

Pharmaceutical process validation guidance for industry: A review

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ABSTRACT: *Validation is a main tool in achieving and maintaining the quality and safety of the final product as per cGMP (current Good Manufacturing Practice). The purpose of this present work is to give introduction, general overview and how to plan, develop, execute process validation of pharmaceutical manufacturing process. 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. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. In pharmaceutical industry, Process Validation performs this task to build the quality into the product and an important tool for quality management of pharmaceuticals.*

Key Words: *Process validation, Quality Assurance, Quality, Pharmaceutical industry*

Introduction

Pharmaceutical process validation is a key element in assuring that these quality assurance goals are met. The concept of validation was first proposed by food and drug Administration (FDA) officials, Ted Byer's and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested at the end, this validation activities will commonly include training on production, material, operating procedure, people involved and monitoring of the system in production. Validation itself does not improve process but confirms that the process have been properly developed and under control. Different agencies defined the validation as follows; Pharmaceutical process validation is a key element in assuring that these quality assurance goals are met. The concept of validation was first proposed by food and drug Administration (FDA) officials, Ted Byer's and Bud Loftus, in the mid 1970's in order to improve the quality of pharmaceuticals. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested at the end, this validation activities will commonly include training on production, material, operating procedure, people involved and monitoring of the system in production. Validation itself does not improve process but confirms that the process have been properly developed and under control. Different agencies defined the validation as follows;

Food and Drug Administration (FDA):

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 [1].

European Commission:

The 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 [2].

World Health Organization (WHO):

The collection and evaluation of data throughout the life cycle of a product from the process design stage through to commercial production and provides scientific evidence that a process is capable of consistently delivering a quality product [3].

Health Canada:

Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of Prospective, Concurrent or Retrospective Validation. [4]

Personnel for validation:

The working party would usually include the following staff members,

1. Head of quality assurance.
2. Head of engineering.

3. Validation manager.
4. Production manger.
5. Head of quality control.
6. Specialist validation discipline: all areas^[5,6].

Need for validation:

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process 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. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control⁷. Adequate validation is beneficial to the manufacturer in many ways ^[7, 8, 11]:

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end product testing.

Validation should thus be considered in the following situations:

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

BENEFITS OF PROCESS VALIDATION:

Process validation has following benefits,

Sr. No.	Benefits
1	Fewer batch failures and may operate more efficiently with greater output.
2	Validation makes good business sense ⁹ .
3	Reduction in rejections and reworks.
4	Reduction in utility cost.
5	Reduced testing process and finished goods.
6	More rapid and accurate investigation into process deviation.
7	Improve employee awareness of processes.
8	More rapid automation ¹⁰ .

Strategy for process validation:

There are following strategy for process validation^[12].

1. Identification of critical process variables and preparation of process flow charts.
2. Preparing process validation protocol.
3. Develop SOPs for executing the method routinely.
4. Selection of three consecutive batches having same batch size and manufacturing formula.
5. The failure to meet the requirements of the validation protocol should be subjected to process revalidation following a thorough analysis of process data and formal discussion by the validation team.
6. Documents like batch manufacturing record, in process and finished product specification, other related documents to BMR and specification, related SOPs and batch packing record all are necessary for process validation.

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 important element required is a good understanding of what validation is. This understanding activity goes beyond the concept of “requiring a minimum of three runs” and understanding must be anchored by sufficient years of practice experience and knowledge.

2. Communication:

Communication is one of the best methods of improving environmental understanding. It is essential for any activity that requires more than one resource to complete. With this point we can understand that conducting effective validation involves multi-departments.

3. Experience:

Validation team should have experienced people to get success in their validation program.

4. Resources:

Resources mean 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 validation and allocate sufficient time to perform validations [13].

5. Budget:

It is important to understand that validation cost money. Validation should not be limited by the budget for successful completion of validation [14].

TYPES OF VALIDATION:

1. Process validation:

As per (1987), process validation is establishing documented evidence which provides a high degree of assurance that a specified process will consistently produce meeting its predetermined specification and quality characteristics. Effective process validation contributes significantly assuring drug quality.

It includes;

- A. Prospective validation
- B. Concurrent validation
- C. Retrospective validation
- D. 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 and distribution system.
- Compresses 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 ensure that all residues are removed to predetermined levels to ensure the quality of the next product to be manufactured.

6. Analytical method validation:

Analytical method 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 through the life cycle 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.

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, where has an impact, direct or indirect, on the quality of a product. The validation approach to programmable logic controller (PLC) is similar, both to one another and to the general overall approach top validation, in that the end user should define each requirement^[15].

TYPES OF PROCESS VALIDATION:

1. Prospective validation:

In prospective validation the validation protocol is executed before the processes put into the commercial use. During the product development stage 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 finished product.

