



## REVIEW ON VALIDATION

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### ABSTRACT

Validation is the process of establishing documentary evidence demonstrating that a procedure, process, and activity carried out in testing and then production maintain the desired level of compliance at all stages. Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the product. Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control. Process validation deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process. Process validation also emphasizes the role of objective measures and statistical tools & analyses and emphasizes knowledge, detection, and control of variability and gives assurance on consistent of quality/productivity throughout life cycle of product.

**KEY WORDS** Validation, Quality, Process of Validation, Qualification, Stages of Validation.

### INTRODUCTION

The concept of validation was first proposed by food and drug administration (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 problem in the sterility of large volume parenteral market. The first validation activities were focused on the process involved in making these products, but quickly spread to associated processes including environmental control, media fills and equipment sanitization and purified water production. In the pharmaceutical industry, it is very important that in addition to final testing and compliance of products, it is also assured that the process will consistently produce the expected result [1].

The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry's greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation [2].

Validation is a concept that has evolved in united states in 1978. The concept of validation has expanded through the years to embrace a wide range of activities from analytical methods used for the quality control of drug substances and drug products to computerized systems for clinical trials, labeling or process control, Validation is founded on, but not prescribed by regulatory requirements and is best viewed as an important and integral part of cGMP [3].

The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. Process controls include raw materials inspection, in process controls and targets for final product [4].

## DEFINITIONS

### European commission

1991 –Validation–“Act of proving, in accordance of GMPs that Any...” process actually leads to expected results.

2000 –“Documented evidence that the process, operated within established Parameters, can perform effectively and reproducibly to produce a Medicinal product meeting its predetermined specifications and quality attributes”.

### US FDA Definition

“Process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its pre-determined specifications and quality characteristics.”

### ICH Definition

Process Validation is the means of ensuring and providing documentary evidence that process within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality.

### WHO Definition

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to expected result [5, 6, 7].

## SCOPE OF VALIDATION

Pharmaceutical Validation is a vast area of work and it practically covers every aspects of pharmaceutical processing activities, hence the pharmaceutical operation will be carried out at least the following areas for pharmaceutical validation.

- Analytical
- Instrument Calibration
- Process Utility services
- Raw materials
- Packing materials
- Equipment
- Manufacturing operations
- Products design
- Cleaning
- Operators [8].

## MERITS OF VALIDATION

- Assurance of quality compliance.
- Optimization of resources and manufacture products at lowest possible cost.
- It is a practice that must be followed for manufacturing, distribution, selling or license.
- Efficient production operation.
- Decreases the risk of manufacturing problems.
- Decreases the risk of failing in GMP [9].

## IMPORTANCE OF VALIDATION

- Assurance of quality
- Time bound
- Process optimization
- Reduction of quality cost
- Minimal batch failures, improved efficiency and productivity
- Reduction rejections
- Improved employee awareness [10].

## ICH & WHO GUIDELINES FOR VALIDATION OF EQUIPMENTS

### ICH Guidelines for Validation of Equipment's

- 1 meter distance from walls and other obstacles.
- Easy to operate, clean and maintainable.
- Working should be at proper commissioned position.
- Certification of equipment.
- Checking of overhead heights.
- Proper source of light.
- Drop down utility system.
- Drug of equipment.
- Layout of equipment.
- Marking of pipelines as per their flow of direction.
- Sop the equipment.
- Tracing of equipment.
- Identification marking for equipment.
- Cleaning of equipment.
- Distinguishing of the equipment.
- Record of each processing [11].

### WHO GUIDELINES FOR VALIDATAION OF EQUIPMENT'S

Equipment must be located, designed, constructed, adapted and maintained to suit the operation.

- Layout and design of equipment.
- Instalment of equipment.
- Production equipment.
- Labeling of fixed pipe work.
- Cleaning of equipment.
- Labelling of equipment.
- Establishment of written procedures for each operation.
- Record keeping [12].

