



PHARMACEUTICAL VALIDATION

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Introduction

- Validation is the documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result.
- ISO definition - 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 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.”

Method validation

- Method validation is the process of establishing the performance characteristics and limitations of a method and the identification of the influences which may change these characteristics and to what extent.
- It is also the process of verifying that a method is fit for purpose , includes
 - Formulation development methods
 - Analytical methods
 - Cleaning methods

When is validation needed?

- Before introduction of a new method into routine use.
 - Whenever the conditions change for which a method has been validated, e.g., instrument with different characteristics
 - Whenever the method is changed, and the change is outside the original scope of the method.
 - Whenever use new drug/materials
- Purpose of validation
- To accept an individual sample as a member of a population under study.
 - To admit samples to the measurement process.
 - To minimize later questions on sample authenticity.
 - To provide an opportunity for resampling when needed.

Requirement/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
- A specific programme for validation activities in place

Scope of validation

- Validation done in a structured way according to documentation including procedures and protocols.
- Validation should be performed for
 - new premises, equipment, utilities and systems
 - new processes and procedures; at periodic intervals;
 - whenever major changes have been made.
- Validation in accordance with written protocols.

Scope of validation

- Demonstrate suitability for new manufacturing formula/method
- A written report on the outcome to be produced.
- 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.)
 - Demonstrate suitability for new manufacturing formula or method

Advantages of validation

- During the process the **knowledge** of process increases
- Assures the **repeatability** of the process
- Assures the **fluency of production**
- Assures that the product is continuously according to the **marketing authorisation**
- **Decreases the risk** of the manufacturing problems
- **Decreases the expenses** caused by the **failures in production**
- **Decreases the risks** of failing in GMP
- **Decreases the expenses** of the every day production even though the validation itself will create expense

Types of Process Validation

- Prospective validation
- Concurrent validation
- Retrospective validation
- Revalidation

Prospective validation

- Conducted prior to market of products
- performed for all new equipment, products and processes.
- It is a proactive approach of documenting the design, specifications and performances before the system is operational.
- This is the most defensible type of validation.
- Carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps.
- Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set.

Prospective validation

- At least 3 batches /trials are then performed and evaluated, and an overall assessment is made.
- If, at the end, the results are acceptable, the process is satisfactory.
- Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory.
- This form of validation is essential in order to limit the risk of errors occurring on the production scale.

Concurrent validation

- It is a process where current production batches are used to monitor processing parameters.
- It gives of the present batch being studied, and offers limited assurance regarding consistency of quality from batch to batch.
- The first three production-scale batches must be monitored as comprehensively as possible.
- Examples of these may be when:
 - A previous validated process is being transferred to a third party contract manufacturer or to another site.
 - Process with low production volume per batch and market demand
 - The product is a different strength of a previously validated product with the same ratio of active or inactive ingredients

Retrospective validation

- It is conducted for a product already being marketed and is based on extensive data accumulated over several lots and over time.
- This validation may be used for older products which were not validated by the fabricator at the time that they were first marketed.
- Retrospective validation is only acceptable for well established detailed processes.
- It will be inappropriate when there have recent changes in the formulation of the products, operating procedures, equipment & facility

Re-validation

- Process re-validation is required when there is a change in any of the critical process parameters ,formulation, primary packaging components, major equipments or premises
- Examples when process re-validation is required when:-
- Changes in raw materials (physical properties such as density ,viscosity, particle size distribution)
 - Changes in source of active raw material manufacturer
 - Changes in packaging material (primary container/ closure system)
 - Changes in the process (Mixing time, drying temperatures & batch size)
 - Changes in the equipment
 - Changes in the plant/facility

Organization for validation

- The qualification and validation work can be organized by employing one or more of the following structures :
 - **The consultant**
 - **The task force**
 - **The dedicated group.**
- Ideally there should be a department in the organization.
- But if it is not possible then, these alternative approaches are used for the work.

Organization for validation

- **The Consultants**
- The consultants is on the commercial basis several consultants undertake the work.
- Consultants can apply the experience gained in the other companies.
- The persons with consultants may not be permanent employees, they may be on contractual basis.
- There is a risk of incomplete job and extra expenses, if the validation job is not completed by the consultants within the bounds of time and cost.

Organization for validation

- The task force
 - The task force concepts refers to **organisation structure with in the company in which persons proficient in different fields are drawn from different departments.**
 - Usually, **persons are drawn from different departments.**
 - The departments are **production, engineering , quality assurance, research and developments.**
 - The **head of the committee** is responsible for validation work.

Organization for validation

- The dedicated group
- In the dedicated group members from the following departments are selected
 - Production
 - Engineering
 - Calibration laboratory
 - Quality control laboratory
 - Maintenance
 - HVAC (Heating Ventilation and Air Conditioning System)
 - Product development

Once the validation team has been constituted and mission have been formalized, the **team will interact with different departments**.

