



## INDUSTRIAL PROCESS VALIDATION OF TABLET DOSAGE FORM: A REVIEW

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### ABSTRACT

The present article gives an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process. The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. Solid dosage forms include tablets and capsules. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. Process Validation is one of the important steps in achieving and maintaining the quality of final product. 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. This overview examines the need for pharmaceutical validation, the various approaches and steps involved.

**Key words:** Validation, Quality Assurance, Approaches to Validation.

### INTRODUCTION

Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials and is the important step in gaining and maintaining the quality of the final product [1]. The word validation simply means ‘assessment of validity’ or ‘action of proving effectiveness’. Validation of the individual steps of the processes is called the process validation. Validation refers to establishing documented evidence that a process or a system, when operated within established parameters can perform effectively and reproducibly to produce a medical product meeting its pre-determined 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.

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

European Commission - 2000 - Validation - “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”.

The concept of validation was first proposed by two food and drug administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970s in order to improve the quality of pharmaceuticals. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, and equipment sanitization and purified water production. The concept of validation was earlier developed for equipment and processes and derived from the engineering practices used in delivery of large pieces of equipment that would be manufactured, tested, delivered and accepted according to a contract the use of validation spread to other areas of industry after several large-scale problems highlighted the potential risks in the design of products.

Validation is an integral part of quality assurance, but the use of this term in connection with manufacturing often gives rise to difficulties. It involves the systematic study of systems, facilities and processes aimed at

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determining whether they perform their intended functions adequately and consistently as specified. A validated operation is one, which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications, and has therefore been formally approved [2].

### Approach to Process Validation

For purposes of this guidance, process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process [3]. This guidance describes process validation activities in three stages. This guidance describes activities typical of each stage, but in practice, some activities might occur in multiple stages.

Stage 1- Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2- Process Qualification: During this stage, the process design is evaluated to determine if the process is 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 [4].

### Benefits of Validation

1. Processes consistently under control require less process support.
2. Will have less down time.
3. Only fewer batch failures and may operate more efficiently with greater output.
4. In addition, timely and appropriate validation studies will transmit a commitment to product quality, which may facilitate pre-approval inspection & expedite the granting of marketing authorization.
5. Validation makes good business sense [5].

### Quality Assurance

Quality assurance is a concept that covers all aspects that influence the quality of a product. It involves developing standards and guidelines to ensure that all the drug products released are of the highest quality used for their intended use. Quality assurance therefore incorporates GMP and other factors, such as product design and development.

The quality of pharmaceuticals has been a concern of the World Health Organization (WHO) since its inception. Without assurance that these medicines are relevant to priority health needs and that they meet acceptable standards of quality, safety and efficacy, any health service is evidently compromised [6].

### Significance and Applications of QA in Pharmaceutical Industry:

- Production and control operations are clearly specified in a written form and GMP requirements are adopted.

- Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.
- The finished product is correctly processed and checked according to the defined procedures.
- Satisfactory arrangements exist to ensure as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed and subsequently handled so that the quality is maintained throughout their shelf life [7].
- Deviations, incidents, change control, market complaints are reported, investigated and recorded.
- Regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.
- There is a system for approving changes that may have an impact on product quality.
- There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system [8].

### The Basic Goals of QA

- Quality of a finished product cannot be inspected or tested; hence each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification.
- To design the process and track the defects.
- The Quality, safety, and effectiveness must be designed and built in to the product.

### Types of Validation

#### 1. Process Validations

As per USFDA (1987): Process Validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications and quality characteristics. Effective process validation contributes significantly to assuring drug quality [9].

It includes;

- Prospective validation
- Concurrent validation
- Retrospective validation
- Revalidation.

#### 2. Equipment Qualification

Equipment validation involves qualifying the design, installation, operation, instrumentation, control system and performance of the equipment. The pharmaceutical companies offer a wide range of equipment validation services whether it is in laboratory or in manufacturing area. Equipment validation helps us to:

- Identify the risk associated with the process, equipment and materials.
- Assess the impact of failure.

#### 3. Facility Validation

Facility validation should include planning, documentation, construction and testing to design

specifications and cGMP requirements. Facility validation can be a tool for enhancing reliability, cost, and quality.

#### 4. Service Validation

This involves qualification activities like:

- Environmental control system e.g. HVAC, AHU
- Water storage & Distribution system.
- Compressed air system.
- Steam distribution system etc.

#### 5. Cleaning Validation

Cleaning validation is the methodology used to assure that a cleaning process removes residues of the active pharmaceutical ingredient of the product manufactured in a piece of equipment, the cleaning aids and ensures that all residues are removed to predetermined levels to ensure the quality of the next product to be manufactured. It involves the cleaning procedure, so as to give a high degree of assurance that the given cleaning process results in equipment/area having product contamination below the acceptable level.

#### 6. Analytical Method Validation

Analytical method of validation is just one type of validation required during drug development and manufacturing. It involves evaluation of product quality attributes through testing to demonstrate reliability is being maintained throughout the lifecycle and that the precision, accuracy, specificity, LOD, LOQ, linearity, selectivity have not been compromised. The analytical method details the steps necessary to perform an analysis. This may include: preparation of samples, standards and reagents, use of apparatus and use of formula for the calculation etc.

#### 7. Vendor Validation

It involves the qualification of the vendor who provides the active material and the excipients required for formulation by conducting audits.

