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## PROCESS VALIDATION: AN ESSENTIALITY IN THE PHARMACEUTICAL INDUSTRY

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### ABSTRACT

Drugs are critical elements in health care. They must be manufactured to the highest quality levels. End-product testing by itself does not guarantee the quality of the product. Quality assurance techniques must be used. In the pharmaceutical industry, process validation performs this task, ensuring that the process does what it purports to do. Validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated we can assure that the final product is of the best quality. This paper presents an introduction and general overview on process validation of pharmaceutical manufacturing process with special reference to the requirements stipulated by the United States Food and Drug Administration (USFDA).

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### Key Words

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## INTRODUCTION

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation<sup>[1]</sup>.

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 (USFDA) 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 in spite of the problems that may be encountered<sup>[2]</sup>.

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 process involved in making these products but quickly spread to associated processes involving environmental control, media fill, equipment sanitization and purified water production<sup>[3,4]</sup>.

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<sup>[5]</sup>.

## NEED OF VALIDATION

1. It would not be feasible to use the equipments without knowing whether it will produce the product we wanted or not.
2. The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
3. The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, and recalls, complaints are the significant parts of the total production cost.
4. Detailed study and control of the manufacturing process- validation is necessary if failure to be reduced and productivity improved.
5. The pharmaceutical industries are concerned about validation because of the following reasons.
6. Assurance of quality.
7. Cost reduction.
8. Government regulation<sup>[6,7]</sup>.

## DEPARTMENT RESPONSIBLE

1. Site validation committee (SVC): Develop site master validation plan, Prepare/ execute/ approve validation studies.
2. Manufacturing department: Prepares the batches as a routine production batch.
3. Quality assurance: Ensure compliance, see that documentations/ procedures are in place, approves protocols and reports.
4. Quality control: Perform testing and reviews protocol and report as needed<sup>[7]</sup>.

## 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.

- Head of quality assurance.
- Head of engineering.

- Validation manager.
- Production manager.
- Specialist validation discipline: all areas<sup>[7]</sup>.

Department /Designation	Responsibility
Manager Production	Responsible for manufacturing of batches and review of protocol and report.
Manager QC	Responsible for analysis of samples collected
Executive QC	Responsible for samples collection and submission to QC
Manager Maintenance	Providing utilities and engineering support
Executive Production	Responsible for preparation of protocol and manufacturing of validation batches
Manager QA	Responsible for protocol authorization and preparation of summary report.

### 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:

1. It deepens the understanding of processes; decreases the risk of preventing problems and thus assures
2. The smooth running of the process.
3. It decreases the risk of defect costs.
4. It decreases the risk of regulatory noncompliance.
5. A fully validated process may require less in-process controls and end product testing<sup>[8,9]</sup>.

### ELEMENTS OF VALIDATION

#### Design Qualification (DQ):-

It is a documented review of the design, at an appropriate stage of stages in the project, for

conformance to operational and regulatory expectations.

DQ check items:

1. Goods manufacturing practices and regulatory requirements.
2. Performance criteria.
3. Facility air flow, movement flow and pressure engines.
4. Reliability and efficiency.
5. Commissioning requirements.
6. Construct ability and installation of equipment.
7. Maintenance and access to critical equipment and instrumentation.
8. Safety and environment impact.

#### INSTALLATION QUALIFICATION (IQ):-

It is a documented verification that all the aspects of a facility, utility or equipment that can affect product quality adhere to approved specifications and are correctly installed.

Important IQ considerations are:

1. Installation conditions (wiring, utilities and functionality).
2. Calibration, preventive maintenance, cleaning schedules.
3. Safety features.

4. Supplier documentation, prints, drawings and manuals.
5. Software documentation.
6. Spare parts list.
7. Environmental conditions (such as clean room requirements, temperature and humidity).
8. Equipment design features (i.e. materials of construction clean ability).

### OPERATIONAL QUALIFICATION (OQ)

It is a documented verification that all aspects of a facility, utility or equipment that can affect product quality operate to intend throughout all anticipated ranges.

