

Process Validation: An Evolving Process in Pharmaceutical Industries

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ABSTRACT:

The present article is all about an overview of Process validation, its basic need in pharmaceutical companies. According to the of the Quality Assurance, it is not necessary that the quality of the product is always tested, it should be integral. It plays a consequential role in substantiating the documentary evidence that the used manufacturing process that includes raw materials, equipments, Critical Process Parameters, unit operations are capable of constantly liberating the product of desired quality. Moreover, it is the bare necessities of the supervisory/ regulatory bodies that the established manufacturing process should be validated for ensuring that used process is capable of delivering quality product as it provides a well written procedures to monitor the critical parameters. Current Industrial activities suggest that the process validation is the pre-requisite for distributing the product to the market. In order to attain the credentials / marketing authorizations from the regulatory bodies, it is mandatory to validate the manufacturing process of the product. Deprivation of documentary evidence concerning the validation of the manufacturing process can lead to rejection of the application for certification from the concerned regulatory bodies.

KEYWORDS: Process Validation, Protocol, Quality Standards, Report, Stability Studies

I. INTRODUCTION:

Validation is defined as the systemic process that permit the documentary evidence which is able to substantiate the performance of particular method /process that meets its predetermined criteria and quality attributes. It is also important that along with the final testing and compliance with the specifications, the results produced should be consistent. Any significant changes to premises, facilities, process and acceptance criteria that could further directly or

indirectly alter the quality of the final product should be validated. [1]

The validation is required to control and improve the productivity.

ORIGIN OF VALIDATION:

A long time ago, the ayurvedic treatment was given to the patients that includes the use of herbs for the treatment that are derived from nature only, there was no other method to produce that herbs. After some years, pharmaceutical companies were established that formulates medicines synthetically and easy to intake. These manufactured medicines were directly marketed and given to the patients. There was no final testing, no CPPs (Critical Process Parameters), no RM (Raw Material testing etc. There were serious consequences that were faced by the patients at that time. These problems lead to the formation of Regulatory Agencies, testing, GMP (Good Manufacturing Practices), Clinical trials before the approval of the medication etc. But that was not sufficient that could prove the adequacy and effectiveness of the product. So, mainly there was need to focus on the control on the manufacturing process of the product that is basically the core of the medicament. Then the first guideline was delivered by FDA about the process to be validated and also tested that assure the product quality along with the periodic retesting of the procedures. After that various development were done by regulatory bodies like CPPs, CQA (Critical Quality Attributes), Design Space, Quality by Design.

Why validation?

- **Assures Quality:** The process validation provides sureness to the customer about the control of quality of the product manufactured.
- **Regulatory Requirement:** For the approval of any product (new) in a pharmaceutical company, it is the basic requirement that the manufacturing process of the product manufactured in the company

should be validated for ensuring that used process is capable of delivering quality product

- **Reduces cost:** The sophisticated facilities and equipment, expensive materials and products, qualified personnel are some significant parts which are regularly used in pharmaceutical industry. So, if the product is validated and monitored at every step, the cost of particular product failure, rejected products, recalls and complaints that directly affect the respective company's economy will reduce and maximize the output.
- **Customer Satisfaction:** Customers are satisfied when the pharmaceutical companies serve the desired quality product and the main objective of the process

validation is to confirm the reliability of the product of the desired standard.

- **Product Liability:** The product is validated at every stage right from the designing, manufacturing as well as on testing also. Even the method used for testing are also validated that all support the product liability.
- **Process optimization:** The main aim of the process optimization is to reduce the time, eliminate the source wastage, unnecessary costs and errors for maximum efficiency.
- **Safety:** It could increase the operation safety as all the instruments / equipments used in the process validation are calibrated. [2]

ELEMENTS OF VALIDATION:



SCHEMATIC DIAGRAM OF EQUIPMENT VALIDATION

- **DQ (Design Qualification):**
It is the first element that provides the documented evidence that address the equipment, utilities, system are designed according to the requirement by the regulatory bodies (GMP compliant design). It should have ISO 9001 certification. It ensures that the instrument/equipment have all the required quality and criteria of performance that enable them to be manifested at all quality aspects.
- **IQ (Installation Qualification):**
As per FDA guideline, it is being stated that "system has the necessary pre-requisite condition to function as expected". In this, it is verified that all static attributes of equipment/instrument have been installed correctly and configured according to the selected user requirement (specific amount of floor space, operating conditions).
- **OQ (Operational Qualification):**
In this, it is verified that all the dynamic attributes comply with the original Design and meet the manufacturer specified operating ranges. All the aspects of the equipment is individually tested like safety features, Blank machine trial, functioning of equipment.

