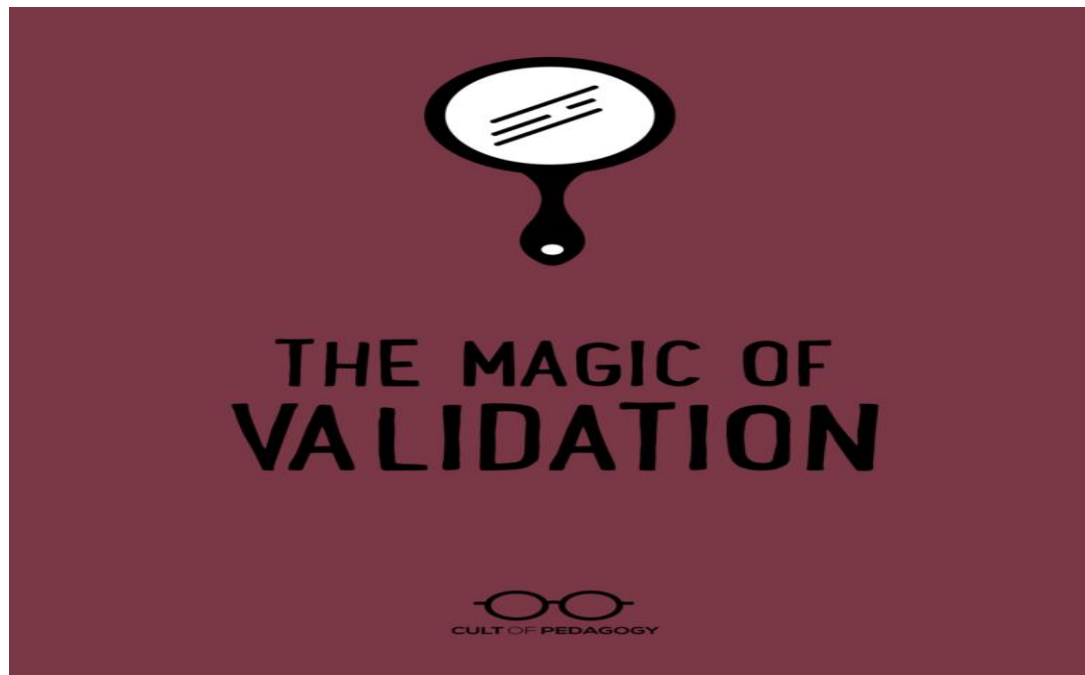


# Validation of Equipment and Analytical Procedure



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# INTRODUCTION

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- **Validation** is defined as “A Documented Programme, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes”.
- Validation is the process of evaluating products or analytical methods to ensure compliance with products or cleaning method requirements

# TERMS & DEFINITION

## ➤ **As per WHO**

Validation means providing documented evidence that any procedure, process, activity or system actually leads to the expected results.

## ➤ **As per FDA**

Validation is establishing documented evidence, which provides a high degree of assurance that a specific process will produce a product meeting its pre determined specification & quality attributes.

## ➤ **History Of Validation**

The concept of validation was first proposed by two FDA officials, **Ted Byers** and **Bud Loftus**, in the mid 1970's in order to improve the quality of pharmaceuticals. It was proposed in direct response to several problems in the sterility of large volume parenteral market.

# IMPORTANCE OF VALIDATION

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- Basic requirement for the product quality system.
- Assures that every lot of each product that is released to the market will consistently meet all the quality requirements.
- Capable of achieving the intended results. Reduction of quality costs
- Process optimization
- Assurance of quality
- Safety
- Increased output
- More rapid automation

# TYPES OF VALIDATION

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## ➤ **Prospective validation**

Done during the product development stage. during this the input resources are selected and clearly specified.

## ➤ **Concurrent validation**

Which is carried out during production. In process quality control parameter are also decided and recorded.

## ➤ **Revalidation**

**Revalidation is as a rule required under-**

Change of formula, equipment, procedure or quality of raw material.

Changes to facilities and installation which influence the process.

On appearance of new finding based on current Knowledge.

## ➤ **Retrospective Validation**

Based on a review and analysis of historical data. May be allowed when the formulation procedure and equipment have not been altered.

# PROCESS VALIDATION

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✓ **Process Validation** is “Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes”.

✓ Process validation involves a series of activities taking place over the lifecycle of the product and process.

The activities relating to validation studies may be classified into three stages:

- Process Design
- Process Qualification
- Continued Process Verification

# STAGES OF VALIDATION

## ❖ **Conduct Installation qualification:**

➤ IQ considerations are:

- ✓ Equipment design features (i.e. material of construction clean ability, etc.)
- ✓ Installation conditions (wiring, utility, functionality, etc.)
- ✓ Safety features.
- ✓ Supplier documentation, prints, drawings and manuals.
- ✓ Software documented.
- ✓ Environmental conditions (such as clean room requirements, temperature, and humidity)

## ❖ **Conduct Operational qualification:**

➤ OQ considerations include:

- ✓ Process control limits (time, temperature, pressure, line speed, setup conditions, etc.)
- ✓ Software parameters.
- ✓ Raw material specifications

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## ❖ **Conduct Performance qualification:**

➤ PQ considerations include:

✓ Acceptability of the product.