OQ considerations include:

1. Process control limits (time, temperature, pressure, line speed and set up conditions).
2. Software parameters.
3. Raw material specifications.
4. Process operating procedures.
5. Material handling requirements.
6. Process change control.
7. Training.
8. Short term stability and capability of the process (latitude studies or control charts).
9. Potential failure modes, action levels and worst-case conditions (Failure Mode and effects).
10. Fault tree analysis.

### PERFORMANCE QUALIFICATION (PQ)

It is a documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria.

PQ considerations include:

1. Actual product and process parameters and procedures established in OQ.
2. Acceptability of the product.
3. Assurance of process capability as established in OQ.
4. Process repeatability, long term process stability<sup>[5,10]</sup>.

### Major Phases in Validation

The activities relating to validation studies may be classified into three:

**Phase 1:** This is the Pre-validation 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 and storage, and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production document, operational qualification and process capacity.

**Phase 2:** This is the Process Validation Phase. It is designed to verify that all established limits of the critical process parameter are valid and that satisfactory products can be produced even under the worst conditions.

**Phase 3:** Known as the Validation Maintenance Phase, it requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures, have been followed. At this stage, the validation team comprising of individuals representing all major departments also assures that there have been no changes/deviations that should have resulted in requalification and revalidation<sup>[11]</sup>. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture. The validation steps recommended in GMP guidelines can be summarized as follows:

1. As a pre-requisite, all studies should be conducted in accordance with a detailed, pre-established **protocol** or series of protocols, which in turn is subject to formal – change control procedures;
2. Both the personnel conducting the studies and those running the process being studied should be appropriately **trained** and **qualified** and be suitable and competent to perform the task assigned to them;

3. All data generated during the course of studies should be formally **reviewed** and **certified** as evaluated against pre-determined criteria;
4. Suitable **testing facilities, equipment, instruments** and **methodology** should be available;
5. Suitable clean room facilities should be available in both the 'local' and background environment. There should be assurance that the clean room environment as specified is secured through initial commissioning (qualification) and subsequently through the implementation of a programme of re-testing – in-process equipment should be properly **installed, qualified** and **maintained**;
6. When appropriate attention has been paid to the above, the process, if aseptic, may be validated by means of "**process simulation**" studies;
7. The process should be revalidated at intervals; and
8. Comprehensive **documentation** should be available to define support and record the overall validation process<sup>[11]</sup>.

Protocols should specify the following in detail:

1. The objective and scope of study- There should already be a definition of purpose;
2. A clear and precise definition of process equipment system or subsystem, which is to be the subject of study with details of performance characteristics;
3. Installation and qualification requirement for new equipment;
4. Any upgrading requirement for existing equipment with justification for the change(s) and statement of qualification requirement;
5. Detailed stepwise statement of actions to be taken in performing the study (or studies);
6. Assignment of responsibility for performing the study;
7. Statement on all test methodology to be employed with a precise statement of the test equipment and/or materials to be used;
8. Test equipment calibration requirements;
9. References to any relevant standard operating procedures (SOP);
10. Requirement for the current format of the report on the study;

11. Acceptance criteria against which the success (or otherwise) of the study is to be evaluated; and
12. The personnel responsible for evaluating and certifying the acceptability of each stage in the study and for the final evaluation and certification of the process as a whole, as measured against the pre-defined criteria<sup>[12]</sup>.
13. All personnel involved in conducting the studies should be properly trained and qualified because they can, and often, have a crucial effect on the quality of the end product. All information or data generated as a result of the study protocol should be evaluated by qualified individuals against protocol criteria and judged as meeting or failing the requirements. Written evidence supporting the evaluation and conclusion should be available. If such an evaluation shows that protocol criteria have not been met, the study should be considered as having failed to demonstrate acceptability and the reasons should be investigated and documented. Any failure to follow the procedure as laid down in the protocol must be considered as potentially compromising the validity of the study itself and requires critical evaluation of all the impact on the study. The final certification of the validation study should specify the pre-determined acceptance criteria against which success or failure was evaluated<sup>[11]</sup>.