- **PQ (Performance Qualification):**
In this, it is verified that the derived process either in isolation or in combination with other facility will repeatedly and consistently produces the drug that could meet the pre-set specifications under anticipated production conditions and in worst case condition. It should be performed in the actual facility along with the controlled procedure, equipment and with the trained personnel. [3]

PROCESS VALIDATION:

- Process Validation is documentary evidence that the process, operated within establish parameters, can perform effectively and reproducibly to produce an intermediate or final product meeting its pre-determined specifications and quality attributes.
- Process validation is conducted for the different type of operations like manufacturing process, Drying process, Micronization process, Blending, centrifugation validation etc.
- The batch size increased up to 10 folds in same facility, same/ similar comparative equipments does not require process validation. But, evaluation/ verification should be done through change control procedure.

PLANNING FOR VALIDATION:

All the validation activities are pre-planned / scheduled. The key elements are mentioned in the VMP (Validation Master Plan)

VALIDATION MASTER PLAN:

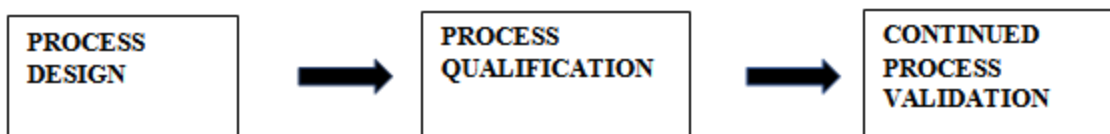
The validation master plan defined the strategy of an organization for conducting the process validation. VMP elaborates upon the types of validation, their scope, methodology, related documentation etc. Annual VMP calendar is prepared for tracking the periodic validation / revalidation of the established (already validated

products) is to be prepared that includes the periodic verification of the product. [4]

Reason of conducting the process validation:

- Development of any New Product.
- Change in the manufacturing site.
- Change in Major Equipment.
- Change in Batch size.
- Change in Process of existing product.
- Change in the Critical Process Parameter of Manufacturing process.
- Change in Vendor of raw material.
- Change in Specifications. [5]

THREE PHASES OF PROCESS VALIDATION



1. PROCESS DESIGN (PRE-VALIDATION PHASE):

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

Initially based on theoretical and scientific knowledge, R&D experiments is established followed by the trials/kilo labs in pilot plant. The R&D submits the PDR and kilo lab trial report, which is the main part of process design. The summary report/ conclusion is drawn for the process design (PDR, Kilo lab trials, trial batches). The knowledge gained through initial R&D work, process design in laboratory and pilot scale, the Batch Production Control Records / Process / SOPs (Standard Operating Procedures), specifications and limits are set. MPCR is prepared based in the designed process. Now the process is designed and ready for the qualification.

2. PROCESS QUALIFICATION (PROCESS-VALIDATION PHASE):

The Process designed is evaluated to determine that whether the process is capable of reproducible commercial manufacturing of product.

It has two elements:

a) DESIGN OF FACILITY AND QUALIFICATIONS OF UTILITIES AND EQUIPMENTS:

The term qualification refers to the activities undertaken to demonstrate that utilities and equipments are suitable for their intended use and perform properly verifying that the above-mentioned system are built and installed in compliance with the design specification/ process requirement.

b) Process Performance Qualification(PPQ):

- After qualification, it is the second phase of process qualification.
- The designed manufacturing process is executed at plant scale with routine trained personnel to produce commercial batches.
- Minimum 3 consecutive batches are to be taken during PPQ.
- Before conducting this stage, a written protocol that specifies manufacturing conditions, control, testing and expected outcome is prepared.

