PROCESS VALIDATION: IMPACT ON PHARMACEUTICAL INDUSTRY

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ABSTRACT
The purpose of this work is to present an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process with special reference to the requirements stipulated by the US Food and Drug Administration (FDA). Quality is the primordial intention to any industry and its products manufactured. Multiple views on obtaining such quality are the current interest in the pharmaceutical industry. Quality assurance techniques must be used to build the quality into the product at every step and not just tested for at the end. It has always been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. Process controls are mandatory in good manufacturing practice (GMP). Validation is the mean of catering enormous benefits to even more than the acceptable quality level which in the global standard scale. Lending importance to validation is increasingly profound in recent years. Validation is the art of designing and practicing the designed steps alongside with the documentation. 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. This overview examines the need for pharmaceutical validation, the various approaches and steps involved, and other pertinent considerations.

Keywords: Process Validation, Quality Assurance, Pharmaceutical Validation, Pharmaceutical manufacturing.

INTRODUCTION
The prime objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently, at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever increasing interest in validation owing to their industry’s greater emphasis in recent years on quality assurance program and is fundamental to an efficient production operation [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 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 in spite of the problems that may be encountered[^2].

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. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, equipment sanitization and purified water production[^3].

In a guideline, validation is act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the expected results. It includes the qualification of systems and equipment. The goal of the validation is to ensure that quality is built into the system at every step, and not just tested for at the end, as such validation activities will commonly include training on production material and operating procedures, training of people involved and monitoring of the system whilst in production. In general, an entire process is validated and a particular object within that process is verified. The regulations also set out an expectation that the different parts of the production process are well defined and controlled, such that the results of that production will not substantially change over time[^4].

**IMPORTANCE OF VALIDATION[^5]**

1. Assurance of quality
2. Time bound
3. Process optimization
4. Reduction of quality cost.
5. Nominal mix-ups, and bottle necks
6. Minimal batch failures, improved efficiently and productivity.
7. Reduction in rejections.
8. Increased output.
9. Avoidance of capital expenditures
10. Fewer complaints about process related failures.
11. Reduced testing in process and in finished goods.
12. More rapid and reliable start-up of new equipments
13. Easier scale-up form development work.
14. Easier maintenance of equipment.
15. Improved employee awareness of processes.
17. Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products).

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.[6]

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.

PROCESS VALIDATION [7,8]

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. Process validation is a requirement of current Good Manufacturing Practices (GMPs) for finished pharmaceuticals (21CFR 211) and of the GMP regulations for medical devices (21 CFR 820) and therefore applies to the manufacture of both drug products and medical devices. Process validation involves a series of activities taking place over the lifecycle of the product and process. The U.S. Food and Drug Administration (FDA) has proposed guidelines with the following definition for process validation: - “PROCESS VALIDATION” is establishing
documented evidence which provides a high degree of assurance that a specific process consistently produces a product meeting its predetermined specifications and quality attributes.*[4,10].

**REGULATORY BASIS FOR PROCESS VALIDATION**

Once the concept of being able to predict process performance to meet user requirements evolved, FDA regulatory officials established that there was a legal basis for requiring process validation. The ultimate legal authority is Section 501(a)(2)(B) of the FD&C Act, which states that a drug is deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or were not operated or administrated in conformity with CGMP. Assurance must be given that the drug would meet the requirements of the act as to safety and would have the identity and strength and meet the quality and purity characteristics that it purported or was represented to possess. That section of the act sets the premise for process validation requirements for both finished pharmaceuticals and active pharmaceutical ingredients, because active pharmaceutical ingredients are also deemed to be drugs under the act. The CGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. Although these regulations do not include a definition for process validation, the requirement is implicit in the language of 21 CFR 211.100, which states: “There 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.”

**PHASES OF VALIDATION** [7, 8]

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 PROCESS VALIDATION** [9,10,11,12,13]

The guidelines on general principles of process validation mentions four types of validation:

A) Prospective validation (or premarket validation)

B) Retrospective validation

C) Concurrent validation

D) Revalidation

**A. Prospective Validation**

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. A series of experiments should be designed to determine the criticality of these factors. Each experiment should be planned and documented fully in an authorised protocol. All equipment, production environment and the analytical testing methods to be used should have been fully validated. Master batch documents can be prepared only after the critical parameters of the process have been identified and machine settings, component specifications and environmental conditions have been determined.
Using this defined process a series of batches should be produced. In theory, the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established to provide sufficient data for evaluation. 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. In practice, it may take some considerable time to accumulate these data\(^9\). Prospective validation is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics, before a product made under a revised manufacturing process is released for distribution.