2. Concurrent validation:

It is similar to prospective, except the operating firm will sell the product during the qualification runs , to the public as its market price. This validation in process monitoring of critical processing documented evidence to show that production process is in its state of control.

3. Retrospective validation :

In this historical data is taken from the records of completed production batches are used to provide the documented evidence that the process as been in ,state of control prior to request for such evidence.

4. Revalidation :

It's the repetition of validation process or part of it. This is carried out when there is any change or replacement in formulation , a equipment plan or site, location, batch size and in the case of sequential batches that do not meet product specifications and is also carried out at specific time intervals in case of no changes.

STAGES OF PROCESS VALIDATION:

There are three stages of validation they are,

Stage 1:-process design or pre-qualification:

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

Stage 2:-process qualification:

During this stage, the process design is confirmed as 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. Tablets are comprises of mixture of active ingredients and excipients which are compressed or molded into a cylinder or biconvex solid. The principle objective of this dosage form is to achieve a predictable therapeutic response to a drug which include into a formulation which is capable of large scale manufacturing with reproducible product quality. Their cost is lowest of all the oral dosage forms. They are lightest and compact of all oral dosage form ^[16,17].

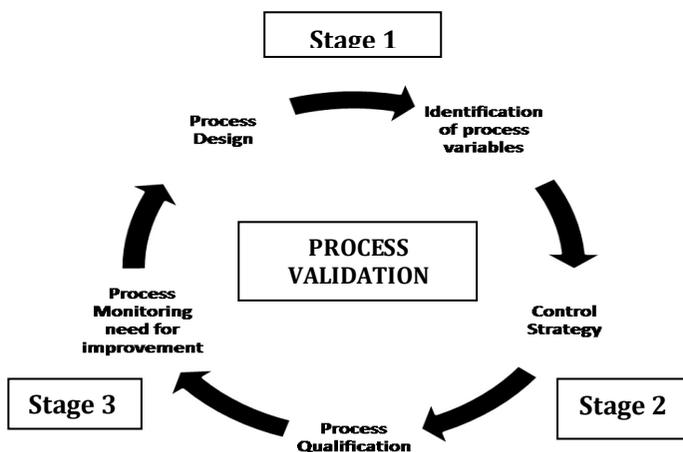


Figure-1: Process validation lifecycle

PHASES OF PROCESS VALIDATION:

The goals of the process validation can be pursued in three stages,

Phase 1:-pre-validation phase:

Developing an understanding regarding the functional relationships between parameters (material and process) and quality attributes. It 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 form.

Phase 2:-process qualification phase:

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.

