



AN OVERVIEW: THE ROLE OF PROCESS VALIDATION IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

The present review article focus on introduction and general overview on process validation in pharmaceutical industry. The word validation simply means "Assessment of validation or action of proving effectiveness". The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. The process validation process parameters are derived from the specifications for the device, component or other entity to be produced by the process. A manufacturer can assure through careful design of the device, processes, process controls and packaging that all manufactured units will meet specifications and have uniform quality. However, in-process and finished product testing still play an important role in assuring that products meet specifications. Validation is defined as a 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. The validation protocol includes inventory control and equipment inspection in the preliminary steps and in-process controls in the subsequent steps. Process controls are mandatory in good manufacturing practices (GMP). The goal of a quality system is to consistently produce products that are fit for their intended use. This review covers need of validation, elements of validation, principles of validation, phases of validation, types of validation.

KEYWORDS: Validation, Good manufacturing practices, consistent, metered dose inhaler.

INTRODUCTION

The concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals.¹ Validation is the act of demonstrating and documenting that a procedure operates effectively. The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance that specific process.² The validation protocol includes inventory control and equipment inspection in preliminary steps and in-process controls in subsequent steps. The purpose of setting validation parameters is to monitor the on-line and off-line performance of manufacturing process. Thus Validation is an integral part of quality assurance³. Validation has become one of the pharmaceutical industry's most recognized and discussed subjects. It is a critical success factor in product approval and ongoing commercialization. Quality is always an imperative prerequisite when we consider any product. Therefore, drugs must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. A process validation protocol is a requirement as stipulated by the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals and is therefore applicable to manufacturing of drugs.

Validation should be considered in the following situation

- Totally new process
- New equipment
- Process and equipment which have been altered to suit changing priorities.
- Process where the end –product test is poor and an unreliable indication of product quality.

Need of validation

- To reduce batch to batch variation.
- To achieve reproducible products of same quality, purity & strength.

Types of process validation

Prospective Validation

This approach to validation is normally undertaken whenever the process for new formula must be validated before routine pharmaceutical production commences. 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 broken down into individual steps. Each step should be evaluated on the basis of experience or theoretical considerations to determine the critical parameters that may affect the quality of the finished product.^{4,5,6}

It's based upon existing & historical process data. Some of the essential elements for retrospective validation are:

- Batches manufactured for a defined period (minimum of 10 last consecutive batches)
- Number of lots released per year
- Batch size/strength/manufacturer/year/period
- Master manufacturing/packaging documents
- Current specifications for active materials/finished products
- List of process deviations, corrective actions and changes to manufacturing documents
- Data for stability testing for several batches
- Trend analyses including those for quality related complaint.

Concurrent Validation: It's nothing more than requalifying, revalidating or even recertifying an ongoing process in response to a significant change in product components manufacturing, equipment, facilities, batch size

or manufacturing procedure. Concurrent validation may be the practical approach under certain circumstances. Examples of these may be:

- when a previously validated process is being transferred to a third party contract manufacturer or to another manufacturing site
- where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients
- when the number of lots evaluated under the retrospective validation were not sufficient to obtain a high degree of assurance demonstrating that the process is fully under control

Revalidation:-It means repeating the original validation effort or any part of it and includes investigation review of existing performance data. Revalidation criteria are given below:

- Major changes in the manufacturing process which may affect the quality of the product.
- Change in the Batch Size
- Change in the Batch Formula.
- Change in manufacturing Location
- Modification/Change in Critical equipment
- Change in the specifications and/or change in the source of Active Pharmaceutical Ingredient (API)
- Change in Primary packing material.

Elements Of Validation^{7,8,9}

Design Qualification (DQ): It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

Installation Qualification (IQ): It is documented verification that all aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications and are correctly installed.

Operational Qualification (OQ): It is documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to Intend throughout all anticipated ranges.

