipients**.
- Essential for stability-indicating methods.

Linearity and Range

- **Linearity:** Ability to obtain results directly proportional to concentration.
- **Range:** Interval between upper and lower concentration levels with acceptable accuracy and precision.

LOD and LOQ

- **LOD:** Lowest amount detectable but not necessarily quantifiable.
- **LOQ:** Lowest amount that can be quantified with accuracy and precision.

Robustness

- Measures the method's **capacity to remain unaffected by small, deliberate variations** in parameters.
- Indicates method reliability during normal usage.

System Suitability

- Ensures the analytical system performs adequately before sample analysis.
- Parameters include:
  - Resolution
  - Theoretical plates
  - Tailing factor
  - %RSD

Documentation and Data Integrity

- All validation activities must be **properly documented**.
- Validation reports should include:
  - Raw data
  - Calculations
  - Conclusions
- Ensures **traceability and regulatory compliance**.

Change Control and Revalidation

- Any change in:

  - Method
  - Instrument
  - Reagents
- Requires evaluation and **revalidation if necessary**.

Good Warehousing Practice (GWP)

Definition:

Good Warehousing Practice (GWP) is a part of Quality Assurance that ensures pharmaceutical products are stored under controlled conditions to maintain their quality, safety, and efficacy from the time of receipt until distribution.1

Objectives:

1. **Prevent Contamination:** Protection from dust, pests, and cross-contamination.[2]
2. **Prevent Mix-ups:** Avoiding confusion between different batches, strengths, or products.[3]
3. **Maintain Stability:** Controlling temperature, humidity, and light.
4. **Security:** Preventing theft and adulteration.[4]

Core Elements of GWP (The "Must-Haves")

1. **Premises & Design:**
   - **Location:** Free from open sewage, drains, or hazardous fumes.
   - **Layout:** Must follow a logical flow to avoid cross-contamination.[5]
   - **Flooring:** Smooth, crack-free, and easy to clean (often epoxy coated).
   - **Loading/Unloading Bays:** Should be covered to protect materials from weather.
2. **Storage Zones (Segregation):**

Pharmaceutical warehouses must have clearly demarcated areas:

   - **Receiving Area:** For cleaning and de-dusting incoming goods.

- **Quarantine Area (Yellow Label):** For materials awaiting QC testing. Access is restricted.
- **Approved/Released Area (Green Label):** For materials passed by QC.
- **Rejected Area (Red Label):** A *locked* area to store failed materials prevents accidental use.
- **Storage Conditions:**
  - *Cold Storage: 2°C - 8°C* (e.g., Insulin, Vaccines).
  - *Cool Storage: 8°C - 25°C.*

3. **Sanitation & Hygiene:**
   - Written sanitation programs (SOPs) must be available.
   - **Pest Control:** Rodent traps and UV fly killers must be installed and logs maintained.
   - Prohibition of eating, drinking, or smoking in storage areas.
4. **Documentation:**
   - **SOPs:** For Receipt, Storage, Cleaning, and Dispatch.
   - **Bin Cards:** Attached to racks showing Stock In, Stock Out, and Balance.
   - **Temperature/Humidity Logs:** Recorded twice daily (manual or digital data loggers).

Materials Management

Definition: Materials management is the scientific process of planning, purchasing, storing, and controlling the flow of materials to ensure the **"5 Rights"**:

1. Right **Quality**
2. Right **Quantity**
3. Right **Time**
4. Right **Source** (Vendor)
5. Right **Price**

Objectives in Pharmacy:

- To ensure continuous supply of drugs/chemicals for production or sale.
- To minimize the money locked up in "Dead Stock" (inventory cost).
- To reduce wastage due to expiry or pilferage.