## VALIDATION OF CONE BLENDER



**Figure 1: Cone Blender**

### 1] Installation Qualification (IQ)

- Verify approved purchase order.
- Verify invoice.
- Check manufacturer and supplier.
- Verify model number and serial number.
- Checking for physical damage.
- Confirm location and installation requirements per recommendation of manufacturer.
- Verify that the required utilities are available.
- Ensure that all relevant documentation is received.
- User manual
- Maintenance manual
- List of change parts
- Electrical drawings
- Mechanical drawings

### 2] Operational Qualification (OQ)

- Verify alarm control.
- Perform calibration requirements, identified in the manual or established by the validation team.
- Operate the equipment at low, medium, and high speed per operation manual to verify the operating control.
- Verify that all switches and push buttons are functioning properly.
- Establish procedures for operation, maintenance, and calibration.
- Establish training program for relevant staff.

### 3] Performance Qualification (PQ)

#### Mixing process:

Procedure:

Fix the mixing or stirring velocity, load the mixer with the product and switch the mixer on. After previously fixed intervals, the mixer should be switched off and samples should be taken from different locations of the product surface. The samples should be analyzed for their active content.

## Unloading:

Procedure:

After determination of the suitable mixing time to achieve product homogeneity, the influence of the unloading process on the homogeneity should be evaluated. Samples should be taken and sent to QC for analysis. Requirements: Homogeneity should remain consistent. Water content of the product: Take samples of the product prior to mixing, after mixing, and after unloading (begin, mid, end). Determine the water content of all sample.

## 4] Test Functions

1. Perform Installation Qualification, Verify equipment identification, required documents, utilities, manual, and drawings.
2. Verify components material.
3. Verify equipment safety features.
4. Operate the blender throughout the range of operating design specifications or range of intended use direction, and motor fixed speed.
5. Verify equipment switches, push-buttons, and rotation.
6. Perform the assay to check the content uniformity on blended granules at different locations.

## VALIDATION OF MIXER GRANULATOR



**Figure 2: Mixer Granulator**

1. Homogenous mixing of dry & wet powders, agglomeration of wet mass and fast dispersion of binding agent.
2. Dust free, high free flowing dosing particles, high uniformity of granule size.
3. Frequency control for bottom driven Impeller Mixer with 3 or 4 blades with exclusive scrape side design and Chopper positioned to make granules.

### 1] Installation Qualification (IQ)

An IQ establishes confidence that the equipment is properly installed. The installation must meet the manufacturer's specified guidelines, along with design changes at installation. Also the supporting electrical utilities must meet all electrical codes.

## Equipment identification

Record the equipment identification number, with equipment manufacturer, purchase order, model number, and equipment number.

## Required Documentation

The manufacturers operation and maintenance manual and SOPs that cover the set up.

- Utility requirements
- Power
- Water
- Compressed air
- Spraying
- Impeller movement
- Pneumatic discharge port.

## Calibration Requirements

- Ammeter
- Voltmeter
- Water pressure gauge
- Air pressure gauge
- Equipment major specifications
- Mixing bowl material of contact, surface finishing, dimensions, capacity.
- Motors two are required
- Discharge port
- Liquid air dispersing system
- Nozzle
- Components coming in contact with product
- Lubrication/ filter

## Equipment Operation

On empty the impeller should run at low speed and also check direction and speed.

### 2] Performance Qualification (PQ)

By using placebo max/min conditions are verified.

### 4] Control Functions:

- Regulators, discharge port opening, spraying button Operational.
- Impeller, timer, bowl on/off & slow/fast buttons.
- Emergency, discharge port on/off.
- Alarm, wash down walls on/off.