Performance Qualification (PQ): It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

PRINCIPLES OF VALIDATION¹⁰

The basic principle is characterized by harmony between the results obtained and requirements, which includes/ supports:

- Specified requirements and objectives
- Available means
- Choices which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

The following scheme may be suggested

- Aim versus objective.
- Process as a whole and flow diagram.
- Challenging the critical process variables.
- Validation protocol.
- Protocol versus report: procedures, sampling, testing, reporting and results.
- Evaluation and recommendations including frequency for re-validation

Phases of Validation^{11,12,13}

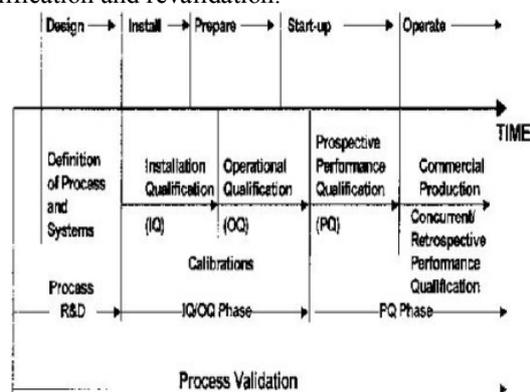
The activities relating to validation studies may be classified into three phases:

Phase 1: Pre-validation phase or the qualification phase, which covers all activities relating to product research and development, formulation, pilot batch studies, scale-up studies, transfer of technology to commercial scale batches, establishing stability conditions, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

Phase 2: Process validation phase (process qualification phase) designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

Phase 3: Validation maintenance phase requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all SOPs have been followed, including change control procedures.

At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in requalification and revalidation.



Phases of Validation

Validation:-Type of Documentation¹⁴

Validation master plan (VMP)

Validation protocol (VP).

Validation reports (VR).

Standard operating procedures (SOP)

Validation Master Plan

A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon by management. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. All validation activities relating to critical technical operations, relevant to product and process controls within a firm should be included in the validation master plan. It should comprise all prospective, concurrent and retrospective validations as well as re-validation. The validation master plan should be a summary document and should therefore be brief, concise and clear. It should not repeat information documented elsewhere but should refer to

existing documents such as policy documents, SOP's and validation protocols and report.^{15,16}

Validation Protocol

A written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points on what constitutes acceptable test results. This document should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested.

The validation protocol provides a synopsis of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance.

Validation Report

The validation report should contain the approved validation protocol, tabulated or graphical results, process monitoring (forms), and all analytical results of the validation batches. The validation report should have a conclusion that explains the manufacturing specialist's (preparer's) statement and opinion. Stability testing on all validation batches must be performed according to the protocol, according to the NDA/ANDA stability plan¹⁶

IMPORTANCE OF VALIDATION

The most compelling reasons to optimize and validate pharmaceutical productions and supporting processes are quality assurance and cost reduction. The basic principles of quality assurance has as their goal and the production of articles that are fit for their intended use.¹⁰ These principles are Quality, safety, and effectiveness must be designed and built in to the product, quality cannot be inspected or tested in the finished products and each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specification. The relationship of quality assurance and process validation goes well beyond the responsibility of any quality assurance functions, nevertheless it is fair to say that process validation is a quality assurance tool because it establishes a quality standard for the specific process.^{17,18}

CONCLUSION

From the study, it can be stated that the process validation process parameters are derived from the specifications for the device, component or other entity to be produced by the process. However, in-process and finished product testing still play an important role in assuring that products meet specifications. Finally, it can be concluded that Process validation is a key element in a quality assurance of the pharmaceutical product as the end product testing is not sufficient to assure quality of product.

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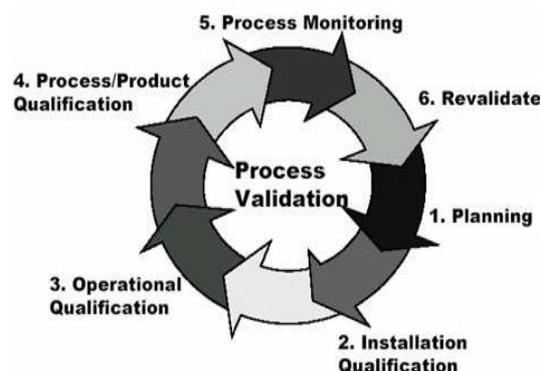


Figure 1: General overview of Process validation