**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. Retrospective validation is only acceptable for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there have been recent changes in the formulation of the product, operating procedures, equipment and facility.

**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.
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
- when the number of batches produced are limited (e.g. orphan drugs).

**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.

**CHANGE CONTROL** [14]

Written procedures should be in place to describe the actions to be taken if a change is proposed to a product component, process equipment, process environment, processing site, method of production or testing or any other change that may affect product quality or support system operations.
All changes must be formally requested, documented and accepted by the validation team. The likely impact / risk of the change on the product must be assessed and the need for the extent of re-validation should be determined.

Commitment of the company to control all changes to premises, supporting utilities, systems, materials, equipment and processes used in the fabrication/packaging of pharmaceutical dosage forms is essential to ensure a continued validation status of the systems concerned.

The change control system should ensure that all notified or requested changes are satisfactorily investigated, documented and authorized. Products made by processes subjected to changes should not be released for sale without full awareness and consideration of the change by the validation team. The team should decide if a re-validation must be conducted prior to implementing the proposed change.

STRATEGY FOR VALIDATION OF METHODS

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to the unknown samples analyzed in the routine. The preparation and execution should follow a validation protocol preferably written in a step-by-step instruction format as follows [15].

- Develop a validation protocol or operating procedure for the validation;
- Define the application purpose and scope of the method;
- Define the performance parameter and acceptance criteria;
- Define validation experiments;
- Verify relevant performance characteristic of the equipment;
- Select quality materials, e.g., standards and reagents;
- Perform pre-validation experiments;
- Adjust method parameters and/or acceptance criteria, if necessary;
- Perform full internal (and external) validation experiments;
- Develop SOPs for executing the method routinely;
- Define criteria for revalidation;
- Define type and frequency of system suitability tests and/or analytical quality control (AQC) checks for the routine; and
• Document validation experiments and results in the validation report.

REGULATION OF VALIDATION \[16\]

The three basic and most important reasons for validation are quality assurance, economics and compliance.

1. Quality assurance

Product quality cannot be assumed for a process by routine quality control testing because of the limitation of statistical sampling and the limited sensitivity if the finished product testing. Quality variations among units within a batch, or among different batches, are seldom detected by testing of finished product samples. Validation challenges the adequacy and reliability of a system or process to meet pre-determined criteria. A successful validation, therefore, provides a high degree of confidence that the same level of quality is consistently built into each unit of the finished product, from batch to batch. The Pharmaceutical Manufacturers Association (PMA) and the FDA have recognized the product quality assurance concept of validation.

2. Economics

The direct economic benefit of validation is a reduction in the cost associated with process monitoring, sampling and testing. The consistency and reliability of a validated process to produce a quality product provide indirect cost savings resulting from a decrease or elimination of product rejections, reworks and retesting. Final release of the product batch would be expedited and free of delays and complications caused by lengthy investigations of process or analytical variances. In addition, product quality complaints and potential product recalls would be minimized.

3. Compliance

Specific current Good Manufacturing Practices (cGMP) references to variation are found in following sections of 21CFR211 211.884(d) - Variation of suppliers test result for components when these results are accepted in lieu of in-house testing after receipt. 211.110 (a) - Validation of manufacturing process to ensure batch uniformity and integrity of drug products. 211.165(e) - Validation of analytical methodologies.

The requirement of validation is also implied in 211.100(a). This section of GMP requires that written procedures and process controls be established to ensure that the drug products have to “identify strength, quality and purity are represented to possess”.
The FDA’s draft Mid Atlantic Pharmaceutical Inspection Guidance Program for Prescription Drug Plants, issued in January 1990, emphasized the importance of validation in the manufacturing process.