#### 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. Process validation is a requirement of current Good Manufacturing Practices (GMPs) for finished pharmaceuticals (21 CFR 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 (Nash, 2003).

The United States Food and Drug Administration (USFDA) 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<sup>[5,13]</sup>.

### TYPES OF PROCESS VALIDATION

**1. Prospective Process Validation-** Where an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put to commercial use. Most validation efforts require some degree of prospective experimentation in order to generate validation support data.

**2. Concurrent Process Validation-** Establishing 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 the manufacture of each production batch.

**3. Retrospective Process Validation-** Where historic data taken from the records of the completed production batches are used to provide documented evidence that the process has been in a state of control prior to the request for such evidence<sup>[14,15]</sup>.

### THE REGULATORY BASIS FOR PROCESS VALIDATION

The concept of process validation from its beginnings in the early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, and sterile product and solid dosage forms considerations. In the early 1990s, the concept of preapproval inspection (PAI) was born and had as one of its basic tenets the assurance that approved validation protocols and schedules were being generated and that comprehensive development, scale-up, and biobatch and commercial batch validation data were required in order to achieve a successful regulatory PAI audit. There are several important reasons for validating a product

and/or process. First, manufacturers are required by law to conform to cGMP regulations. Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality. Although the original focus of validation was directed towards prescription drugs, the FDA Modernization Act of 1997 expanded the agency’s authority to inspect establishments manufacturing over-the-counter (OTC) drugs to ensure compliance with cGMP. 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 administered in conformity with cGMP. The cGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess<sup>[4,5,16,17]</sup>.

### PRE-REQUISITES FOR PROCESS VALIDATION

Before process validation can be started, manufacturing equipment and control instruments as well as the formulation must be qualified. The information on a pharmaceutical product should be studied in detail and qualified at the development stage, i.e., before an application for marketing authorization is submitted. This involves studies on the compatibility of active ingredients and recipients, and of final drug product and packaging materials, stability studies, etc. Other aspects of manufacture must be validated including critical services (water, air, nitrogen, power supply, etc.) and supporting operations such as equipment cleaning and sanitation of premises. Proper training and motivation

of personnel are prerequisites to successful validation<sup>[18,19,20]</sup>.

### 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<sup>[21]</sup>. Validation of pharmaceutical process equipment involves the following<sup>[22]</sup>:

1. **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 manufacturer's recommendation in a proper manner and placed in an environment suitable for its intended purpose.
2. **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:
3. **Component Operational Qualification**, of which calibration can be considered a large part.
4. **System Operational Qualification** to determine if the entire system operates as an integrated whole.
5. **Process Performance Qualification:** This verifies that the system is repeatable and is consistently producing a quality product<sup>[23]</sup>.

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<sup>[24]</sup>.

### APPROACHES TO PROCESS VALIDATION

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc). 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:

1. extensive product testing,
2. simulation process trials,
3. challenge/worst case trials, and
4. Control of process parameters (mostly physical)<sup>[25]</sup>.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to the extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the normality of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are within compendia specifications<sup>[26]</sup>.

### 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:

1. Title and objective of study.
2. Reference to protocol.
3. Details of material.
4. Equipment.
5. Programmes and cycles used.
6. Details of procedures and test methods.
7. Results (compared with acceptance criteria).
8. Recommendations on the limit and criteria to be applied on future basis <sup>[9, 27]</sup>.

From the study, it can be stated that Process validation is a major requirement of cGMP regulation for finished pharmaceutical products. 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. 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 the quality of finished product.