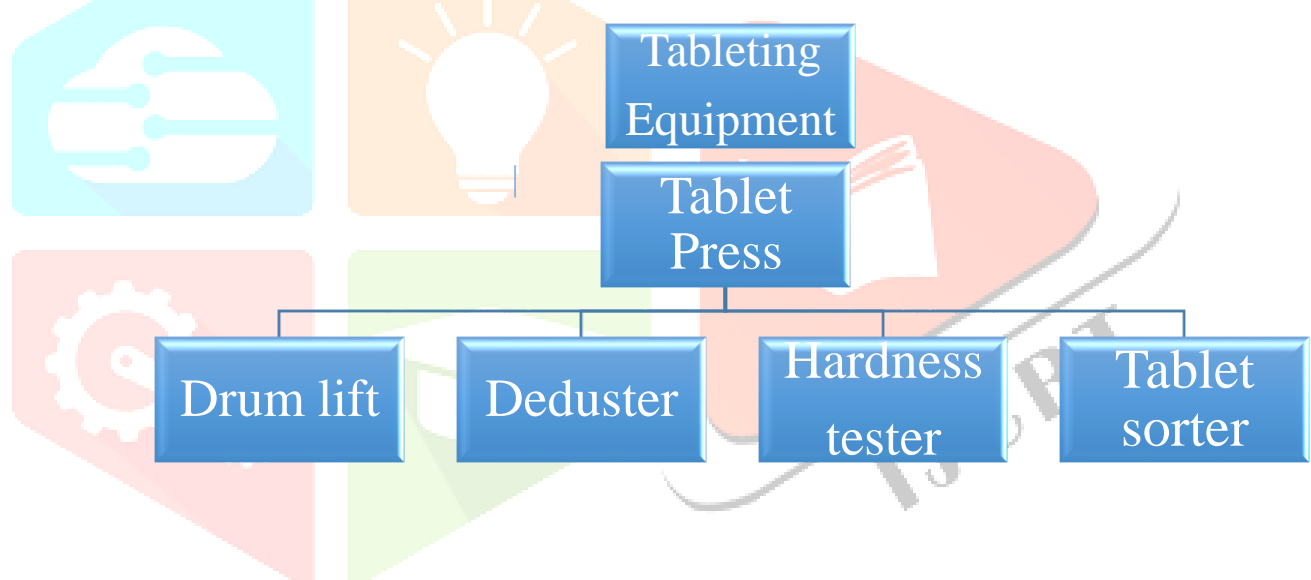
## VALIDATION OF TABLET COMPRESSION MACHINE

### A 45-STATION TABLET PRESS



**Figure 3: Tablet Compression Machine**

The press is automatic, high speed rotary press. A motor drives the press at speeds that vary from 410 to 1630 tablets per minute (rpm). The material being tableted is fed from a hopper by gravity through the feed frame into dies. Regulating the weight adjusting cam controls the weight of material in each tablet can be adjusted.



**Figure 4: Components of tableting equipment**

### 1] Installation Qualification (IQ)

The supporting electrical utilities must meet all electrical codes. The information required for an IQ evaluation is equipment identification, required documentation, equipment utility requirements, major component specifications, component material, lubricants and equipment safety features.

#### Equipment Identification

- Record the equipment identification numbers, along with the following information:
- Model number
- Serial number
- Company assigned equipment number and Location of the equipment

## Required Documentation

Record the equipment manufacturer's operation and maintenance manual and drawings.

Record the SOP that cover the setup, operation and cleaning of the tablet press.

## 2] Operational Qualification (OQ)

An OQ evaluation should establish that the equipment can operate within specified tolerances and limits. The mechanical ranges of the tablet press are challenged, along with the basic tablet press operations. The tablet press will be validated for its operating ability, not how well it makes tablets. Information required for the OQ evaluation is: calibration of the instruments used to control the tablet press, equipment control functions (switches and push buttons) and equipment operation (cam tracks, upper punches, lower punches, feed frames, take off bars, rotor head direction, tablet press speed).

## Calibration requirements

Verify that all the critical instruments on the equipment have been logged into the calibration system, have calibration procedures in place and are in calibration at the time of qualification testing. Record all information for calibrated instruments used to control the tablet press.

## Equipment Control Functions

The objective of testing equipment control functions is to verify that the switches and push buttons on the tablet press operate per the manufacturer's specifications. The tests will be performed with the tablet press empty. Operate each control and verify its proper position.

## 3] Performance Qualification (PQ)

Once the equipment is properly installed and functioning within is properly installed and functioning within specified operating parameters, it must be shown that the tablet press can operate reliably under routine, minimum and maximum operating conditions.