A TYPICAL VALIDATION BLUEPRINT OF EQUIPMENT VALIDATION

Introduction

1. Installation qualification
   - Facilities
   - Utilities
   - Equipment

2. Operation qualification
   - Testing Protocols for Utilities and Equipment

3. Validation
   - Testing protocols for products and Cleaning systems

4. Documentation

5. Validation of the QA testing laboratory

6. SOPs

7. Training of personnel

8. Organization charts

9. Schedule of events

When an organization follows the precepts of total quality management (TQMI), the concept of continuous improvement would routinely be used. When process validation is used as a quality assurance tool instead of a final examination, an organization’s operations will improve or stay at the highest quality level possible. The effort will be properly documented, and the overall attitudes of all the affected personnel will be positive. Finally, a more logical approach to pre approval inspections and other FDA technical interactions will be affected. When the validation activity becomes the focal point of an organizational unit’s effort to carry out its own technical responsibilities, quality standards will be maintained for the product and manufacturing process from the design and development stages and throughout the commercial life of the product. The concept of validation had to be redefined and re-evaluated to accommodate the technical
changes. Traditional validation concepts and procedures that were acceptable years ago may no longer be applicable to today’s operations and equipment. A practical understanding of the validation concepts and when and how to apply them is of greater importance to ensure a meaningful, efficient, effective, and economical validation program. Because practicality and compliance are both important aspects of validation. Finally, as with any project, the validation is not complete without the necessary documentation. Special attention should be afforded to the physical appearance of the report, as well as its technical contents [17, 18].

THE PHARMACEUTICAL PROCESS EQUIPMENT

The key idea of validation is to provide a high level of documented evidence that the equipment and the process conform to a written standard. The level (or depth) is dictated by the complexity of the system or equipment. The validation package must provide the necessary information and test procedures required to provide that the system and process meet specified requirements [19]. Validation of pharmaceutical process equipment involves the following [20]

Installation Qualification:

This ensures that all major processing and packaging equipment, and ancillary systems are in conformity with installation specification, equipment manuals schematics and engineering drawing. It verifies that the equipment has been installed in accordance with manufacturers recommendation in a proper manner and placed in an environment suitable for its intended purpose.

Operational Qualification:

This is done to provide a high degree of assurance that the equipment functions as intended. Operational qualification should be conducted in two stages:

Component Operational Qualification, of which calibration can be considered a large part.

System Operational Qualification to determine if the entire system operates as an integrated whole.

Process Performance Qualification:
This verifies that the system is repeatable and is consistently producing a quality product\textsuperscript{[21]}. These exercises assure, through appropriate performance lists and related documentation, that equipment, ancillary systems and sub-systems have been commissioned correctly. The end results are that all future operations will be reliable and within prescribed operational limits. At various stages in a validation exercise there are needs for protocols, documentation, procedures, specifications and acceptance criteria for test results. All these need to be reviewed, checked and authorized. It would be expected that representatives from the professional disciplines, e.g., engineering, research and development, manufacturing, quality control and quality assurance are actively involved in these undertakings with the final authorization given by a validation team or the quality assurance representative \textsuperscript{[22]}.

**Responsible Authorities For Validation**

The validation working party is convened to define progress, coordinate and ultimately, approve the entire effort, including all of the documentation generated. The working party would usually include the following staff members, preferably those with a good insight into the company's operation.

- Ø Head of quality assurance
- Ø Head of engineering
- Ø Validation manager
- Ø Production manager
- Ø Specialist validation discipline: all area.

<table>
<thead>
<tr>
<th>Department /Designation</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manager Production</td>
<td>Responsible for manufacturing of batches and review of protocol and report.</td>
</tr>
<tr>
<td>Manager QC</td>
<td>Responsible for analysis of samples collected</td>
</tr>
<tr>
<td>Executive QC</td>
<td>Responsible for samples collection and submission to QC</td>
</tr>
<tr>
<td>Manager Maintenance</td>
<td>Providing utilities and engineering support</td>
</tr>
<tr>
<td>Executive Production</td>
<td>Responsible for preparation of protocol and manufacturing of validation batches</td>
</tr>
<tr>
<td>Manager QA</td>
<td>Responsible for protocol authorization and preparation of summary report.</td>
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Fig.1
Validation team

A multidisciplinary team is primarily responsible for conducting and supervising validation studies. Personnel qualified by training and experience in a relevant discipline may conduct such studies.

Responsibilities of validation team

Creates updates and reviews/approves individual project validation plans and validation deliverables.

Ensures validation compliance with the company validation master plan and project validation plan. As mentioned in fig No: 1

Coordinates, implements, verify elements of VMP.

Consults on, evaluates and approves changes.

Reviews and approves IQ/OQ/PQ procedures and plans.

Reviews test results and makes recommendations regarding release.

Assess risks and develops contingency plan.

CONCLUSION

From study, it can be stated that Process validation is a major requirement of cGMP regulation for finished pharmaceutical products. It is necessary, before approval of a new drug, that an accurate and reliable assessment for its effectiveness and safety for the intended indication and target patient population is demonstrated. Validation has been proven assurance for the process efficiency and sturdiness and it is the full fledged quality attributing tool for the pharmaceutical industries. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry.

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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