PROCESS VALIDATION OF SOLID DOSAGE FORM: A REVIEW

Kavita*, Gaurav Khurana, Sandeep Chaudhary

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Department of Pharmaceutics, Bela, Distt. Ropar, Punjab, India.

ABSTRACT

The validation process consists of identifying and testing all aspects of a process that could affect the final test or product. 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 validated. Validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised. So in this article we emphasis on the process validation phases, planning of validation and regulatory requirements of process validation.

Key words: Accuracy, precision, planning, reliability, regulatory, strength.

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]. The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, many regulatory agencies such as the United States Food and Drug Administration (FDA) also require that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and process controls are important. The purpose is to monitor the performance of the manufacturing process and then validate it [2]. Validation refers to establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes. Thus, 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 control\(^3\). Pharmaceutical Process Validation is the most important and recognized parameters of CGMPs. The requirement of process validation appears of the quality system (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goal are met.\(^4\)

**REGULATORY REQUIREMENTS FOR PROCESS VALIDATION**\(^4\)

FDA regulation describing current good manufacturing practices (CGMPs) for finished pharmaceuticals are provided in 21 CFR parts 210 and 211. The CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably. Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that “here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess”. The CGMP regulations regarding sampling set forth a number of requirements for validation: samples must represent the batch under analysis (§211.160 (b)(3)); the sampling plan must result in statistical confidence (§ 211.165(c) and (d)); and the batch must meet its predetermined specifications (§ 211.165(a)). The CGMP regulations also provide norms for establishing in-process specifications as an aspect of process validation. Section 211.110(b) establishes two follow when establishing in-process specifications. The first principle is that “in-process specifications for such characteristics shall be consistent with drug product final specifications”. The second principle is this regulation further requires that in-process specifications “shall be derived determined by the application of suitable statistical procedures were appropriate”. The CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (§ 211.42). Equipment must be of appropriate design, adequate size, and suitable located to facilitate operations for its intended use (§ 211.63). Automated, mechanical and electronic equipment must be calibrated, inspected, or checked according
to the written program designed to assure proper performance (§ 211.68). In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process material and finished product meet predetermined quality requirements and do so consistently and reliability throughout product lifecycle.

**ACCORDING TO US FDA**

**In 1978,** [6]

“A validation manufacturing process is one which has been proved to do what it purports or is represented to do. The proof of validation is obtained through the collection and evaluation of data, preferably, beginning from the process development phase and continuing the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, system, building, personnel), but it also includes the control on the entire process for repeated batches or runs”.

**In 1987,** [7]

“Process validation is establishing documented evidence which provides a high degree of assurance that a specific process (such as the manufacture of pharmaceutical dosage forms) will consistently produce a product meeting its predetermined specifications and quality characteristics”.

**In 2008,** [7]

“Process Validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products”.

**In 2011,**

“The revised guidance also provides recommendations that reflect some of the goals of FDA’s initiative entities “Pharmaceuticals CGMPs for the 21st century – A Risk-Based Approach,” particularly with regards to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality tools and concepts”.

**ACCORDING TO EMEA**

**In March 2012,** [4]

“Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medical product meeting its predetermined specifications and quality attributes.”
Continuous process verification (PCV) has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. This approach is based on the knowledge from product and process development studies and/or previous manufacturing experience. CPV may be applicable to both a traditional and enhanced approach to pharmaceutical development. It may use extensive in-line, on-line or at-line monitoring and/or controls to evaluate process performance. \[8\] Process validation should confirm that the control strategy is sufficient to support the process design and quality of the product. The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. \[8\]

OBJECTIVES OF PROCESS VALIDATION

1. The manufacturing process, in addition to the individual equipment, must be validated.
2. The goal is to create a robust manufacturing process that consistently produces a drug product with minimal variation that adheres to quality criteria of purity, identity, and potency.
3. A validation plan for the manufacturing process should be drafted and executed by engineers in order to satisfy guidelines. The validation plan usually involves just a PQ section.
4. Just as equipment validation, major changes after the initial validation will result in the need for subsequent revalidation.
5. In the end, process validation will ensure a robust product that is highly reproducible overtime.

ADVANTAGES OF PROCESS VALIDATION

1. Expanded real time monitoring and adjustment of process.
2. Enhanced ability to statistically evaluate process performance and product variables.
3. Enhanced data and evaluation capabilities and increased confidence about process reproducibility and product quality.
4. Improved ability to set target parameters and control limits for routine production, correlating with validation results.
5. Enhanced reporting capability.