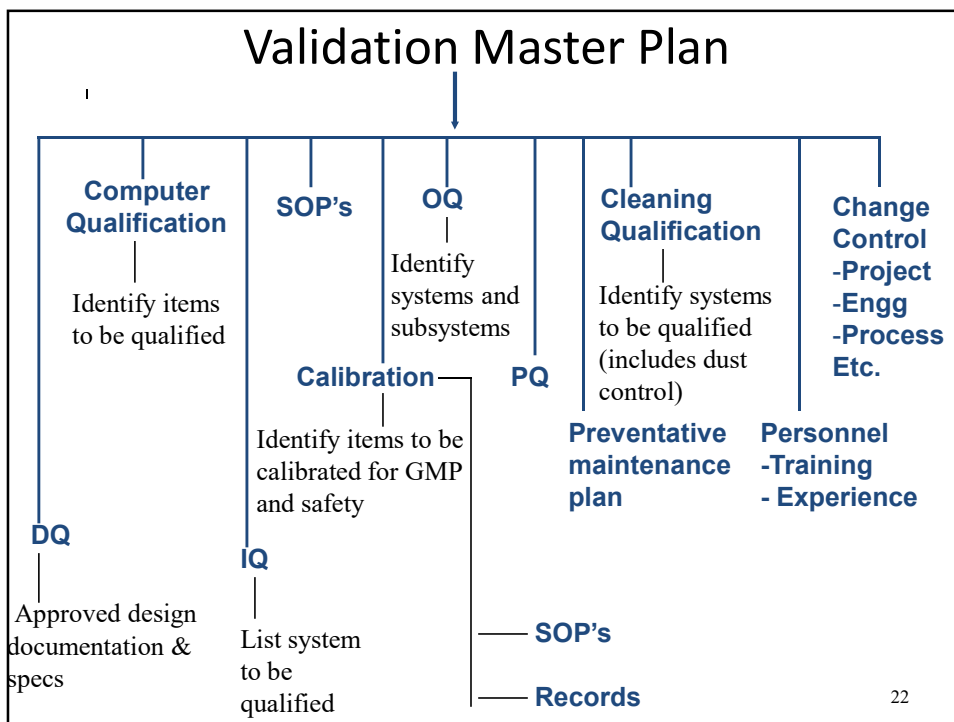
Documentation of validation

- The validation activity **cannot be completed without proper documentation** of each and every minute activity with utmost details.
- Documentation of validation is **generally different types** such as:
 - Validation Master Plan (VMP)
 - Validation protocols (VP)
 - Validation reports (VR)
 - Standard Operating Procedures (SOPs)

Validation Master Plan(VMP)

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

- In short, it is a documented evidence that provides a high degree of assurance that a specific process will consistently produce a product the meets its predetermined specifications and quality attributes.



Why to perform VMP?

- VMP has become an important component an **industry standard and regulatory requirement as well.**
- 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.

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Who performs VMP?

Members:

- Validation manager,
- Quality Assurance dept.
- Member from production
- Member Engineering (utilities)
- Member from Calibration lab
- Member from QC lab
- Member from Maintenance
- Member from HVAC dept
- Member from Product development lab

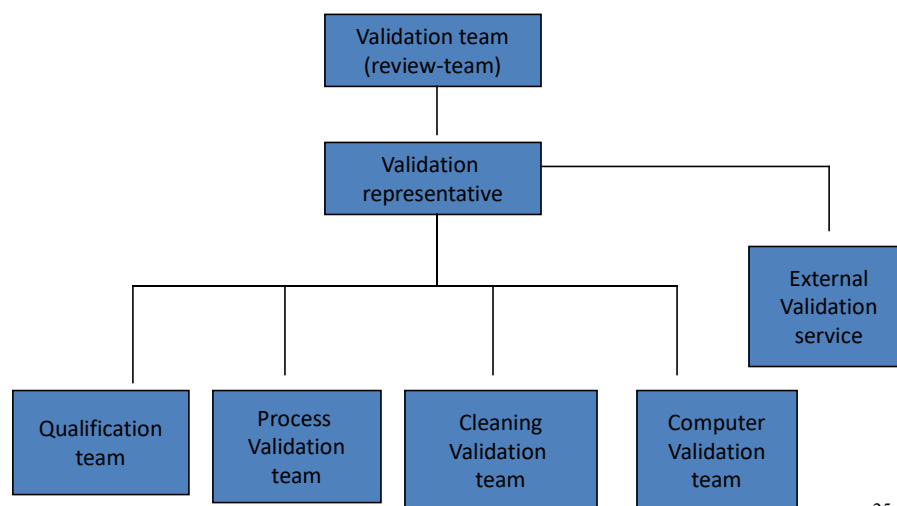
Qualification:

- Qualification must be in accordance with the job requirement in combination with experience.
- the resumes of validation team members are presented in a separate folder, including contract help.

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Who performs VMP?

Organization chart:



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Validation Master Plan

- **The Validation Master Plan could consist of:**
 - Introduction and objectives
 - Approval page and table of contents
 - Facility and process description
 - Personnel, planning and scheduling
 - Responsibilities of committee members
 - Process control aspects
 - Equipment, apparatus, processes and systems to be validated
 - Acceptance criteria
 - Documentation e.g. validation protocols and reports
 - SOPs
 - Training requirements

Validation protocols

- **Protocol consists of :**
 - Objectives of the validation and qualification study
 - Site of the study
 - Responsible personnel
 - Description of the equipment
 - SOPs
 - Criteria for the relevant products and processes

Validation reports

- **Report consists of :**
 - Title Objective of the study
 - Refer to the protocol
 - Details of material
 - Equipment
 - Programmes and cycles use
 - Details of procedure and test methods

Which Factors/content are considered in VMP?