## 4] Test Functions

1. Perform Installation Qualification.
2. Perform general operational controls verification testing.
3. Operate system throughout the range of operating design specifications or range of intended use.
4. Verify that all safety devices of the tablet press are operating as specified in the manual.
5. Verify that recommended lubricants are used during machine operation.
6. Perform controller security challenges to verify that specified parameters cannot be altered without appropriate supervisory control.
7. Perform capability and consistency studies to check the weight variation of each product as per SOP [13].



## BASIC PRINCIPAL FOR PROCESS VALIDATION

The basic principle for validation may be stated as follows

### 1] Installation Qualification (IQ)

Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendation of the supplier of the equipment are suitably considered.

### 2] Operational Qualification (OQ)

Establishing by objective evidence process control limits and action levels which result in product that all predetermined requirements.

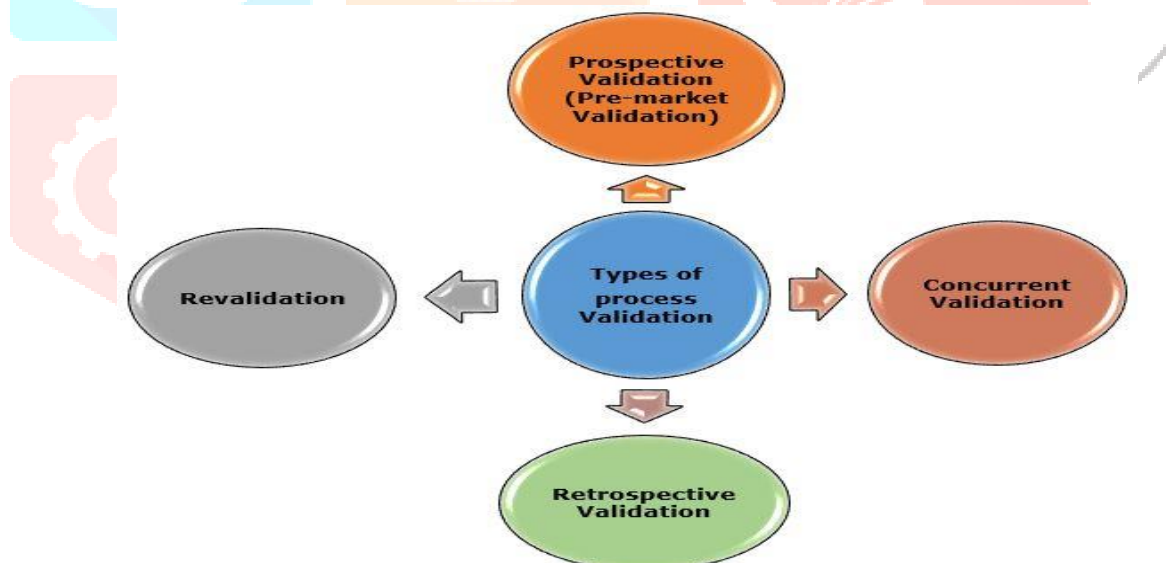
### 3] Performance Qualification (PQ)

Establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

### 4] Re-Qualification (RQ)

Modification to, or relocation of equipment should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system of the preventive maintenance program [14].

## TYPES OF PROCESS VALIDATION



**Figure 5: Types of Validation**

### 1] Prospective Validation:

It is defined as the established documented evidence that a system does what it purports to do based on a preplanned protocol. This validation usually carried out prior to distribution either of a new product or a product made under a revised manufacturing process. Performed on at least three successive production-sizes (Consecutive batches).

In Prospective Validation, the validation protocol is executed before the process is put into commercial use. During the product development phase, the production process should be categorized into individual steps.

During the processing of the validation batches, extensive sampling and testing should be performed on the product at various stages, and should be documented comprehensively. Detailed testing should also be done on the final product in its package.

These should be incorporated into the Batch manufacturing and packaging record or into appropriate standard operating procedures.

**2] Concurrent Validation:** It is similar to prospective, except the operating firm will sell the product during the qualification runs, to the public at its market price, and also similar to retrospective validation.

This validation involves in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the production process is in a state of control.

In exceptional circumstances it may be acceptable not to complete a validation program before routine production starts.