ESSENTIALS OF PHARMACEUTICAL 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 control. Adequate validation is beneficial to the manufacturer in many ways:

- 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 defect costs.
- 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 situation

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

BASIC CONCEPT OF PROCESS VALIDATION\[9\]

- Calibration, verification and maintenance of process equipment.
- Prequalification or revalidation.
- Establishing specifications and performance characteristics.
- Selection of methods, process and equipment to ensure the product meets specifications.
- Qualification or validation of process and equipment.
• Testing the final product, using validated analytical methods, in order to meet specifications.
• Challenging, auditing, monitoring or sampling the recognized critical key steps of the process.

PHASES IN PROCESS VALIDATION \[9\]
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.

**TYPES OF VALIDATION** \[10\]
1. Equipment validation
2. Process validation
3. Analytical method validation
4. Cleaning validation
1. EQUIPMENT VALIDATION

(a) Installation Qualification (IQ)

This is the first step in validation. This protocol insures that the system/equipment and its components are installed correctly and to the original manufacturer’s specifications. Calibration of major equipment, accessory equipment, and/or utilities should be performed in this step as well IQ provides documented evidence that the equipment or system has been developed, supplied and installed in accordance with design drawings, the supplier's recommendations and In-house requirements. Furthermore, IQ ensures that a record of the principal features of the equipment or system, as installed, is available and that it is supported by sufficient adequate documentation to enable satisfactory operation, maintenance and change control to be implemented.

(b) Operational Qualification (OQ)

This step proceeds after the IQ has been performed. In the OQ, tests are performed on the critical parameters of the system/process. These are usually the independent and/or manipulated variables associated with the system/equipment. All tests data and measurements must be documented in order to set a baseline for the system/equipment. OQ provides documented evidence that the equipment operates as intended throughout the specified design, operational or approved acceptance range of the equipment, as applicable. In cases where process steps are tested, a suitable placebo batch will be used to demonstrate equipment functionality. All new equipment should be fully commissioned prior to commencing OQ to ensure that as a minimum the equipment is safe to operate, all mechanical assembly and pre-qualification checks have been completed, that the equipment is fully functional and that documentation is complete.

(c) Performance Qualification (PQ):

This is the third and final phase of validation. This phase tests the ability of the process to perform over long periods of time within tolerance deemed acceptable. PQ is performed
on the manufacturing process as a whole. Individual components of the system are not tested individually. The purpose of PQ is to provide documented evidence that the equipment can consistently achieve and maintain its performance specifications over a prolonged operating period at a defined operating point to produce a product of predetermined quality. The performance specification will reference process parameters, in-process and product specifications. PQ requires three product batches to meet all acceptance criteria for in-process and product testing. For utility systems, PQ requires the utility medium to meet all specifications over a prolonged sampling period.

2. PROCESS VALIDATION

Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.

Types of Process Validation
(A) Prospective validation
(B) Retrospective validation
(C) Concurrent validation
(D) Revalidation

(A) Prospective validation

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

(B) Retrospective validation

Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and
will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment. This approach is rarely been used today because it’s very unlikely that any existing product hasn’t been subjected to the Prospective validation process. It is used only for the audit of a validated process.

(C) Concurrent validation
Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

(D) Revalidation
Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. Possible reasons for starting the revalidation process include:

- The transfer of a product from one plant to another.
- Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.
- The necessity of periodic checking of the validation results.
- Significant (usually order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.

3. ANALYTICAL VALIDATION
Analytical Validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised.

4. CLEANING VALIDATION
Cleaning validation is a documented process that proves the effectiveness and consistency in cleaning a pharmaceutical production equipment. Validations of equipment cleaning procedures are mainly used in pharmaceutical industries to prevent cross contamination and adulteration of drug products hence is critically important. The prime purpose of validating a cleaning process is to ensure compliance with federal and other standard regulations. The most important benefit of conducting such a validation work is the identification and correction of potential problems previously unsuspected, which could compromise the safety, efficacy or quality of subsequent batches of drug product produced within the equipment. The objectives of equipment cleaning and cleaning validation in an Active Pharmaceutical Ingredient (API) area are same as those in pharmaceutical production area. In both these areas efforts are necessary to prevent contamination of a future batch with the previous batch material. The cleaning of 'difficult to reach' surface is one of the most important consideration in equipment cleaning validation. Equipment cleaning validation in an API facility is extremely important as cross contamination in one of the pharmaceutical dosage forms, will multiply the problem.

IMPORTANCE OF VALIDATION\[^{[10]}\]

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 is establishes a quality standard for the specific process.