Contents of VMP:

- Methodology
- Qualification
 - DQ
 - IQ
 - OQ
 - PQ
- Personnel
- Schedule
- Preventative maintenance
- Change control
- Procedure
- Documentation
- Appendices

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Which Factors/content are considered in VMP?

Methodology:

- This section should address the **predetermined requirements by identifying the standards** that are to be applied to the facility.
- These are then used in the **development of the acceptance criteria** that are used to judge the validation.
- It also involves **planning and execution of documents** such as, protocols, records, reports, or other.
- The standards will involve **three elements**:
- **Regulatory and guidance documents**
- **National standards**
- **Company standards**

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Which Factors/content are considered in VMP?

Qualification:

- This section encompasses all aspects of the design, procurement, installation, and commissioning process.
- Instrument performance/ qualification:
 - DQ, ID, OQ,PQ etc..
- Providing documented evidence that the design of the facility and equipment meet the requirements of the user specification and GMP.

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Which Factors/content are considered in VMP?

Personnel:

- “ Each person engaged in supervising the manufacture, processing, packaging or holding [of] a drug product shall have the education, training, and experience, or a combination thereof, to enable that person to perform the assigned functions.”
- The VMP should lay down the principles for personnel requirements.
- It must address the aspects like; experience of personnel (written biographies or CV), in-house training reports, etc.,

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Which Factors/content are considered in VMP?

Schedule:

- The working program is essential and should be prepared at an early stage.
- A good plan will contain all the necessary features which are to be considered during execution of a plan and determines the control of the project.
- It ensures that all the personnel involved in the VMP are not only aware of the engineering targets, but also the validation targets.

Preventative maintenance:

- This is the responsibility of Site maintenance and Operation dept.
- This activity should be performed during the design phase, and the documentation required should be, included in the requisition.

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Which Factors/content are considered in VMP?

Change Control:

- This section of VMP should lay down requirements for a set of procedures for change control that cover:
 - The project through design, construction, and commissioning
 - The ongoing change that will inevitably occur in both the process and the equipment and engineering aspects.

Procedures:

- These cover engineering standards used in the project design, through to commissioning phases, and the facilities standard procedures (SOPs).

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Which Factors/content are considered in VMP?

Documentation:

- This section usually used to identify the documentation that should be produced for the processing like;
- Factory acceptance documents
 - IQ documents
 - OQ documents
 - PQ documents

Appendices:

- The appendix is mostly used VMP to hold the information of type of documents and formats that will be used in the execution stage.

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How VMP is prepared?

(contd..)

Protocol:

- VMP includes the incorporation of information into formal written protocols, which serve as guides for executing the appropriate validation activities.
- Protocols should be developed for IQ, OQ, PQ.
- The information included in specific protocols are:
 - Description of the system
 - Qualification objective
 - Scope
 - Responsibilities and data collection procedures
 - Test procedures, specific acceptance criteria
 - Documentation procedures
 - Summary and deviation report

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How VMP is prepared?

(contd..)

Installation Qualification: IQ

- It is performed to verify that the installed components are the ones specified, that they are properly identified, and so on, as stated in the construction documents in accordance with the specific requirements of the user.
- IQ protocol includes:
 - Spec. ref., including purchase orders and contract no.s
 - Verification of Calibration of critical installed components
 - Verification of procedure (e.g., operation, maintenance, cleaning, change control)
 - Verification of major components
 - Verification of control and monitoring devices
 - Verification of utilities connections
 - Lubricants
 - Final drawing, Reference manuals

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How VMP is prepared?

(contd..)

Operational Qualification: OQ

- This involves the testing of various components of the system, process, or equipment to document proper performance of these components.
- OQ protocol includes:
 - Verification of test equipment calibration
 - Verification of controls and indicators
 - Computer control system testing
 - Verification of sequence of operations
 - Verification of major components of operation
 - Verification of alarms
 - Power failure/recovery testing
 - Functionality testing of distribution system, valves, etc.
 - System initial sampling

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How VMP is prepared?

(contd..)

Performance Qualification: PQ

- This involves challenging the system, process, or equipment to provide evidence of appropriate and viable operation.
- PQ protocol includes:
 - System sampling
 - Equipment -start tests
 - System invasive tests
 - Equipment robustness test
 - Appropriate data/results

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How VMP is prepared?

(contd..)

Change control procedure:

- This procedure is essential for the continual operation of the system, process, or equipment and provides a **formal mechanism for monitoring changes during the continued operation of the system.**
- The **proposed changes that can affect the validated status of a system** are reviewed by the validation team or **responsible personnel and the proposed corrective action is approved.**
- Sufficient **detailed documentation is necessary for each critical change to maintain control over the system with the passage of time.**

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How VMP is prepared?

(contd..)