3. Continued Process Verification (Validation Maintenance Phase):

- The goal of third stage is continual assurance that the process remains in a state of control (Validated state) during the commercial manufacturing.
- The continued process verification is evaluated through Product Quality Review Report

(PQR).[6]

TYPES OF PROCESS VALIDATION:

There are mainly 4 approaches to process validation that are presented below:

- a) Prospective validation
- b) Concurrent validation
- c) Revalidation
- d) Retrospective validation

a) Prospective validation:

- It is the documented evidence prepared prior to the Process implementation and the distribution of a new product in the market.
- Prospective validation is performed for all new product processes before routine production commences.
- Prospective validation of a product process is completed before the commercial distribution of the final drug product manufactured
- The Equipment Qualification is done & validation protocol is made before starting prospective validation.
- The batch size of the product under validation shall be minimum one tenth of the commercial scale batch.
- Minimum three batches are considered for prospective process validation.

b) Concurrent Validation

- Concurrent process validation is established & documented evidence that the process is in a state of control during the actual implementation of the process. This is normally performed by conducting in-process testing and / or monitoring of critical operations during manufacturing.
- It is preferred under conditions when Batches are produced infrequently, or batches are produced by a validation process that has been modified (vendor change of key RM, modification in process, facility change etc.)
- Minimum three batches are considered for concurrent process validation.
- Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of batches.

c) Retrospective Validation:

- The retrospective validation is done for the purpose of data generation, demonstration of trend

analysis or as per requirement.

- Batches selected for retrospective validation are the representative of all batches produced
- During the review period, including any batches that failed to meet specifications and sufficient in number to demonstrate process consistency.
- Retained samples can be tested to obtain data to retrospectively validate the process.
- Data of 10-30 batches is considered for retrospective process validation.
- It is based in the historical and testing data of previously manufactured batches and is not much preferred by the regulatory as well as industries.

d) Revalidation:

- It is done to confirm the initial validation for a periodic review.
- It provides the assurance that already validated process is performing within the established parameters and capable of producing desired quality attributes.
- The re-validation of the manufacturing process is done as per the pre-approved protocols.
- Prior to conducting the process revalidation exercise, evaluation for the requirement of formal risk assessment

is conducted.

- Evaluation is performed to check the availability of suitable equipments, utilities and other required facilities.
- The product is revalidated according to pre scheduled period. [7-8]

NUMBER OF BATCHES TO BE TAKEN IN PROCESS VALIDATION:

- As for the new process, there is less knowledge/ details available. So, there is requirement of more demographic data to authenticate the consistent performance.
- If less than two batches are taken consideration in process validation, it will not be sufficient to substantiate the batch-to-batch variations.
- If more than three batches are taken consideration then it will increase the cost of manufacturer as well as it will take more time to validate product.
- If the desired quality of the product is attained in first batch, then maybe it is an accidental / co-accidental case.

- If the required results are attained in second batch, then maybe it is assumed as acceptable or it is regular.
- If the aspired results are also obtained in third batch and are up to the mark as previous batches then it could be said that the product is validated. Same fact could be applied when there is equipment validation.

Process Validation is performed through the pre-approved protocol and training is imparted to the participants of the process validation team regarding the protocol / procedure for conducting the validation.[9]

The main components of process validation protocol are presented below:

- Approval of Protocol
- Objective
- Scope
- Validation Team & Responsibilities
- Details of Equipments
- Validation Procedure
- Sampling Plan
- Acceptance Criteria & Test Methods to be Followed
- Training
- In process parameters [10]

b) **Responsibility:[12]**

DEPARTMENT	RESPONSIBILITY
Executive / Designee QA	Preparation of the protocol and report and also for the proper execution of the process validation.
Head / Designee Production	Review and implementation of the protocol , planning of the process validation and also to ensure that the process is being carried out as per Cgmp requirements, checking the report and to provide training to concerned production staff.
Head / Designee Engineering	Review the protocol for checking of suitability of equipments selected for process / cleaning validation and provide proper maintenance during validation activities to avoid breakdown
Head / Designee EHS	Review the validation protocol for process, personnel and environment safety for process related risk
Head / Designee Quality Control	Managing analysis of the samples generated during validation exercise , including the additional testing as and when required as per the sampling plan given in the protocol , review of analytical data , validation protocol and report and to provide training to concerned QC staff .
Head / Designee R&D	Reviewing of the proletoocol and critical parameters and evaluation of the validation batches and report .

1. Approval of Protocol:

Protocol is approved after review by the team members who reviewed the protocol. Protocol is approved by the Head of Quality Assurance Department before initiating the validation exercise.

2. Objective

It summarizes the reason & purpose behind conducting the process validation activity.It is the short description of validation exercise.