VALIDATION DOCUMENTS\[^{[5]}\]

VALIDATION MASTER PLAN (VMP)\[^{[11,12,13]}\]: A validation Master Plan (VMP) is a comprehensive document describing the applicable validation requirements for the
facility, and providing a plan for the meeting those requirements. The VMP is used, managed, and enforced throughout the life of a process to ensure quality. The document defines the validation approach, specifies the responsibilities of each of the validation team member, and is important effort at the beginning of a project. The description of following systems are necessary to control validation activities as well as the ongoing operation of the system, process, or equipment:

- Protocol and documentation preparation
- Protocol execution
- Documentation control
- Change control

**PROTOCOL**: VMP includes the incorporation of information into formal written protocols, which serve as guides for executing the appropriate validation activities. Protocols should be developed for IQ, OQ, PQ. The information included in specific protocols are:

- Description of the system
- Qualification objective
- Scope
- Responsibilities and data collection procedures
- Test procedures, specific acceptance criteria
- Documentation procedures
- Summary and deviation report

**Installation Qualification (IQ)**: It is performed to verify that the installed components are the ones specified, that they are properly identified, and so on, as stated in the construction documents in accordance with the specific requirements of the user. IQ protocol includes:

- Verification of Calibration of critical installed components
- Verification of procedure (e.g., operation, maintenance, cleaning, change control)
- Verification of major components
- Verification of control and monitoring devices
- Verification of utilities connections
Operational Qualification (OQ): This involves the testing of various components of the system, process, or equipment to document proper performance of these components. OQ protocol includes:

- Verification of test equipment calibration
- Computer control system testing
- Verification of sequence of operations
- Power failure/recovery testing
- Functionality testing of distribution system, valves, etc.
- System initial sampling

Performance Qualification (PQ): This involves challenging the system, process, or equipment to provide evidence of appropriate and viable operation.

**OPERATING PROCEDURE**: Procedures must be prepared for all operations to be performed during the execution of a protocol. Called as Validation operating procedures, SOP’s, operating manuals.

**CHANGE CONTROL PROCEDURE**: This procedure is essential for the continual operation of the system, process, or equipment and provides a formal mechanism for monitoring changes during the continued operation of the system. The proposed changes that can affect the validated status of a system are reviewed by the validation team or responsible personnel and the proposed corrective action is approved. Sufficient detailed documentation is necessary for each critical change to maintain control over the system with the passage of time.

The following are descriptions of the essential parts of the VMP:

1. The **Approvals** section contains the signatures and job titles of the people who author and approve the Validation Master Plan.

2. The **Publication Record** contains the revision history of the VMP. The VMP is meant to be a working document. That is, it changes to reflect the changing reality of a rapidly moving facility with many projects or even just a few. Therefore we have to plan for change and be ready to change the plan.

3. The **Responsibilities** section defines who is responsible for what.

4. The **Introduction** specifies the company, business unit, and location. It gives an overview of the business and explains why the project is being implemented. In this
section the author may focus on how the new process or equipment will add to the overall quality of the facility.

5. The Scope defines the limits of the validation project and details which equipment is included in the project and which is not.

6. In the Design Description, the design of the new installation or process. In the case of a new process in existing equipment, the critical process parameters and how they affect product quality. With new equipment or facilities, the design description will include physical characteristics such as size or volume, and descriptions of supporting utilities or materials of construction.

7. Commissioning & Qualification. If a system has no significant impact on the quality of the product, then you may decide that normal commissioning is sufficient.

8. Computer System Validation. Provide the rationale for validating or not validating each computer system that affects the quality of the product.

9. List of Required Standard Operating Procedures. This section is also composed in tabular form and can also serve as a tracking mechanism for the progress of the project.

10. The Equipment and Utility System Descriptions. The purpose and operational concept of each system. In addition, you should think through at this time what qualification tests you will conduct and consider how you will determine acceptance criteria.

11. Quality Systems. Once the new process is validated, the FDA wants to know how you intend to keep it in a validated state until the last batch of product is produced. The VMP demonstrates how you intend to accomplish that by laying out the list of SOP’s that support the validated systems. There are some of the procedures that you should have:

**VALIDATION PROTOCOLS:** Controlled documents that describe how to perform a specific validation work/event. They can reference SOPs, specifications, and Manufacturing records, acceptance criteria.

**VALIDATION REPORTS**

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

- Title and objective of study;
• Reference to protocol;
• Details of material;
• Equipment;
• Programmes and cycles used;
• Details of procedures and test methods;
• Recommendation on the limit and criteria to be applied on further basis

CONCLUSION:
Validation includes the incorporation of information into formal written protocols, which serve as guides for executing the appropriate validation activities. 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 have as their goal and the production of articles that are fit for their intended use. In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process material and finished product meet predetermined quality requirements and do so consistently and reliability throughout product lifecycle.

REFERENCES
12. US Food and Drug Administration, 21 CFR 2. parts 210 and 211.

For Correspondence:
Kavita
Email: kavita.keshwar@gmail.com