Change control procedure:

Various changes can be categorized as:

- a. Process equipment and system hardware change control
- b. Software change control
- c. Process change control
- d. Multiple changes
- e. Emergency changes
- f. Planned changes
- g. Repetitive changes

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Cleaning validation

- Cleaning validation (CLV) is a **written evidence that determines the a specified cleaning procedure will lead to reliable and repeatable results in the cleaning of surfaces with and without contact with the product.**
- It is shown that the following criteria are fulfilled:
 - The concentration of active substances on product contact surfaces will not exceed specified limits.
 - The concentration of highly active substances (e.g., hormones or cytostatics) on surfaces without contact with the **product will not exceed specified limits.**
 - The concentration of **other pharmacologically active substances (e.g., process and cleaning materials or disinfectants)** in the product to follow will not exceed specified limits
 - The number of **germs on product contact surfaces will not exceed specified limits.**

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Contents of CLV plan

The CLV plan should contain following points:

- Which manufacturing processes must be validated (product matrix)
- Which kind of validation (prospective, retrospective or concurrent) must be done
- Schedule of the validation of product process
- Number of batches that must be used for validation (normally 3 batches)
- batches of the quantity assigned for production)
- Responsibilities

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Contents of CLV program

- Purpose of validation
- Responsibilities
- Composition of the product (formulation)
- Description of
 - Substance that should be detected
 - Cleaning procedure
 - Sampling method
 - Analytical method used
 - Evaluation methods used for the result
 - Acceptance criteria

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Contents of CLV plan

- Description of the plant to be cleaned and of the sampling location
- Description of the sampling procedure
- Time between end of production and sampling
- No. of test runs (test runs must be performed by qualified personnel only)
- Description of procedure in case of exceeded acceptance criteria

Calibration Master Plan(CMP)

CALIBRATION

- To maintain the accuracy and precision of test equipment at all times.
- To ensure highest level of confidence in all measurement that affect materials disposition decision, with unbroken chain of traceability to national standard.
- To determine whether the equipment is still fit for its intended purpose.
- It is based on the comparison of a primary standard or instrument of known accuracy with another equipment (to be calibrated)
- It is used to detect, correlate, report or eliminate by adjustment of any variation in the accuracy of the equipment being calibrated.

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Why Calibrate?

- **Components age and equipment undergoes changes in temperature or humidity or sustains mechanical stress, performance degrades.**
- Some times the test results become unreliable due to instrument fault- is **called drift.**
- While drift cannot be eliminated, it can be detected and either corrected or compensated for through the process of calibration.
- Historical Issues
 - Cost, cost,....
 - Limited technical oversight or understanding
 - Most staff afraid of it...

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Why Calibrate?

If it's done right, this gives you!

- Properly calibrated equipment provides confidence that your products/services/results meet their specifications
- Calibration
 - Optimizes resources;
 - Ensures consistency; and
 - Ensures measurements (and perhaps products) are compatible with those made elsewhere.
- By making sure that your measurements are based on international standards, you promote acceptance of your products/services/results.

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EQUIPMENT CLASSIFICATION

- **Critical instrument** is an instrument within an equipment/system where the operation, contact, data, control, alarm or failure may have a direct impact on the quality of a product.
 - 1.The instrument/component controls critical process that may affect product quality.
 - 2.The instrument/component is used to monitor the parameters of the manufacturing process.
 - 3.Failure or alarm of the instrument/component will have a direct impact
- **Non-critical instrument** is an instrument within an equipment/system where the operation, contact, data, control, alarm or failure will have no impact on the quality of the product.

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CALIBRATION INTERVAL

Depending on:

- Classification of Critical or non-critical
- Usage (light or heavy usage)
- Handling (light or heavy handling)
- Manufacturer's recommendation
- Reference to NIST or accreditation body guideline for a specific measurement system

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CALIBRATION INTERVAL

- **Periodic Review**
- The Calibration Master Plan shall be reviewed once in one year to ensure compliance and to determine whether a change is required due to following reasons.
 - 1. Changes in the Calibration Approach
 - 2. Changes in Key Calibration Requirements.
 - 3. Modication or renovation of existing facility.

Criticality Assessment Team (CAT)

- The representatives of following disciplines shall represent the CAT:
 - Manufacturing
 - Engineering / Instrumentation
 - Quality Assurance
- The manufacturing person shall sign the Calibration calendar to accept that the specification of the listed instrument and its limits are appropriate to the related product and process.
- The Engineering representative shall confirm that all instruments are recorded and scheduled for calibration appropriately within the Calibration calendar
- The QA representative shall also sign the Calibration calendar to qualify that the specification of the listed instrument and its limits are appropriate to the related product and process.
- QA have the final signature to approve the Calibration

RANGE AND LIMITS

- While deciding on calibration ranges and limits, the manufacturer's accuracy and the process requirements shall be taken into account.
- For example, an instrument would normally be calibrated across its operating or full range.
- **Calibration Accuracy:** The agreed specific working accuracy of the instrument.
- This is usually set at the manufacturer's accuracy, but could be relaxed or increased to reflect the process requirements.
- **Calibration Failure Limits:** The limits set for instrument failure, as determined by the process requirements or results go beyond the acceptance criteria.
- If the calibration failure limits are exceeded then a possible non-conformance has occurred, and the response should be documented.
- **Calibration Acceptance Limits:** The limits set for instrument Acceptance
- If the readings are go beyond calibration acceptance limits then a possible **non-conformance has occurred**, and the response should be documented.