#### 8. Computer System Validation

Computer validation encompasses computers, which directly control process or system or collect analytical data. Computer validation includes the qualification of all software and hardware, which has an impact, direct or indirect, on the quality of a product. The validation approach to programmable logic controller (PLC) hardware and personal computers (PCs) is similar, both to one another and to the general overall approach to validation, in that the end user should define each requirement.

#### Validation Protocol

Validation protocol is a written plan stating how validation will be conducted including test parameters, product characteristics, production equipment and design points on what constitutes acceptable test results [10].

The protocol should specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs. The test condition for these runs should

encompass upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greater chance of process or product failure compared to ideal conditions. Such conditions have become widely known as “worst case” conditions or “most appropriate challenge conditions”.

The validation protocol should satisfy the following in detail [11]:

- General information
- Objective
- Background/revalidation
- Summary of development and technical transfer from R&D or another site activity to justify in process testing and controls any previous validations. Before formal cleaning validation programs were instituted, visual inspection was the primary means of determining equipment cleanliness (Lingnau J et al., 1989).
- List of equipments and their qualification status
- Facilities qualification
- Process flow chart
- Manufacturing procedure narrative
- List of critical processing parameters and critical excipients
- Sampling, test and specification
- Acceptance criteria

#### Elements of Validation

1. Equipment and process (DQ, IO, OQ, PQ).
2. System to assure timely revalidation.
3. Documentation.

#### 1. Equipment and Process

The equipment and process should be designed and/or selected so that product specifications are consistently achieved. This should be done with the participation of all appropriate groups that are concerned with assuring a quality product. e.g. engineering design, quality personnel and production operations [12].

**Design Qualification:** It includes document verification of the design of equipment and manufacturing facilities. User requirements should be considered when deciding on the specific design of a system or equipment. A suitable supplier should be selected for the appropriate system or equipment.

**Installation Qualification:** Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances [13].

**Operational Qualification:** Systems and equipment should operate correctly and their Operations should be verified in accordance with an operational qualification protocol. Critical operating parameters should be identified. Operational qualification should include verification of operation of all system elements, parts, services, controls, gauges and other components.

**Performance Qualification:** Documented verification that equipment or systems operate as expected under routine productions the operation is reproducible, reliable and in a state of control. The purpose of

performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process [14].

## 2. System to Assure Timely Revalidation

There should be a quality assurance system in place, which requires revalidation whenever there are some challenges in packing, formulation, equipment or process which could impact on the product effectiveness characteristics and whenever there are changes in product characteristics. The quality assurance procedures should establish the circumstances under which revalidation is required. The extent of revalidation will depend upon the nature of changes and how they impact upon different aspects of production that had previously been validated.

## 3. Documentation

It is essential that the validation program is documented and that the documentation is properly maintained. Approval and release of the process for use in routine manufacturing should be based upon a review of all validation documentation, including data from the equipment qualification, and product/package performance testing to ensure compatibility with the process. For routine production, it is important to adequately record process details (e.g. time, speed, temperature & equipment used) and to record any changes which have occurred. A maintenance log can be useful in performing failure investigations concerning a specific manufacturing lot [15].

## Pre-Requisites for Successful Validation

There are some elements or tools that are required for conducting effective validations. Each are presented and discussed in the following sections:

**1) Understanding:** The single most important element required is a good understanding of what validation is. This understanding activity goes beyond the basic definition of validation, beyond the concept of “requiring a minimum of three runs” and understanding must be anchored by sufficient years of practical experience and knowledge. It will permit sound and logical decisions even under most intense situations [16].

**2) Communication:** Communication is one of the best methods of improving environment understanding. Communication is essential for any activity that requires more than one resource to complete. This point is understandable considering that conducting effective validation involves multi-departments.

**3) Co-operation and Focus:** Multiple departments that sometimes interact during the course of executing validation program are project management, accounting,

quality control, project engineering, process engineering, quality assurance, facilities; regulatory etc should have a commendable co-operation.

**4) Experience:** A firm must have resources with solid validation experience to get success in their validation program.

**5) Resources:** Resources means personnel who will plan and execute equipment on which validations will be performed on materials with which to conduct validations. Laboratories that will perform necessary analysis should provide necessary funding for the validations and allocate sufficient time to perform validations [17].

**6) Plan:** Conducting validations within most companies will involve a number of departments and disciplines. These disciplines need a perfect plan in order to get good team synergy.

**7) Budget:** It is important to understand that a successful validation must be done to completion and it should not be limited by a budget assembled by personnel who have no appreciation for what is required to successfully complete validation. Further, it is important to understand that validations cost money [18].

**8) Standard Operating Procedures (SOP's):** The SOPs capture activities that routinely occur within an organization. Departments charged with abiding by or following these SOPs must first be trained against these SOPs.

**9) Quality Control lab support:** In most of the validations, some laboratory testing will be required. In most cases this testing is handled by the QC group. QC is expected to provide results in timely manner. So often, the wait for the receipt of analytical results cases the entire validation project to come to halt. Because validations are based on the results obtained.

## CONCLUSION

It is concluded that the Process validation is an important part of among all validation like equipment validation, cleaning validation, vender validation etc. Process validation is a step to assure the identity, strength, purity, safety and efficacy of pharmaceutical drug product validation is the most common word in the drug development, manufacturing and specification of finished product.

From the review study it is concluded that the pharmaceutical validation and process controls are important to assure that the drug product meet standards for the identity, strength, quality, purity and stability.

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