



Validation Master Plan

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Presentation Overview

1. Definition
2. Qualification and Validation
3. Qualification
4. Validation
 - Process Validation
 - Cleaning Validation
 - Analytical method
5. Change Control
6. Revalidation

Definition

Validation Master Plan- PIC/S

- A document providing information on the company's validation work programme.
- It should define details of and timescales for the validation work to be performed.
- Responsibilities relating to the plan should be stated.

Definition

Validation Master Plan. (WHO guideline):

- The validation master plan is a **high-level document that establishes an umbrella validation plan** for the entire project and summarizes the manufacturer's overall philosophy and approach.
- 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.

Qualification or validation?

A system must be *Qualified* to operate in a *Validated* process:

Qualify: a system and/or equipment

Validate: a process

E.g. *Qualify* an **autoclave**, whereas you *validate* a **Sterilisation process**

Definition

Qualification:

Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications properly installed, and/or work correctly and lead to the expected results

Validation.

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

Validation Master Plan (VMP)

1. Qualification and Validation
2. Planning for Validation
3. Documentation
4. Qualification
5. Process Validation
6. Cleaning Validation
7. Change Control
8. Revalidation

Purpose of VMP

The VMP should present an overview of the entire validation operation, its organisational structure, its content and planning.

A VMP helps management:

- to know the validation plan –plan for time, people & money, and
- understand the necessity for the programme;

A VMP helps all members of the validation team:

- to know their tasks and responsibilities.

A VMP helps GMP inspectors:

- to understand the firm's approach to validation and organisation of all validation activities.
- Organisational structure, its content and planning.

Is it one time activity?

- Qualification and validation can not be considered once-off exercises, For example, the start-up of a new manufacturing operation.
- It is an ongoing programme should follow its first implementation.

Validation

Basic Risk Analysis (BRA)

VMP

Detailed Risk Analysis (RA)

Qualification

Validation of Computerized Systems

Validation

Design Qualification (DQ)

Installation Qualification (IQ)

Operational Qualification (OQ)

Performance Qualification (PQ)

Process Validation

Cleaning Validation

Analytical Methods Validation

User requirement specifications

The requirements and specifications for the utility or equipment should be defined by the user and documented in the URS.

The URS should be used when selecting the required utility or equipment from an approved supplier, and to verify suitability throughout the subsequent stages of

VMP procedure

- Purpose & Scope
- Responsibility
- Validation policy
- Qualification of facilities, systems, equipment & utilities
- Validation: Process, cleaning, analytical methods & CSV
- Personal qualification
- Documentation format: Protocols and Reports
- Requalification & revalidation: while change & periodic
- planning and scheduling;
- change control – Qualification and Validation based on risk
- Reference to existing documents.
 - Validation schedule



Qualification of Facility, Equipment & system

Qualification

- **Design Qualification:** Documented verification that the proposed design of facilities, systems and equipment is suitable for the intended purpose.
- **Installation Qualification:** Documented verification that the installations (such as machines, computer system components, measuring devices, utilities and manufacturing areas) used in a processor system are appropriately selected and correctly installed in accordance with established specifications.

Qualification

- **Operational Qualification:** Documented verification that the system or subsystem operates as intended over all anticipated operating ranges.
- **Performance Qualification:** Documented verification that the equipment or system performs consistently and reproducibly within defined specifications and parameters in its normal operating environment (i.e. in the production environment)

Develop a Validation Master Plan

Qualification	Purpose
Design Qualification (DQ)	<p>Design specifications to ensure that all specified design elements have been included and that</p> <ul style="list-style-type: none">• the design meets the relevant regulatory and statutory requirements.
Installation Qualification (IQ)	<p>Verifies that</p> <ul style="list-style-type: none">• the equipment/system/process is installed correctly,• supplied as specified,• integrated into the site calibration and maintenance systems and available for use.
Operational Qualification (OQ)	<p>Verifies that</p> <ul style="list-style-type: none">• the equipment/system/process is operating correctly,• compliant with functionality requirements and• integrated into the systems and QMS.
Performance Qualification (PQ)	<p>Verifies that</p> <ul style="list-style-type: none">• the equipment/system/process is continuously meeting performance criteria for routine use and• performing adequately for routine use in commercial production.

Design qualification

Design qualification

- DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

User requirement specifications :

Consider the following for URS;

- Product Requirements
- Process & Operation Requirements
- Operating Ranges
- GMP, Operation & Safety Requirements

Design qualification

URS:

- The requirements and specifications for the utility or equipment should be defined by the user and documented in the URS.
- The URS should be used when selecting the required utility or equipment from an approved supplier, and to verify suitability

Factory Acceptance Test and Site Acceptance Test

- Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site, prior to the subsequent stages of qualification.