NON CONFIRMANCE REPORT

- **Non-Conformance**
- A non-conformance investigation shall be conducted when a critical instrument has failed to meet the acceptance criteria for the calibration.
- If the ‘as found” **results indicate that the instrument is outside the calibration limits, then** the following actions are taken:
 - 1. Previous calibration labels shall be removed, where applicable.
 - 2. An ‘out of calibration’ label shall be attached.
 - 3. A non-conformance report shall be raised for all failed critical instruments.
 - 4. The action to repair, adjust, or replace the instrument shall be followed.
 - 5. The impact study shall be done as per the current version of SOP on corrective & Preventive action.
- In the event of non-conformance, on the basis of impact study the QA department shall be informed to recall of approved /dispatched products.

PERIODICITY

- **Periodicity**
 - The periodicity of calibration shall be based on the Category of instrument Critical instrument, Non Critical Instrument.
- **In-house calibration**
 - The frequency of calibration is once in a year for non critical Instruments & once in half year for critical Instruments or as defined in the respective sop of the instruments.
- **External agency calibration**
 - The frequency of calibration is once in a year for non critical Instruments & once in half year for critical Instruments or as defined in the respective sop of the instruments.

GRACE PERIOD FOR CALIBRATION

- **External agency calibration**
 - The frequency of calibration is once in a year for non critical Instruments & once in half year for critical Instruments or as defined in the annual calibration calendar.
- **Equipment/Instruments requiring scheduled calibration will have a standard grace period. As given below:**
 - Annual calibrations will have a grace period of ± 14 days.
 - Half-yearly calibrations will have a grace period of ± 10 days.
 - Quarterly calibration will have a grace period of ± 7 days.
 - Monthly calibration will have a grace period of ± 4 days.
 - **Daily calibration will have no grace period and should be done on every working day.**

REFERENCE STANDARD&MATERIAL

- **Primary standard**
 - Highest accuracy order in the measurement system
 - Traceable to National or International standard
- **Reference Standard**
 - It shall be calibrated by a body that can provide traceability.
 - Such reference standard of measurement held by the laboratory shall be used for calibration only.
 - It shall be calibrated before and after any adjustment
- **Reference Materials**
 - Where possible, it shall be traceable to SI units of measurement, or to Certified Reference Materials.
 - Internal Reference Material shall be checked as far as is technically and economically practical

CALIBRATION IDENTIFICATION

- Status of equipment calibration shall be available and affixed to the equipment where applicable.
- Equipment identification shall bear the following information:
 - ✓ name of equipment
 - ✓ serial no.
 - ✓ date calibrated
 - ✓ status
 - ✓ schedule of next calibration and
 - ✓ initial/signature of the person who performed the calibration

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CALIBRATION PROCESS

- **Calibration process must be managed and executed in a professional manner:**
 - A particular place for all calibration operations to take place and keeping all instruments for calibration
 - A separate room is preferred because (1) **better environmental** control and (2) **better protection against unauthorized handling or** use of the calibration instruments.
 - The performance of all calibration operations is assigned as the **clear responsibility of just one person.**
 - Calibration procedures, **used for quality control functions, are controlled by the international standard ISO 9000.**
 - It requires **that all persons using calibration equipment be adequately trained.**

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OUT OF CALIBRATION

- If any instrument met out of calibration
 - Remove equipment from use
 - Out of Calibration Investigation to be carried out to determine the source of inaccuracy
 - Evaluate the impact on the final product quality and other previously measured data
 - All investigation findings should be documented

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CALIBRATION RECORDS

- Calibration Master Plan
 - Include the control of all critical measurement equipment that contain the following details
 - Name
 - Identification by model # and serial #
 - Location
 - Owner/Responsible
 - Calibration Frequency
 - Calibration due date
- Calibration Certificate
- Calibration Procedure

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CALIBRATION CERTIFICATE

- Name and address of contracted calibration laboratory
- Name and address of client
- Description and identification of item calibrated
- Environment conditions when calibration was made
- Date of receipt of instrument, date of calibration and date of next calibration
- Calibration method
- Result of calibration
- Signature and title of person responsible for the calibration
- External calibration contract shall be awarded to Accredited by the nation institution



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Validation process of some specific dosage forms (Tablets)

- Identify the key physicochemical properties of the drug substance that need to be considered in developing the formulation; such as the following:
 - Solubility of the drug substance throughout the physiological p H range.
 - Particle size distribution
 - Surface area.
 - Morphology.
 - True and bulk density.
 - Material flow and compressibility.
 - Hygroscopicity .
 - Melting point.

Validation of tablets..

- Identify some common process variables may change during the manufacture of tablets are
 - Particle size of drug substance
 - Bulk density of drug substance/excipients
 - Powder load in granulator
 - Amount and concentration of binder
 - Mixer speed and mixing times
 - Granulation moisture content
 - Milling conditions
 - Lubricant blending times
 - Tablet hardness
 - Coating solution spray rate

Evaluation of process

- **MIXING/BLENDING:**
- May occur once/several times in tablet manufacturing process.
- Ex.1: Direct compression granulation may involve one blending step.
- Ex.2: Wet granulation formulation may involve two mixing/blending steps.
- Following physical properties of drugs and excipients are considered in creating a uniform mix / blend:
 - Bulk density.
 - Particle shape.
 - Particle size distribution.
 - Surface area.

- Other factors to be considered are ;
 - Mixing / blending technique
 - diffusion(tumble), convection (planetary), pneumatic(fluid bed), shear mixing.
 - Mixing / blending speed- low/high shear & rpm.
 - Mixing / blending time- less time leads to less mixing.
 - Over mixing leads to de-mixing.
 - Drug uniformity.
 - Excipient uniformity.
 - Two key excipients are : Lubricants and Colorants.
 - Equipment capacity/ load – less than the capacity leads to over mixing.;
 - More than the capacity leads to inefficient mixing.