✓ Assurance of process capability as established in OQ.

✓ Process repeatability, long term process stability

## ❖ **Re – Qualification:**

Modification to or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure.



# SCOPE OF VALIDATION

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- Analytical
- Instrument Calibration
- Raw materials
- Packaging materials
- Equipment
- Facilities
- Manufacturing operations
- Product Design
- Cleaning

# EQUIPMENT VALIDATION

Principle of Equipment validation is that it must be

Designed, constructed, adapted, maintained

to perform the operations which are to be carried out.

Equipment layout and design must aim to minimize the risk of errors permit effective cleaning and maintenance To avoid cross contamination, dust and dirt build up. any adverse effect on quality of products. Equipment must be installed to minimize risk of errors and contamination.

Equipment and instruments-

suitable for the tests to be confirmed.

Defective Equipment-

should be Removed and Labeled

Washing, cleaning and drying of equipment -

on scheduled basis, procedures and records should be maintained.

# QUALIFICATION POLICY FOR EQUIPMENTS TO BE VALIDATED

- Instruments used in production and quality control.
- New systems and equipment
- Qualification done in accordance with predetermined and approved qualification protocols.
- The results have to be recorded and reflected in qualification reports.

## DESIGN QUALIFICATION

Functional and operational specifications of the instrument and details in the selection of the supplier.

What are to be considered??

- Analytical problems
- Use of equipment
- Environment
- Functional and performance specifications.

# INSTALLATION QUALIFICATION

It tells whether the equipment is properly installed and whether it is suitable for that environment.

**Equipment management group** ➡ **Support groups** ➡ **Plant engineering group**

## **Documented records for the installation**

Installation qualification report includes details, e.g.

- ❖ The supplier and the manufacturer
- ❖ System or equipment name
- ❖ Model and serial number
- ❖ Date of installation

# **OPERATIONAL AND PERFORMANCE QUALIFICATION**

## **OPERATIONAL QUALIFICATION**

It demonstrates that an instrument will function according to its operational specification in the selected environment.

### **DOCUMENTED RECORDS**

☐ Training of operators provided-training records

☐ Systems and equipment released for routine use after completion of operational qualification, provided that all calibration, cleaning, maintenance, training and related tests results were found to be acceptable.

## **PERFORMANCE QUALIFICATION**

It demonstrates that an instrument consistently performs according to a specification appropriate for its routine use.

### **DOCUMENTED RECORDS-**

Performance qualification report shows satisfactory performance over a period of time, carried out long to prove that the equipment is under control and turns out product of specified quality consistently.

# CONTENT OF EQUIPMENT VALIDATION

1. Application S.O.P's
2. Utilisation list
3. Process description
4. Test instrument utilized
5. Test instrument calibration
6. Critical parameters
7. Test function
8. Test function summaries

# VALIDATION PROTOCOLS

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Validation protocol contain two section:-

1.Procedure

2.Form

Specific protocols (SOP's) that provide detailed information on what is to be validated.

Validation Protocols consist of:

- A description of the process, equipment, or method to be validated.
- A description of the sampling procedure including the kind and number of samples.
- Acceptance criteria for test results.
- Schedule or criteria for revalidation.

# EXAMPLE OF EQUIPMENT VALIDATION

## Dissolution Apparatus – INSTALLATION QUALIFICATION

Following points are to be considered.

1. Preventive maintenance of  
Dissolution Apparatus.

2. Utilities

3. Environmental conditions:

As per the USP standards,

**“The dissolution Apparatus should be kept in an environment that do not provide additional motion/ agitation/ vibration to the rotating element of the apparatus.”**





# Operational Qualification

- It is also known as system suitability test
- Performed using USP Calibrator tablets: e.g.  
**USP Prednisolone Tablets (disintegrating type)**  
**USP Salicylic acid Tablets (non-disintegrating type)**
- Test is considered successful if the percent of drug released within 30 min. falls within the pre-established range.
- This test **must be conducted for each of the vessels** contained within a dissolution apparatus.

## Some additional tests:

As per the guidelines of Validation for Dissolution test Apparatus,

- It is mandatory to perform

**1. Temperature Distribution Study &**

**2. Rotation Speed Study**

# VALIDATION SUMMERY REPORT

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- ❑ VSR is a controlled document which lists all current validation documentation to demonstrate that processes are validated and specifies any revalidation requirements.
- ❑ Each VSR document number is referenced on the Process Validation Master Plan, for ease of document retrieval.
- ❑ The VSR contains:
  - ❑ Process title.
  - ❑ Applicable uncontrolled documentation.
  - ❑ List of all validation documentation.
  - ❑ Revalidation requirements.
  - ❑ Recurring validation requirements.