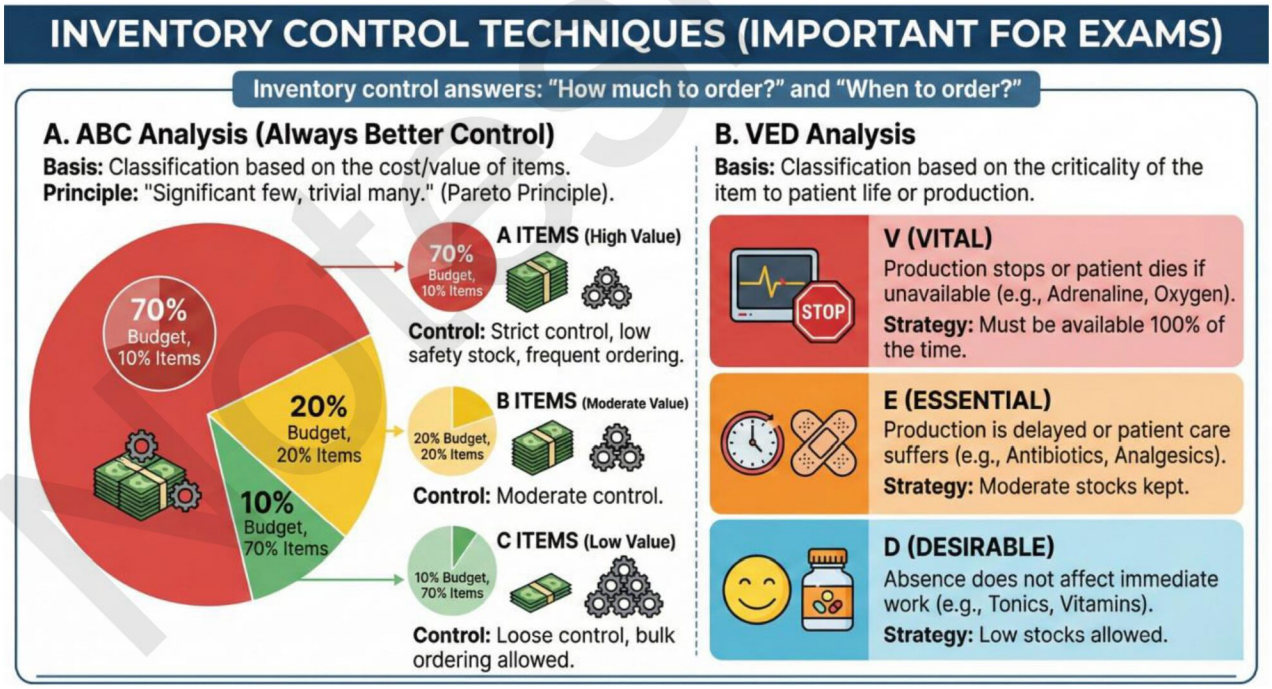
Inventory Control Techniques (Important for Exams)

A. ABC Analysis (Always Better Control)

- **Basis:** Classification based on the **cost/value** of items.
- **Principle:** "Significant few, trivial many." (Pareto Principle).
    - **'A' Items (High Value):** 10% of total stock items but consume **70% of the budget**.
        - *Control:* Strict control, low safety stock, frequent ordering.
    - **'B' Items (Moderate Value):** 20% of items, consume **20% of the budget**.
        - *Control:* Moderate control.
    - **'C' Items (Low Value):** 70% of items, consume only **10% of the budget**.
        - *Control:* Loose control, bulk ordering allowed.

B. VED Analysis

- **Basis:** Classification based on the **criticality** of the item to patient life or production.
    - **V (Vital):** Production stops or patient dies if unavailable (e.g., Adrenaline, Oxygen).
        - *Strategy:* Must be available 100% of the time.
    - **E (Essential):** Production is delayed or patient care suffers (e.g., Antibiotics, Analgesics).
        - *Strategy:* Moderate stocks kept.
    - **D (Desirable):** Absence does not affect immediate work (e.g., Tonics, Vitamins).
        - *Strategy:* Low stocks allowed.



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