Wet granulation

Control parameter Fixed	Variable monitor	Response (Test)
<ul style="list-style-type: none"> • Granulation equipment • Batch size 	<ul style="list-style-type: none"> • Mixing speed • Amount of granulating fluid • Feed rate • Granulation time • Total load of materials 	<ul style="list-style-type: none"> • Drug content uniformity • Water/solvent content • Particle size & distribution • Consumption of amount of binder solution

- **Wet granulation**

- What type of wet granulation technique will be used?
- Will it be low shear (e.g., Hobart), high shear (e.g., Diosna, GEI-Collette) or fluid bed (e.g., Glatt, Fluid Air)?
- Each technique will produce granules with different physical properties and will require monitoring of different processing parameters.
- Wet granulation parameters to be considered during development and validation are:

- **Binder addition:**

- Should the binder be added as a granulating solution or dry like the other excipients?
- Adding the binder dry avoids the need to determine the optimal binder concentration and a separate manufacture for the binder solution.

- **Binder concentration:**

- The optimal binder concentration will need to be determined for the formulation.
- If the binder is to be sprayed, the binder solution needs to be dilute enough so that it can be pumped through the spray nozzle.
- It should also be sufficiently concentrated to form granules without overwetting the materials.

Wet milling

- Wet granules that have a wide aggregate range can lead to inefficient drying.
- Factors to be considered are;
- Equipment size and capacity.
- Screen size.
- Mill speed.
- Feed rate – related to above three factors.

Fluid bed dryer (drying)

Control parameter Fixed	Variable monitor	Response (Test)
<ul style="list-style-type: none"> Hot air blow speed Porosity of filter bags Bowl size 	<ul style="list-style-type: none"> Inlet/outlet temperature Drying temp Product temp Drying time Humidity of air 	<ul style="list-style-type: none"> Moisture content Particle size & distribution LOD Density of powder

- DRYING:
- Determination & justification of the type of drying technique required.
- Depends on factors such as drug / formulation properties and equipment availability. Parameters to be considered :
- Inlet / outlet temperature.
- Airflow.
- Moisture uniformity.
- Equipment capability / capacity.

- **MILLING**
- An optimal particle size / size distribution for the formulation needs to be determined. Factors to be considered are;
- Mill type.
- Mill speed.
- Sreen size.
- Feed rate.
- **TABLET COMPRESSION**
- Appropriate flow during the process is required.
- Inadequate flow leads to 'rat holing'.
- Factors to be considered are;
- Tooling.
- Compression speed.
- Compression / ejection force. (to be continued...)

IPQC

- Following in-process tests should be examined;
 - Appearance.
 - Hardness.
 - Tablet weight.
 - Friability.
 - Disintegration.
 - Weight uniformity.

- TABLET COATING
 - Done for various reasons like
 - stability, taste masking, controlled release, product identification, aesthetics, safety-material handling.
 - Key areas to consider are;
 - Tablet properties.
 - Residual solvent level.
 - Equipment type.
 - Coater load.
 - Pan speed.
 - Spray guns
 - Application spray rate.
 - Tablet flow.
 - Inlet / outlet temperature and air flow.
 - Coating solution.
 - Coating weight. (to be continued...)

- Appearance testing of the tablets is critical during the coating operation.
- Items to look includes;
 - Cracking / peeling of the coating.
 - Surface roughness.
 - Color uniformity.
 - Coating efficiency should be determined for the coating operation.
 - The efficiency will determine the amount of coating solution overage that may be required.

ANALYTICAL METHOD VALIDATION

Analytical Method Validation

- Method validation is the process of proving that an analytical method is acceptable for its intended purpose.

Why validate the method ?

- To determine performance of method and parameters using equipment that is:
 - Within specification
 - Working correctly
 - Adequately calibrated
- Competent operators
- Development of new methods for new components.

Why is Method Validation Necessary?

- To increase the value of test results
- To justify customer's trust
- To trace criminals
- To prove what we claim is true
 - To support health care

E.g.

- To value goods for trade purposes
- To check the quality of drinking water

Responsibility of Analytical Chemist

- To increase reliability of laboratory results
- To increase trust of laboratory customers
- To prove the truth

When should Methods be Validated?

- New method development
- Revision of established methods
- When established methods are used in different laboratories/different analysts or show different results etc.
- QC indicates method changes
- Comparison of methods

What are methods requires validated documentation?

- CHROMATOGRAPHIC METHODS
- SPECTROPHOTOMETRIC METHODS
- CAPILLARY ELECTROPHORESIS METHODS
- PARTICLE SIZE ANALYSIS METHODS
- DISSOLUTION METHODS
- TITRATION METHODS
- AUTOMATED ANALYTICAL METHODS

How should Methods be Validated?