**CONCLUSION**

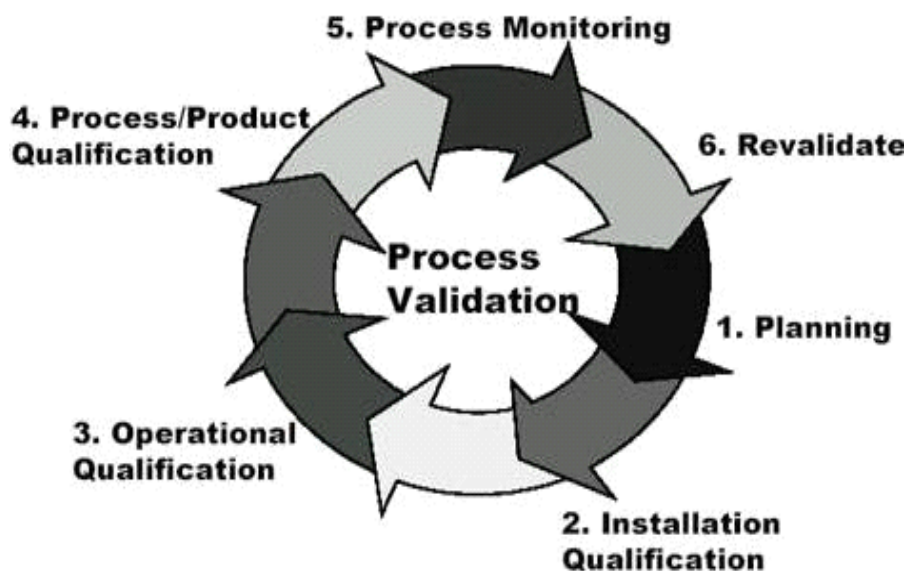


Figure No.1: General view of process validation

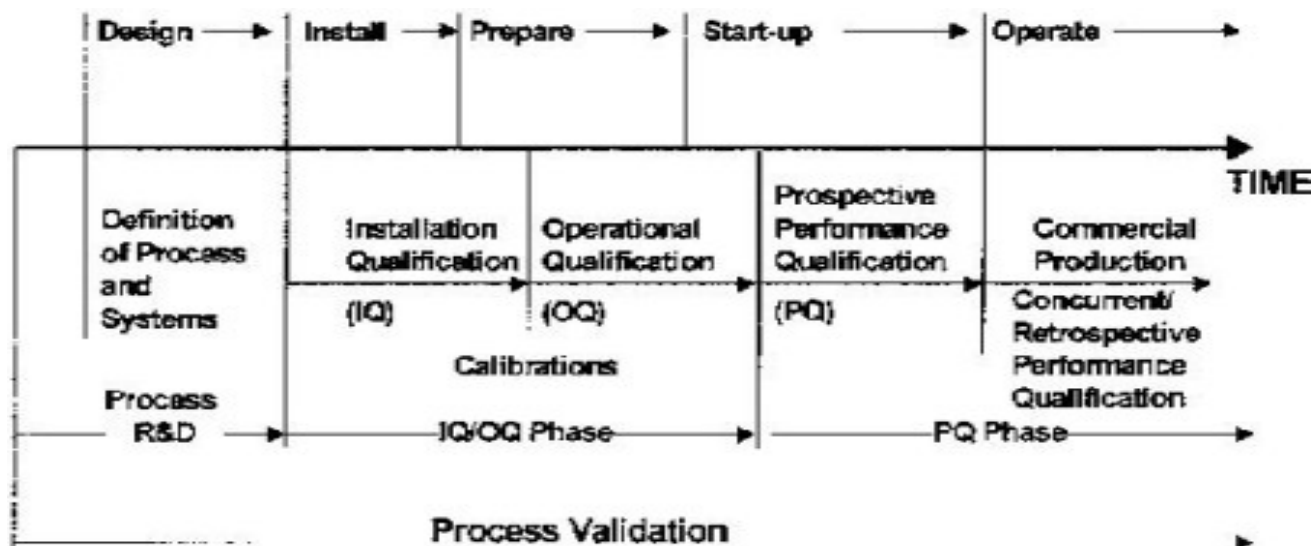


Figure No. 2: Process validation timeline for a new process

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