

**Review article****A review on process validation****Rupinder Singh*, Ujjwal Nautiyal, Senthil Kumar, Chandra kant**** Himachal Institute of Pharmacy, Ramphur Ghat Road, Paonta Sahib, Distt-Sirmour, HP – 173025***ARTICLE INFO:****Article history:**

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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. Process validation is an important component in the design, prototyping and manufacturing process and assures that a process will consistently produce product, meeting its predetermined quality characteristics and attributes. As quality is always an imperative prerequisite when we consider any product therefore, drugs must be manufactured to the highest quality levels. Also end-product testing by itself does not guarantee the quality of the product so 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 because according to ISO 9000:2000, it had proven to be an important tool for quality management of pharmaceuticals.

1. Introduction

In an environment of increasing global cutting edge competition where countries with lower production costs quickly catch up technologically, a new thinking is required in order to meet the competition. A proactive way of meeting the increasing competition is to focus on maximizing the utilization of existing technology and faster than the competitors, being able to continuously introduces and make use of new technology, In this endeavor out sourcing of the products to cheaper third party/own location is gaining world wide acceptance. Once the manufacturing site is approved the next step entails regulatory submission for marketing authorization. In support of which process validation data plays an important role.

The Supportive data should show pharmaceutical equivalence between the product manufactured at the donor and recipient site. The data should show that the process is under control with no significant variation in the critical parameters. A successful industrial validation thus entails a strategic approach encompassing the whole chain. A manufacturer may decide to validate a process to improve overall quality, eliminate scrap, reduce costs, and improve customer satisfaction, or other reasons[1-3].

1.1 Validtion in general according to different regulatory bodies

USFDA defines process validation as 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 defines process validation is establishing 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[4,5].

1.2 Regulatory requirement for process validation

The basic principles of quality assurance have as their goal the production of articles that are fit for intended use. These principles may be stated as follows.

- Quality, Safety and effectiveness must be designed and built in to the product.
- Quality can't be inspected or tested in to finished product.
- Each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all the quality and design specification.

In this regard process validation is a key element in assuring that these quality assurance goals are met. By successfully validating a process it is possible to reduce the dependence up on intensive in process and finished product testing. Process validation as defined by various regulatory agencies is given below:

USFDA defined process validation as “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”.

The WHO CGMP’s defines process validation as “Establishing documented evidence, which provides a high degree of assurance that a planned process will consistently perform according to the intended specified outcomes”.

The European commission guide defines process validation as “Establishing documented evidence that the process, operated with in established parameters, can perform effectively and reproducibly to produce a medicinal product meeting it’s predetermined specifications and quality attributes.” The process validation guidelines issued by different bodies are similar to great extent and as our product is destined for UK market.

All the key elements of a validation program should be clearly defined and documented in a validation master plan or equivalent documents. It should contain precise data of:

- Validation policy
- Organizational structure of validation activities
- Summary of facilities, systems, equipment and process to be validated.
- Documentation format to be used for protocols and reports.
- Planning and scheduling.
- Change control
- Reference to existing documents[6,7]

2.Types of process validation[8-10]

2.1Prospective validation

- This type of validation activity is normally completed prior to the distribution and sale of the drug product.
- It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, giving product of the desired quality would constitute a proper validation of the process.
- It is preferred that the validation batches made should be of the same size as the intended production scale batches. When this is not practical, a reduced batch size corresponding to at least 10% of the intended batch size for full-scale production can be considered.

The validation protocol should contain the following elements:

- Short description of the process.
- Summary of critical processing steps to be investigated.
- In process, finished product specification for release.
- Sampling plan.
- Departmental responsibilities
- Proposed timetable

The validation study is to be documented in the validation report, which should include the following: Batch analytical data

- Certificate of analysis.
- Batch manufacturing record
- Report on unusual findings
- Conclusions and recommendations
- Signature of approval

2.2 Concurrent validation

- The type of validation is carried out during routine production activity and in exceptional cases (Lcw volume products).
- The document requirements are same as prospective validation.
- The decision to carry out concurrent validation must be justified, documented approved by authorized person.

2.3 Retrospective validation

- This type of validation is acceptable only for well-established processes, without any change in the composition of the product, operating procedures and Equipments.
- The source of data for this type of validation may include batch documents Process control charts, maintenance logbooks, process capability studies, Finished product data, including trend data and stability data.
- Batches selected for retrospective validation should be representative of all batches made during the review period including any batches that fail to meet the specification.
- The data generated from 10 to 30 batches should be examined to assess process consistency.

2.4 Revalidation

Revalidation provides the evidence that changes in a process introduced intentionally/unintentionally do not adversely affect process characteristics and product quality. Revalidation may be required in following cases:

- Change in formulation, procedure or quality of pharmaceuticals ingredients.
- Change in equipment, addition of new equipment and major breakdown (Maintenance, which affect the performance of the equipment.)
- Major change of process parameters.
- Change in site
- On appearance of negative quality trends.
- Batch size change.

3. Phases of validation[11,12]

Each of these elements requires a pre-approved protocol with acceptance criteria and a report summarizing the results.

What is an IQ ?