3. Scope

It includes the applicability and scope of the validation activity.

4. Validation Team & Responsibilities

It includes the details of the validation team as well as their roles & responsibilities.

a) Validation Team:

- QA (Quality Assurance)
- QC (Quality Control)
- Production
- Engineering
- EHS (Environment, Health and Safety)
- R&D (Research and Development) [11]

Head / Designee Quality Assurance	Approval of the protocol and report .
Head Quality Assurance	Final approval of the protocol and report .

5. Details of Equipments:

This section contains the name of the equipments to be used in the validation activity along with their qualification status. According to the regulatory guidance, only qualified equipments should be used for the manufacturing of the product.

6. Validation Procedures

It contains the elaborated details regarding the methodology of the Validation exercise for instance number of batches to be taken for the validation, reference of the documents (like SOPs, BPCRs etc.) related to the validation activities, usage of solvents (recovered and fresh), batch size, any specific raw material vendor name etc. [13]

7. Sampling Plan

This section defined the sampling procedure like sampling tool details, requirement of additional sampling etc. as well as the sampling plan like number samples, sampling locations etc. Some part of sampled material is retained as control sample for future reference. The sampling is done from different locations in such a manner that sampled material represents the whole batch.[13]

8. Acceptance Criteria & Test Methods to be Followed:

This section describes the acceptance criterion for each test i.e., in-process test, intermediate tests & Finished Good tests as well as the test methods to be followed for conducting the tests.

9. Training:

After approval of the validation protocol, training is provided to participants from each department (QA, QC, Production). For training purpose, copy of the protocol is shared to the authorized trainers for imparting the training. Training is provided in every shift for covering each participant. Record of the training is maintained for future reference. The training is delivered to the employee so that they could completely implicit the practical procedure

regarding the commencement of process validation.[15]

10. In-process Parameters to be Monitored

In this section, details of the manufacturing operations & their process parameters; in-process tests& their limits as well as the details of the critical process parameters etc. are elaborated.[16]

PROCESS VALIDATION REPORT:

After the completion of process validation, A validation report is prepared with cross reference to It comprises:

- Batch details
- Raw material used
- Equipment details
- In process parameters
- In process testing results
- Quality results
- Yield data
- Deviation details (if any)
- Summary & Conclusion [17-18]

QUALITY STANDARDS THAT ADJUNCT THE VALIDATION ATTEMPT

1. EQUIPMENT CALIBRATION:

Calibration is the process that demonstrate that particular instrument / equipment produces the results within the specification in comparisons to the reference / standards when calibrated. Due to the regular use of instruments / equipments, any type of detriment can happen that could lead to shift in the measurements.It is pivotal for justifying the process validation. This assures the correct performance of the instrument/ equipment.

2. LOG BOOK SYSTEM:

There are different types of log books to maintain the day-to-day record in every department.

These are the vehicles that are supplement to the process validation. These are the documented evidence of the activities performed during Process validation for instance usage of the equipment/ instrument, training records.

3. ONLINE MONITORING BY IPQA:

The ongoing validation batches are online reviewed by the IPQA chemist. The IPQA chemist verifies:

- The status label of equipment and process stage.
- Line clearance has been done.
- whether the manufacturing is done following the instructions mentioned in the protocol and BPCR.
- Equipment Logbooks are filled online with sign and date.
- The samples are properly sent time to time as mentioned in the protocol & the in-process slips are enclosed properly with the BPCR.
- Gowning system has been followed.
- Batch documents are filled online by the production department.
- Calibration status of the equipment in which the validation batches are operating.
- Temperature and relative humidity of the areas complying with the SOP.
- The stored API have proper quarantine, under test, sampled, approved /rejected labels.
- Material stored as per recommended storage area.

4. RECORD GENERATION:

The company system includes issuance of the master production control records (MPCR) and Batch Production and control records (BPCR). These documents include CPPs and CQA which are to be monitored during execution of process validation. [19]

STABILITY STUDIES:

The stability studies are done to determine the shelf life or retest period of product under the scope of the study. The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with the time under the influence of a variety of environmental factors such as temperature, humidity and light. Minimum three batches or all validation batches are kept in stability chamber for stability analysis on the product.