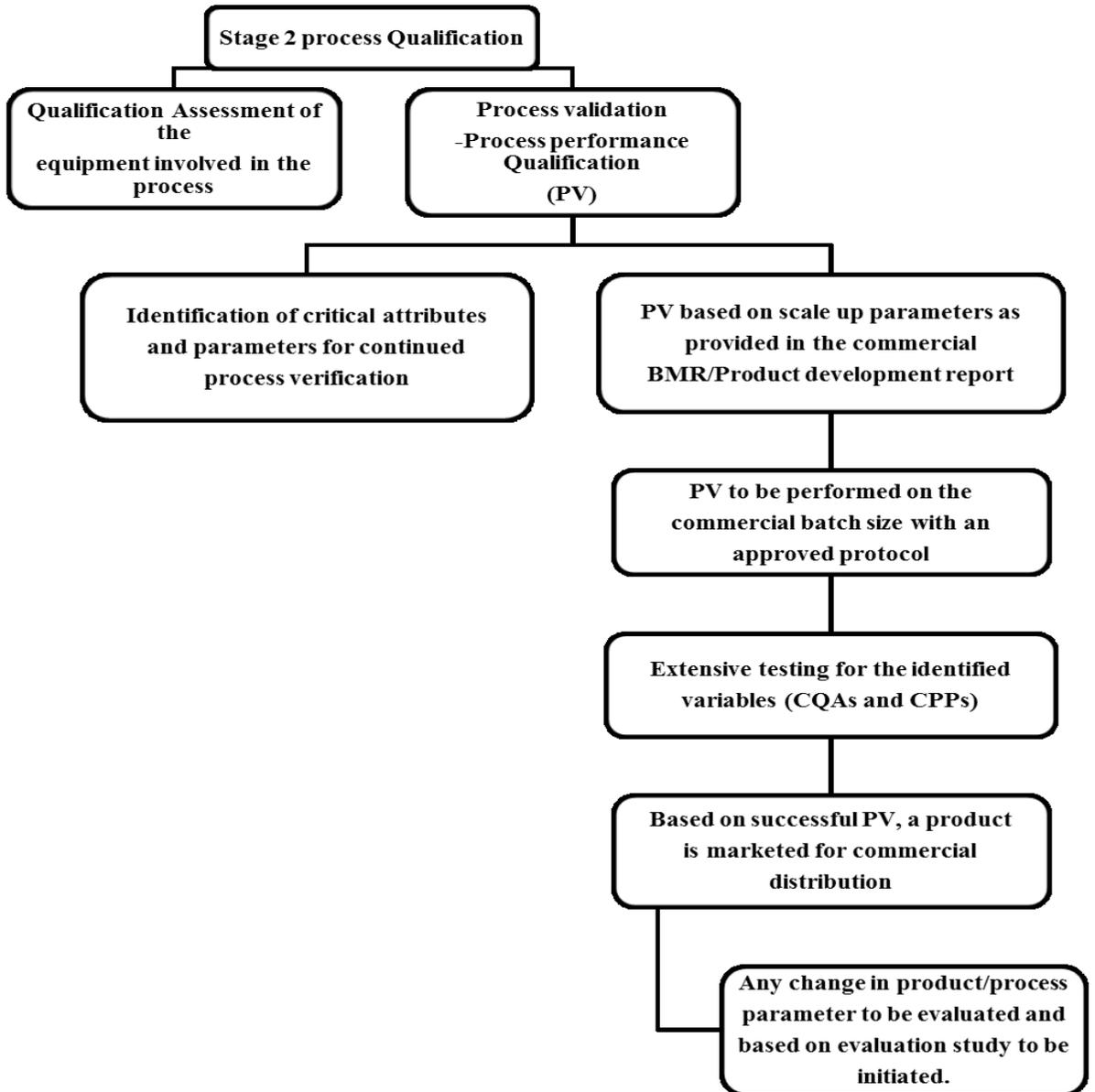


Figure-2: Flow diagram for Stage 2: Process Qualification]

Phase 3:-validation maintenance phase:

It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation¹⁸. The validation steps recommended in GMP guidelines can be summarized as follows ^[18]:

- As a pre-requisite, all studies should be conducted in accordance with a detailed, pre-established protocol or series of protocols, which in turn is subject to formal – change control procedures;
- Both the personnel conducting the studies and those running the process being studied should be appropriately trained and qualified and be suitable and competent to perform the task assigned to them;
- Suitable testing facilities, equipment, instruments and methodology should be available;
- Suitable clean room facilities should be available in both the 'local' and background environment. There should be assurance that the clean room environment as specified is secured through initial commissioning (qualification) and subsequently through the implementation of a programme of re-testing – in-process equipment should be properly installed, qualified and maintained;
- Comprehensive documentation should be available to define support and record the overall validation process

Protocols should specify the following in detail ^[19]:

- The objective and scope of study. There should already be a definition of purpose;
- A clear and precise definition of process equipment system or subsystem, which is to be the subject of study with details of performance characteristics;
- Installation and qualification requirement for new equipment;
- Any upgrading requirement for existing equipment with justification for the change(s) and statement of qualification requirement;
- Detailed stepwise statement of actions to be taken in performing the study (or studies);
- Assignment of responsibility for performing the study;
- Statement on all test methodology to be employed with a precise statement of the test equipment and/or materials to be used;
- References to any relevant standard operating procedures (SOP);
- Acceptance criteria against which the success (or otherwise) of the study is to be evaluated;
- The personnel responsible for evaluating and certifying the acceptability of each stage in the study.

All personnel involved in conducting the studies should be properly trained and qualified because they can, and often, have a crucial effect on the quality of the end product. All information or data generated as a result of the study protocol should be evaluated by qualified individuals against protocol criteria and judged as meeting or failing the requirements. Written evidence supporting the evaluation and conclusion should be available. If such an evaluation shows that protocol criteria have not been met, the study should be considered as having failed to demonstrate acceptability and the reasons should be investigated and documented. Any failure to follow the procedure as laid down in the protocol must be considered as potentially compromising the validity of the study itself and requires critical evaluation of all the impact on the study. The final certification of the validation study should specify the pre-determined acceptance criteria against which success or failure was evaluated ^[18].

CONCLUSION

Process validation is critical measure in the development of pharmaceuticals. Expertise in these areas can contribute to various significant factors, such as regulatory compliance, greater acceptance of the product in the market ultimately greater profitability. Validation could in fact lead to greater profitability and other benefits ^[20, 21]. Experience of the personnel and the whole group performing validation is of major importance because knowledge gained in past helps in development of pharmaceuticals in the right way. A strong mentoring and training program is another prerequisite for successful validation. All the Pharmaceutical companies must maintain very strong and stringent rules so that all its manufactured products are effectively validated so quality safety and hence efficacy of their products is maintained. Ultimately the validation effort reduces the risk to the patient therefore our goal is achieved.

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