Design qualification

Eg: Hydrogenation Reactor:

User requirement

1. Process material Acidic
2. Immiscible liquids
to be mixed for rxn
3. High pressure hydrogenation
4. No gas leakage
5. Safety issue
6. Oil in thermowell
etc..

Design Component

MOC- GL/ hastaloy
Turbine type agitator
& higher RPM ?
Pressure rating ?
Mechanical seal
Rupture disc/Safety valve
Food grade oil (GMP)

Installation Qualification

IQ should include, but not be limited to the following:

- Installation of equipment, piping, services and instrumentation check to current engineering drawings and specifications;
- Verification of materials of construction.
- Calibration requirements;
- Collection and collation of supplier operating procedure/WI and maintenance requirements;

Installation Qualification

Demonstrate that equipment has been Installed as per design and installation requirements.

Installation check list:

- *Civil requirements*
- *Electrical*
- *Production*
- *Measuring instruments*
- *Utilities & Piping*
- *Safety Issues*
- *Operation manuals & SOPs*
- *Critical stages*
- *Spare parts list etc*

Operational qualification

OQ should include, but not be limited to the following:

- tests that meets the **functionality requirement** of processes, systems and equipment;
- tests to include a condition or a set of conditions encompassing **upper and lower operating limits**, and “worst case” conditions.
- finalisation of **calibration, operating and cleaning procedures**,
- operator training and preventative maintenance requirements.
- Conclusion to approve/ release the facilities, systems and equipment.

Operational qualification

To demonstrate that the equipment will perform as per design within specified parameters.

- Define critical tests for OQ with Acceptance criteria
- Prepare testing procedures to cover upper and lower operating limits
- Calibrate measuring devices
- Operation & Cleaning procedure
- Preventive maintenance plan
- Prepare OQ report

Performance qualification

PQ should include, but not be limited to the following:

- test, using production materials, qualified substitutes or simulated product,
- test to include a condition or set of conditions encompassing upper and lower operating limits.
- Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.
- Also considered as **process validation**

Documents

URS

Purchase orders

Engineering drawings

MOC certificates

test certificates & tractability certificates

Operating manuals

Calibration procedures & certificates

Safety instructions

Qualification protocol & Reports etc

Process Validation

1. Prospective validation
2. Concurrent validation
3. Retrospective validation
 - Revalidation as required

Process validation

To Demonstrate with **Documented Evidence** that a Specific 'Manufacturing **Process**' is **Capable of Performing** in a **Reliable and Consistent** Manner to Deliver a Homogenous Product Meeting Defined **Quality Attributes Consistently**.

Purpose:

- High degree of assurance
- Consistency
- Documented proof
- Built-in Quality

Process Validation

- Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation).
- In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation).
- Processes in use for some time should also be validated (retrospective validation).

Process Validation : Pre-requirement

The following shall be ensured prior to Process validation;

- Facilities, systems and equipment to be used are qualified
- Instruments are calibrated
- Analytical testing methods are validated.
- Process is reviewed and ready (development report with QbD concept)
- Protocol is prepared , reviewed and approved.
- Personnel involved in the validation are appropriately trained.

Prospective Validation

- It is establishing documented evidence prior to **process implementation** that a system what it purports to do based on a **preplanned protocol**.
- It is conducted **prior to distribution** of either a **new product** or a **product made under a modified Production process**, where modifications are significant and may affect product characteristics.
- This is a preplanned scientific approach and includes initial stages of equipment validation.

Concurrent Validation

- It is establishing documented evidence that a process does what it purports to do, based on information generated during actual implementation of the process.
- It may be practical approach under certain circumstances.
 - When a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site .
 - When number of batches produced are limited.
 - Revalidation due to changes eg Increase batch size

Retrospective Validation

It is establishing documented evidence that a system does what it purports to do, based on **review and analysis of historical information**. It has become synonymous with achieving validation by documenting all historical information, e.g. release data for existing products and using that data to support position that process is under control.

- where the process ; Critical quality attributes and critical process parameters have been identified; controls have been established;
- There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability;

Evaluate : Min 30 batches and Cpk within the limit

Validation protocol contents

- the objectives & Scope;
- the responsible personnel
- description of the SOPs
- equipment or instruments to be used;
- calibration requirements;
- standards and criteria as appropriate;
- the stage of validation
- the critical processes parameters; critical operations
- sampling, testing and monitoring requirements; additional test
- stress testing where appropriate;
- predetermined acceptance criteria
- review and interpretation of results;
- deviations
- conclusion

Re-validation

Revalidation.

- Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner.
- Repeated validation of a previously validated system (or a part thereof) to ensure continued compliance with established requirements.