# ANALYTICAL METHOD VALIDATION

- ❑ Analytical methods play a vital role in new drug development, Preformulation and formulation studies, stability studies and quality control testing.
- ❑ This method must be simple, specific, accurate, precise, economical and convenient. The method should be validated during its development and use.
- ❑ Analytical validation refers to the evaluation and proving that an analytical method serves the intended purpose.
- ❑ Analytical validation ensures that the selected analytical method will give reproducible and reliable results adequate for Intended Purpose.

# Validation Steps

## Phase 1 –

- **Define the application, purpose and scope of the method.**
- **Analytes? concentration? Sample matrices?**
- **Develop an analytical method.**
- **Develop a validation protocol.**

## Phase 2 –

- **Qualification of instrument.**
- **Qualify/train operator.**
- **Qualification of material.**
- **Perform pre-validation experiments.**

## Phase 3 –

- **Adjust method parameters and/or acceptance criteria if necessary.**
- **Perform full validation experiments.**
- **Develop SOP for executing the method in routine analysis.**
- **Document validation experiments and results in the validation report.**

# **EXAMPLES OF METHODS THAT REQUIRE VALIDATION DOCUMENTATION**

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

# Published Validation Guidelines

- ❖ **1978-Current Good Manufacturing Practices (cGMPs)**
- ❖ **1987-FDA Validation Guideline**
- ❖ **1989-Supplement 9 to USP XXI**
- ❖ **1994-CDER Reviewer Guidance: Validation of Chromatographic Method**
- ❖ **1995 ICH Validation Definitions: Q2A, Text on Validation of Analytical procedures**
- ❖ **1997 ICH Validation Methodology: Q2B, Validation of Analytical Procedures**
- ❖ **1999 Supplement 10 to USP 23 <1225>: Validation of Compendial Methods**
- ❖ **1999 CDER “Bio analytical Method: Validation for Human Studies”**
- ❖ **2000 CDER Draft “Analytical Procedures and Method Validation”**

# TYPICAL ANALYTICAL PERFORMANCE CHARACTERISTICS USED IN METHOD VALIDATION

- Specificity (Selectivity)
- Linearity
- Range
- Accuracy
- Precision
- Detection Limit
- Quantitation Limit
- Robustness
- System Suitability Testing

# SPECIFICITY AND LINEARITY

## 1. Specificity –

Specificity of a method refers to the ability of the method to measure accurately and specifically the substance of interest in the sample as impurities, degradation products. For this the test results of analysis of samples containing other ingredients is compared with the samples without containing ingredients.

Determination

Identification tests : Assay and impurity test(s)

- Impurities are available
- Impurities are not available

## 2. Linearity

Linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

Determination

Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. For the establishment of linearity, a minimum of five concentrations is recommended.



# RANGE AND ACCURACY

## 3. Range

Range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Determination

The specified range is normally derived from linearity studies and depends on the intended application of the procedure.

## 4. Accuracy

Accuracy of an analytical method is the closeness of test results obtained by that method to the true value.

Determination

Accuracy should be established across the specified range of the analytical procedure.

Assay

- Drug Substance
- Drug Product

Impurities (Quantitation)

# PRECISION AND DETECTION LIMIT

## 5. Precision

Precision of an analytical method is the degree of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogenous sample.

Determination

A sufficient number of aliquots of a homogeneous sample are assayed to be able to calculate statistically valid estimates of standard deviation or relative standard deviation, which is calculated as,  $RSD = S. D. / \text{Mean} \times 100$  and it indicates-

- Repeatability
- Intermediate precision
- Reproducibility

## 6. Detection Limit (LOD)

LOD of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated, under the stated experimental conditions.

Determination

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental.

- Based on visual examination
- Based on signal to noise ratio

# QUANTITATION LIMIT AND RUGGEDNESS

## 7. LOQ

LOQ of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

## DETERMINATION

Several approaches for determining the detection limit are possible, depending on whether the procedure is a non-instrumental or instrumental.

- Based on visual examination
- Based on signal to noise ratio

## 8. Ruggedness

Ruggedness of an analytical method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as different laboratories different analyst, different instruments, different lots of reagent, different elapsed assay times, different assay temperatures, different days, etc.

# ROBUSTNESS

## 9. Robustness

Robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

### Determination

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study.

### System Suitability Testing

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such.

# **REVALIDATION MAY BE NECESSARY IN THE FOLLOWING CIRCUMSTANCES:**

- ✓ Changes in the synthesis of the drug substance;
- ✓ Changes in the composition of the finished product;
- ✓ Changes in the analytical procedure;
- ✓ The degree of revalidation required depends on the nature of the changes.
- ✓ Certain other changes may require validation as well.

# CONCLUSION

## **Validation is a**

- A quality tool that makes lot of sense. Validation provide the good quality product and the equipment .
- A prevention based activity important part of quality building process.
- Expensive in the beginning later will "save the money back“.
- Risk-based assessment of what need to be validated or verified.
- The process must be under control. Validation as such does not improve the process.
- Validation give the surety that equipment having the good qualification like design, operation, installation, and performance qualification which have pre-determined.
- Validation data should be generated for the all types of the product and the equipment to demonstrate the adequacy of the manufacturing process