The decision to carry out concurrent validation must be justified, documented and approved by authorized personnel.

Documentation requirements for concurrent validation are the same as specified for prospective validation

### 3] Retrospective Validation

It is defined as the established documented evidence that a system does what it purports to do on the review and analysis of historical information.

This is achieved by the review of the historical manufacturing testing data to prove that the process has always remained in control. This type of validation of a process for a product already in distribution.

Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

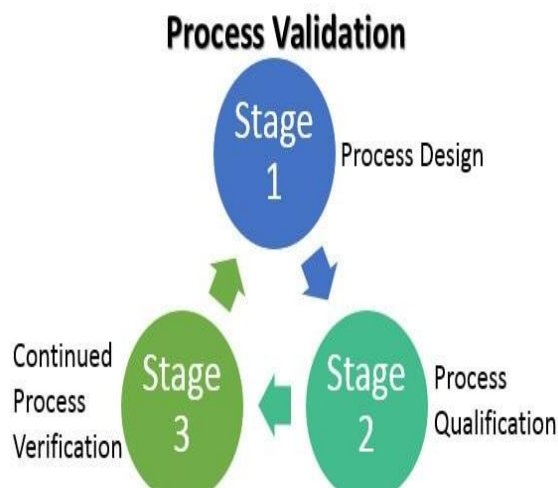
### 4] Revalidation

Re-validation provides the evidence that changes in a process and/or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process.

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation [15].

## PROCESS VALIDATION STAGES

The Process validation activities can be described in three stages.



**Figure 6: Process Validation stage**

### Stage 1 – Process Design

The commercial process is defined during this stage based on 100% knowledge gained through development and scale-up activities.

### Stage 2 – Process Qualification

During this stage, the process design is confirmed as 100% being capable of reproducible commercial manufacturing.

### Stage 3 – Continued Process Verification

Ongoing assurance is gained during routine production that the process remains in a state of control [16, 17].

## PROCESS VALIDATION OF ANY ONE DOSE FORM

### Validation of solid dosage forms

There are numerous factors that should be considered when developing and validating solid dosage forms.

### Compressed tablets

#### 1] Tablet Composition

Provide the reason for the presence of each ingredient in the formula.

#### 2] Process Evaluation and Selection

1. Determination of the optimal blending time
2. Remixing and segregation of components
3. Content uniformity
4. Distribution of active ingredient in the overall mix. E.g. direct compression of formulations, the type of blender, length of blending operation and the intensity of shear during the blending operation will be different depending upon the „objective“.

5. Possible interaction between the process and its effects on tablet (core) compression. E.g.: rpm of compression machine.
6. Characteristics of blend
7. Bulk density
8. Particle size distribution
9. Moisture.
10. Any ingredient in the formulation affecting the density of the final blend to a greater extent than any other ingredient
11. Colour uniformity
12. Different sized loads in the blender.

### 3] Wet Granulation

#### 1. Evaluation of blender depends on

Binder concentration

Solubility in granulation solution

Behavior during the drying step

#### 2. Evaluation of Mixed granulation

1. Compare density of wet granulation versus dry powder mix.
2. Determine the optimum density powder flow & tablet formulation.
3. Amount of granulating solution required for optimum granulation.
4. Compact ability of granulation.
5. Optimal mixing time.

#### 3. Evaluation of drying step and dried granules

1. Determine the optimal moisture content of the dried granules.
2. Particle size distribution of dried granules.
3. Density of dried granules.
4. Equipment and/or instrument conditions required promoting drug.
  1. Airflow
  2. Inlet temperature
  3. Outlet temperature
  4. Dryer efficiency
  5. Load to be dried.

#### 4] Milling operation for the dried granules

1. Particle size distribution
2. Dissolution (if applicable)
3. Granule disintegration

#### 5] Tablet (core) Compression

1. Appearance
2. Color uniformity
3. Stability
4. Moisture pick up versus percent relative humidity
5. Powder flow from hopper
6. Separation or uniformity in feed frame
7. Special requirements needed. E.g. Screen to dump powder
8. Optimal speed of tablet press
9. Tablet parameters at varying speeds of compression machine [18, 19, 20 ]

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