The IQ ensures that all equipment has been installed correctly with applicable inputs (e.g., power or compressed air), all environmental conditions have been met (e.g., temperature or humidity or air quality), all required calibrations have been performed (e.g., pressure gauges or temperature gauges), all safety measures have been implemented and the equipment has been entered into the manufacturer's PM (Preventive Maintenance) and calibration systems to ensure proper maintenance.

What is an OQ ?

The OQ demonstrates that the process produces conforming product throughout the range of process inputs, which include process parameters (e.g., temperature, pressure or time), raw material specifications, production logistics (e.g., personnel or multiple shifts) and duplicate sets of equipment where appropriate (e.g., multiple production lines). Including worst-case combinations of process parameters is critical to demonstrate that the entire range of process parameters will produce acceptable product. Training of manufacturing operators on the manufacturing procedures is also required. These procedures must be approved either by the validation team as an attachment to the OQ protocol or through the manufacturer's document control system if it allows a controlled-release of procedures prior to completion of the process validation.

What is a PQ?

The PQ demonstrates that the process consistently produces acceptable product. Often this is interpreted as producing three lots at the nominal process parameter(s). This three-lot guidance is based on a statement in the FDA's preamble to the Quality System Regulation. Although this practice has been widely adopted by industry, the minimum number of lots required for a PQ is the responsibility of the manufacturer and should be based on the specific production logistics, such as the number of manufacturing shifts and production lines.

4. Stages of process validation[13]

Stage 1 – Process design: The commercial 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 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.

4.1 General considerations for process validation[13]

It emphasizes the importance of making the entire process validation program more effective and efficient through the use of:

- Good project management and robust scientific knowledge management
- *Uniform collection and assessment of information* about the process which should *seek to reduce* the chance for redundant information gathering and thereby *enhance the accessibility* of such information later in the product lifecycle
- Process Simulation
- An integrated team approach that includes expertise from a variety of disciplines
- Project plans
- The support of senior management.

4.2 Key points of the process validation approach are[13]

- A successful validation program depends upon information and knowledge from product and process development.

This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. It emphasizes the importance of process control, pointing out the importance of both QA professional and the line operator in providing feedback and continued process verification.

- The need for ongoing data analysis, within and between production batches.
- Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product.
- Emphasizing that effective process validation contributes significantly to assuring drug quality.

4.3 Process validation protocol format

- Purpose
- Scope
- Responsibility
- Process History
- Process Description/Flow
- Processing Variables/controls
- Worst case challenge and Rationale Validation
- Process Change Control

5. Approaches to validation process

There are two basic approaches to the validation of the process itself. These are the experimental approach and the approach based on the analysis of historical data. The experimental approach, which is applicable to both prospective and concurrent validation, may involve.

- Extensive product testing
- Simulation process trials,
- Challenge/worst case trials, and
- Control of process parameters.

6. Validation documents[14,15]

6.1 Validation Master Plan: This document describes the overall company commitment to validation.

6.2 Validation Protocols: Controlled documents that describe how to perform a specific validation work/event.

6.3 Validation Reports: It summarizes the data and declares the disposition of the item validated.

7. The validation report

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized (signed and dated). The report should include at least the following:

- Title and objective of study
- Reference to protocol
- Details of material
- Equipment
- Programs and cycles used
- Details of procedures and test methods.
- Result (compared with acceptance criteria), and
- Recommendations on the limit and criteria to be applied on future basis.

8. Protocol for process validation of solid dosage forms (tablets)

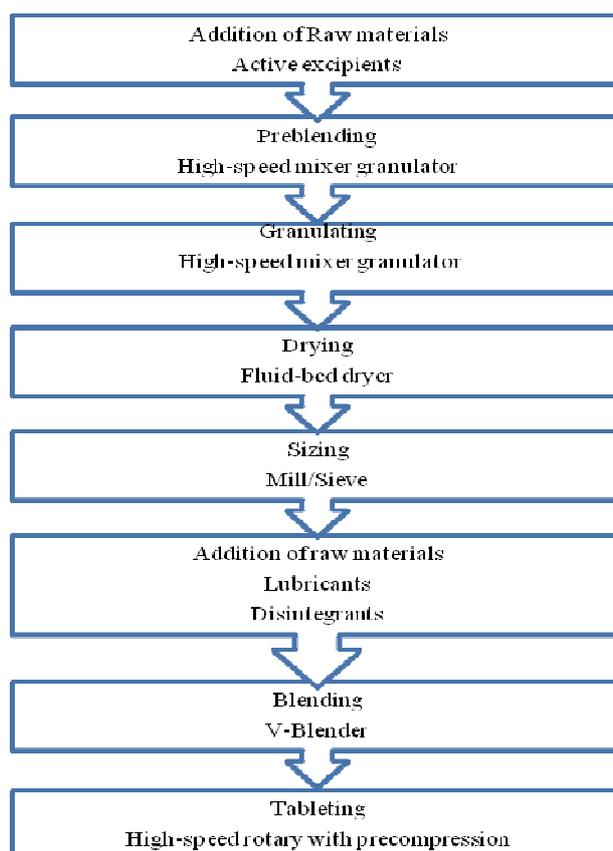


Figure1: Process Overview

9. Conclusion

From study, it can be stated that Process validation is an essential process in pharmaceutical organizations. It is a key element in assuring that the quality goals are met. Successfully validating a process may reduce the dependence upon intensive in process and finished product testing in that case pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured. Finally, it can be concluded that Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product.

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