1. Validation in a group of laboratories

- Collaborative studies
- Inter-laboratory comparisons

2. Validation in a single laboratory

- Comparisons with CRMs (Certified Reference Material)
- Comparisons with other methods that are validated

Considerations Prior to Method Validation

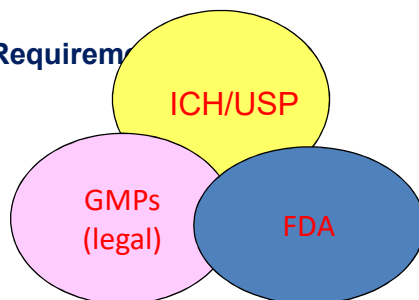
- Suitability of Instrument
 - Status of Qualification and Calibration
- Suitability of Materials
 - Status of Reference Standards, Reagents, Placebo Lots
- Suitability of Analyst
 - Status of Training and Qualification Records
- Suitability of Documentation
 - Written analytical procedure and proper approved protocol with pre-established acceptance criteria

Validation Steps

- Define the application, purpose and scope of the method.
- Analytes? Concentration?
- Develop a analytical method.
- Develop a validation protocol.
- Qualification of instrument.
- Qualify/train operator
- Qualification of material.
- Adjust method parameters and/or acceptance criteria if necessary.
- Perform full validation experiments.
- Develop SOP for method of analysis.
- Document validation experiments and results in the validation report.

Purpose of Method Validation

- Identification of Sources and Quantitation of Potential errors
- Determination if Method is Acceptable for Intended Use
- Establish Proof that a Method Can be Used for Decision Making
- Satisfy FDA Requirements



What is NOT a Analytical Method Validation?

Calibration

The Process of Performing Tests on Individual System Components to ensure Proper function

- For example
 - HPLC Detector calibration
 - Wavelength Accuracy/ Linear Range/ Noise Level detection.

System Suitability

- Test to verify the proper functioning of the operating system, i.e., the electronics, the equipment, the specimens and the analytical operations.

Validation Requirements & Parameters

- Specificity
- Linearity
- Range
- Accuracy
- Precision
 - Repeatability
 - Intermediate Precision
 - Reproducibility
- Limit of Detection
- Limit of Quantitation
- Ruggedness
- Robustness

Specificity/Selectivity

- **Selectivity:**
 - The ability of the method to determine accurately the analyte of interest in the presence of other components in a sample matrix under the stated conditions of the test.
- **Specificity** is a state of perfect selectivity

Specificity/Selectivity

- **Confirmation vs repeatability**
 - Confirmation: Measure by more than one technique
 - Repeatability: Measure several times by one technique
- **How to establish selectivity:**
 - Compare the response of the analyte in a test mixture with the response of a solution containing only the analyte.

Specificity/Selectivity

The procedure to establish selectivity:

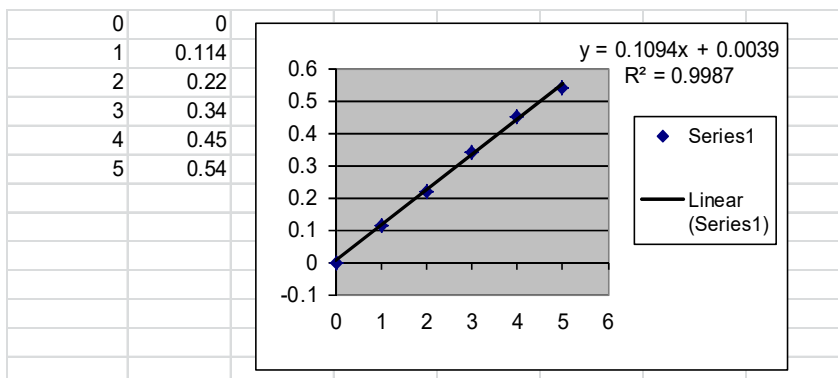
- Analyze samples and reference materials
- Assess the ability of the methods to confirm identity and measure the analyte
- Choose the more appropriate method.
- Analyze samples
- Examine the effect of interferences

Linearity

- The ability of the method to obtain test results which are proportional to the concentration of the analyte.
- Linearity should be evaluated by;
- By Visual Inspection of plot of signals vs. analyte concentration
- By Appropriate statistical methods
 - Linear Regression ($y = mx + b$)
 - Correlation Coefficient, intercept (b), slope (m)
- Acceptance criteria: Linear regression $r^2 > 0.95$ (0.999)
- **Requires a minimum of 5 concentration levels**

Linearity

Linear regression r^2



Visual inspection is required

Range

- **RANGE** is an analytical procedure shows the interval between the upper and lower concentration (amounts) of analyte in the sample as compared to standard/reference
- Acceptable range having linearity, accuracy and precision.
- For Drug Substance & Drug product Assay
 - 80 to 120% of test Concentration
- For Content Uniformity Assay
 - 70 to 130% of test Concentration
- For Dissolution Test Method
 - +/- 20% over entire Specification Range

Accuracy

- Closeness of the test results obtained by the method to the true value.
- Should be established across specified range of analytical procedure.
- Should be assessed using a minimum of 3 concentration levels, each in triplicate (total of 9 determinations)
- Should be reported as:
 - Percent recovery of known amount added

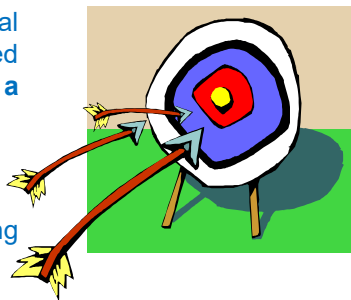


Accuracy Data

Amount Added (mg)	Amount Found (mg)	Percent Recovery/accuracy
0.0	0.0	---
50.2	50.4	100.5
79.6	80.1	100.6
99.9	100.7	100.8
120.2	119.8	99.7
150.4	149.7	99.5

Precision

- Precision is an analytical method that the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogenous sample
- Should be investigated using homogeneous, authentic samples.