Cleaning Validation

- Equipment and utensils shall be cleaned, maintained and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.
- Pharmaceuticals can be contaminated by potentially dangerous substances
- Essential to establish adequate cleaning procedures
- “Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure” (PIC/S)
- “The data should support a conclusion that residues have been reduced to an ‘acceptable’ level” (FDA)

Cleaning Validation

Strategy on cleaning validation

- Product contact surfaces
- After product changeover
- Between batches in campaigns
- Bracketing products for cleaning validation
- Periodic re-evaluation and revalidation

Cleaning Validation

Cleaning Validation protocol:

- Objective of the validation
- Responsibility for performing and approving validation study
- Description of equipment to be used
- Interval between end of production and cleaning, and commencement of cleaning procedure
- Possible residues
- Cleaning procedures to be used (Parameters to be monitored/controlled)
- Number of cleaning cycles performed consecutively
- Sampling procedures used and rationale Sampling locations (Rinse and Swab)
- Testing method for residue
- Acceptance Limits with Justifications

Analytical Method validation

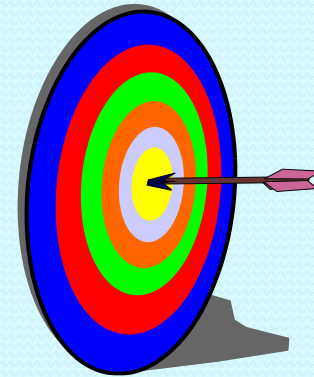
Analytical Method shall be validated for its intended purpose or verified for its suitability

Method validation is the process of planned and systematic study to confirm that it is suitable for its intended use.

- ❑ Method is reliable, accurate & reproducible

Validation Parameters/characteristics

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



Characteristics to be validated

Analytical procedure Characteristics	Identificat ion	Tests for impurities		Assay
		Quantita tive	Limit test	
Accuracy	No	Yes	No	Yes
Precision- Repeatability	No	Yes	No	Yes
Intermediate precision	No	Yes	No	Yes
Specificity	Yes	Yes	Yes	Yes
Limit of Detection	No	Yes	Yes	No
Limit of Quantitation	No	Yes	No	No
Linearity	No	Yes	No	Yes
Range	No	Yes	No	Yes
Robustness *	No	Yes	No	Yes

Computerized Systems Validation

1. GMP-related computerized systems should be validated. validation depends on the diversity, complexity, and criticality of the computerized application.
2. Appropriate installation and operational qualifications should demonstrate the suitability of computer hardware and software to perform assigned tasks.
3. Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured).
4. Written procedures should be available for the operation and maintenance
5. Where critical data are being entered manually, there should be an additional check on the accuracy of the entry.
6. Changes to computerized systems should be documented and validated/ tested
7. A back-up system should be provided.

Water system design

Water system design

1. Constructed of suitable materials such as stainless steel
2. Polished surface & proper welding to prevent microbial film
3. Sanitary fittings & connections
4. Pipes sloped so water does not pool and can drain easily
5. Circulate the water
6. Incorporate non-return valves (NRV)

Water system

The water system documents should have

- ↗ Valves / Sampling points
- ↗ drain points
- ↗ instrumentation
- ↗ flow rates/ velocity
- ↗ Schematic diagram

Validation for water systems consists of three phases

- Phase 1: 2 – 4 weeks
- Phase 2: 4 weeks
- Phase 3: 1 year

Changes that require revalidation

- Software changes/controllers
- Site changes
- Operational changes
- Change of source of material
- Change in the process
- Significant equipment change
- Production area changes
- Support system changes

VMP

VMP should contain at least:

- Validation policy
- Organizational structure
- Identifies validation items (products, processes, systems)
- Summary of facilities, systems, equipment, processes to be validated
- Documentation format for protocols and reports
- Planning and scheduling
- Change control
- Training requirements

VMP

VMP should state who is responsible for:

- Preparing the VMP
- The protocols and SOPs
- Validation work
- Report and document preparation and control
- Approval/authorisation of validation protocols and reports in all stages of validation process
- Tracking system
- Training needs in support of validation

VMP

VMP should contain:

- Validation list/plan with timeline (What to validate)
 - Specific process considerations
 - Specific characteristics briefly outlined
- premises, systems and equipment
- processes
- products
- Cleaning
- Analytical method etc

Reference

- <https://www.picscheme.org>
- www.who.int/medicines/areas/.../validation-without-appendices-2016-05-17.pdf
- https://ec.europa.eu/health/sites/health/files/files/pharmacos/docs/doc99/gmpanx15_en.pdf
- <https://www.validation-online.net/user-requirements-specification.html>
- ▶ www.usp.org
- ▶ www.ich.org
- ▶ www.fda.gov/cder/

Questions?