The product should be evaluated under storage conditions that should be sufficient to cover storage, its shipment and subsequent use. The long-term testing should cover a minimum of 12 months duration and should be continued for a period of time sufficient to cover the proposed retest period. The product can be kept on two storage conditions i.e., long term and accelerated. [20]

II. CONCLUSION:

From the above study it is concluded that process validation has become an important component in pharmaceutical industries standard as well as regulatory requirement too for providing the consistent and reliable product. Validation is the most important and recognized parameter of cGMP. It is a continue event till the product or lifecycle. It is a pivotal step for assuring the manufacturing as well as the quality and efficacy of the product.

REFERENCES:

- [1]. Harpreet K, Gurpreet S, Nimrata S. Pharmaceutical process validation: a review. *Journal of Drug Delivery and Therapeutics*. 2013;3(4).
- [2]. Sarvani V, Elisha RP, Nama S, Pola LM, Rao CB. Process validation: An essential process in pharmaceutical industry. *International Journal of Medicinal Chemistry and Analysis*. 2013;3(2):49-52.
- [3]. Immel BK. A brief history of the GMPs for pharmaceuticals. *Pharmaceutical technology*. 2001 Jul;25(7):44-53.
- [4]. Ahir KB, Singh KD, Yadav SP, Patel HS, Poyahari CB. Overview of validation and basic concepts of process validation. *Sch. Acad. J. Pharm*. 2014;3(2):178.
- [5]. Akers J. Simplifying and improving process validation. *PDA Journal of Pharmaceutical Science and Technology*. 1993 Nov 1;47(6):281-4.
- [6]. Matthews BR. Drug Product—Manufacture and Process Validation. In *International Pharmaceutical Product Registration 2016* Apr 19 (pp. 226-249). CRC Press.
- [7]. Rajpal G, Arya RK, Kunwar N. Basic concept of process validation in solid dosage form (tablet): a review. *Journal of Drug Delivery and Therapeutics*. 2016 Aug 6;6(4):79-87.
- [8]. Varshney PR, Shah ME, Patel PA, Rohit MI. Different aspects involved in process validation. *Innovare Journal of Science*. 2013;1(2):16-9.
- [9]. Katz P, Campbell C. FDA 2011 Process Validation Guidance: Process Validation Revisited. *Journal of GXP Compliance*. 2012 Sep 1;16(4).
- [10]. Nikam UA, Jadhav AV, Salunkhe VR, Magdum CS. An overview of pharmaceutical process validation of solid



- dosage form. *Journal of Current Pharma Research*. 2013;3(2):824.
- [11]. Deshmukh OJ, Lahoti SR, Rajendra VB, Gulecha BS, Rawat PK, Kulkarni SA. Prospective process validation of gliclazide tablet. *AJPTR*. 2011;1(3):244-54.
- [12]. Singh SP, Dhaker K, Namdev A, Khinchi MP, Bhatnagar S. A Review on Process Validation. *PharmaTutor*. 2016 Dec 1;4(12):9-19.
- [13]. Jacob A, Gowrav MP. Pharmaceutical Validation and Process Control. *International Journal of ChemTech Research*. 2018;11(08):80-8.
- [14]. Sharma S, Singh G. Process Validation in Pharmaceutical Industry; An Overview. *Journal of Drug Delivery and Therapeutics*. 2013 Jul 14;3(4):184-8.
- [15]. Sharma A, Saini S. Process Validation in Pharmaceutical Industry: A Review. *Pharma science monitor*. 2013 Apr 15;4(3).
- [16]. Dukandar AD, Tandel FB, Jha LL, Prajapati MP. Process Validation of Ibuprofen Film Coated Tablets. *International Journal for Pharmaceutical Research Scholars*. 2015;4(2):169-88.
- [17]. Sandhya C, Bonthagarala B, Sai PD, Sivaiah KV. Process validation: An essential process in pharmaceutical industry. *International Journal of Advances in Scientific Research*. 2015;1(4):179-82.
- [18]. Singh P, Kashyap P, Gidwani B. Pharmaceutical Validation as Per Ich Guidelines. *Pharma Science Monitor*. 2017 Jan 1;8(1).
- [19]. Swarbrick J. Pharmaceutical process validation. Nash RA, Wachter AH, editors. New York: Marcel Dekker; 2003 May.
- [20]. Zothanpuii F, Rajesh R, Selvakumar KJ. A review on stability testing guidelines of pharmaceutical products. *Asian J Pharm Clin Res*. 2020;13(10):3-9.