Precision

Precision... Considered at 3 Levels

- Repeatability
- Intermediate Precision
- Reproducibility

Repeatability

- Precision under **repeatability** conditions:
 - Same method on identical test items, in the same laboratory, by the same operator, using the same equipment, within short time intervals.
- Should be assessed using minimum of 9 determinations (3 concentrations/3 replicates)

Intermediate Precision

<ul style="list-style-type: none"> ▪ Express within-laboratory variations. 	Day 1	Day 2
	100.6	99.5
<ul style="list-style-type: none"> ▪ Studies should include varying days, analysts, equipment, etc 	100.8	99.9
	100.1	98.9
<ul style="list-style-type: none"> ▪ Expressed in terms of standard deviation, relative standard deviation (coefficient of variation) and confidence interval. 	100.3	99.2
	100.5	99.7
	100.4	99.6
	Mean = 100.5	Mean = 99.5
	RSD = 0.24%	RSD = 0.36%

Grand Mean = 100.0 RSD = 0.59%

Reproducibility

- Precision under **reproducibility** conditions
- Same method on identical test items, in different laboratories, with different operators, using different equipment.

Lab 1		Lab 2		Lab 3	
Day 1	Day 2	Day 1	Day 2	Day 1	Day 2
Man 1	Man 2	Man 1	Man 2	Man 1	Man 2
3 Prep	3 Prep	3 Prep	3 Prep	3 Prep	3 Prep

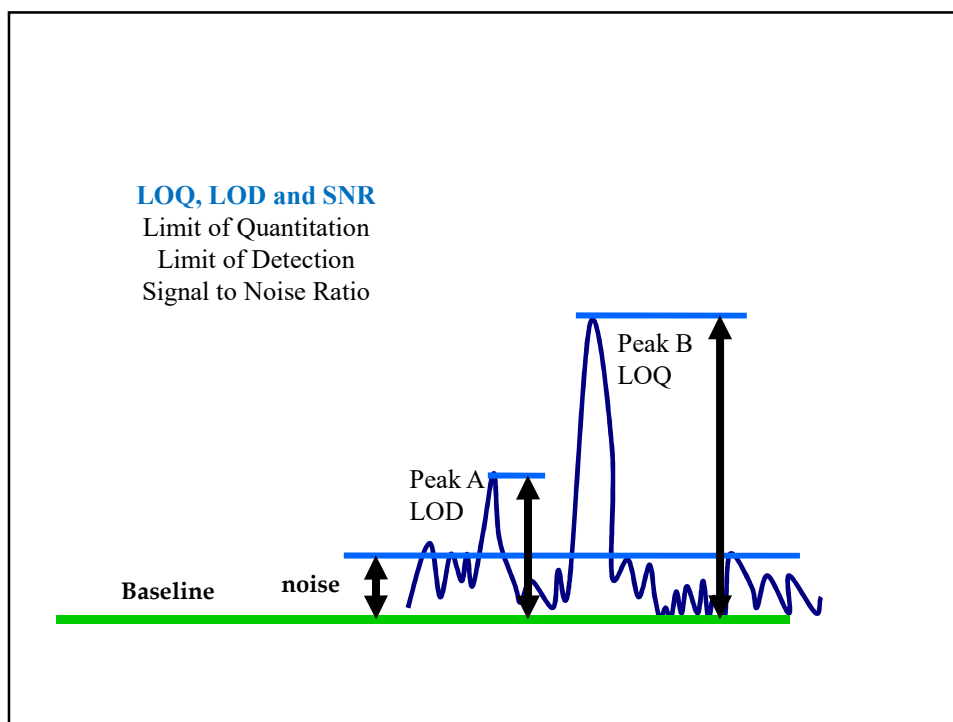
Limit of Detection (LOD) / Limit of Quantitation (LOQ)

LOD

- Lowest amount of analyte in a sample that can be detected but not necessarily quantitated.
- Estimated by Signal to Noise Ratio (SNR) of 3:1.

LOQ

- Lowest amount of analyte in a sample that can be quantified with suitable accuracy and precision.
- Estimated by Signal to Noise Ratio of 10:1.



Robustness

- Robustness is the Capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.
- **Determination:** Comparison results under differing conditions with precision under normal conditions
- **Examples of typical variations in analytical method**
 - Influence of variations of pH in a mobile phase
 - Influence of variations in mobile phase composition
 - Different columns (different lots and/or suppliers)
 - Temperature
 - Flow rate

Ruggedness

- **Degree of reproducibility of test results under a variety of conditions**
 - Different Laboratories
 - Different Analysts
 - Different Instruments
 - Different Reagents
 - Different Days
- **Expressed as %RSD**

Re-validation

- **When**
 - Method parameters have been changed
 - The scope of the method has been changed
 - Synthetic methods have been changed
 - Impurity profile has been changed
- **What**
 - Preferably everything. Exceptions should be scientifically justified.

THANK YOU

Questions..?