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# An overview of pharmaceutical validation

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**ABSTRACT**

Facilities and processes of pharmaceutical production impact the quality of the products significantly. Hence even after the regulatory approval, regulatory agencies require the manufacturer to test its drug product for identity, strength, quality, purity and stability before release into commercial use. But it is difficult to assure the quality of product by in-process and finished product inspection and testing. Hence to meet this requirement, an in-depth understanding of the processes and their performance is significant to develop quality processes. Validation is the tool which establishes a high degree of assurance that all processes meet their intended specifications. Hence pharmaceutical validation becomes significant in pharmaceutical industry. This overview summarizes the various aspects of pharmaceutical validation.

**Keywords:** Validation, Process Validation, Installation Qualification, Operational Qualification, Validation Protocol

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## INTRODUCTION

Drug product development is a long process which covers drug discovery, laboratory testing, preclinical studies in animals, clinical trials in human, regulatory registration and approval. Facilities involved and processes handled during drug development impact the quality significantly. Hence even after regulatory approval, to further improve the safety and efficacy of the drug product, regulatory agencies necessitate the manufacturer to test its drug product for identity, strength, quality, purity and stability before release the drug product for commercial use. To implement the requirements, pharmaceutical validation becomes significant. The concept of validation had its first formal appearance in United States in 1978 however; the origin of validation in the healthcare industry is from the terminal sterilization process failures in the early 1970s. "Validation" means assessment of validity or act of proving the effectiveness and it is a defined program which, in combination with routine production methods and quality control techniques, provides documented assurance that a system is performing as intended and/or that a product conforms to its predetermined specifications. Pharmaceutical validation provides significant benefits which are listed in Table 1. This overview summarizes the various aspects of pharmaceutical validation [1-3].

## VALIDATION PRINCIPLES

Drug products produced should be fit for its intended use. To meet this principle, a thorough understanding of the processes and its performance is important. Assurance of quality of product by in-process and finished product inspection and testing is difficult. However, processes should be controlled to meets the quality specifications. To develop a quality processes, various factors like selection of quality materials, components, product and process design, control of processes, in-process control, and finished product testing should be considered. Validation of system can establish a high degree of assurance that the system meets its intended specifications [4, 5].

## THE PHARMACEUTICAL PROCESS EQUIPMENT VALIDATION

Validation of equipment is based on its complexity and the critical nature of that equipment towards quality of the final product. Installation and operational qualification assure the equipment, ancillary systems and sub-systems commissioned correctly through appropriate performance tests and related documentation [4].

## INSTALLATION QUALIFICATION (IQ)

Examination of equipment design, determination of calibration, maintenance and adjustment requirements are done in this stage of validation. Reference number is given to the equipment and its accessories after proper identification. The allotted reference number should

be used to identify the equipment validation and other related documents. During IQ, all installed equipment should be checked against the equipment supplier's specifications and purchase specifications. To assure reliable and meaningful results, these checks should be repeated number of times. During IQ, company should document preventive maintenance requirements for installed equipment and the preventive maintenance schedule should be incorporated into the routine maintenance schedule [1, 4-7, 9].

**OPERATIONAL QUALIFICATION (OQ)**

During OQ, critical operating parameters for the equipment and systems should be identified and studies are carried out for critical variables. Studies includes condition or a set of conditions including both upper and lower operating limits referred to as "worst case" conditions. After satisfactory completion of OQ, operating procedures and operator instructions documentation should be finalized for the equipment which will be used for the training of operators in the requirements for satisfactory operation of the equipment. Satisfactory completion of IQ and OQ process should allow the formal "release" of the equipment for the next stage in the process validation exercise as long as calibration, cleaning, preventive maintenance and operator training requirements have been finalised and documented [1, 4-6, 9].

**PROCESS VALIDATION**

Process validation concept was first applied to the pharmaceutical industry in the 1970s and it is a requirement of the Current Good Manufacturing Practices Regulations for finished pharmaceuticals, 21 CFR Parts 210 and 211, Good Manufacturing Practice Regulations for Medical Devices, 21 CFR Part 820, and therefore, is applicable to both pharmaceuticals and medical devices manufacture. In Guideline on General Principles of Process Validation (1987) contained a definition for process validation which states "A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes" [1, 4-7, 9].

**PROCESS VALIDATION DECISION**

Decision to carry out process validation or not is determined using following steps. ***Step 1:*** Consider whether the process output can be verified by monitoring and measurement. ***Step 2:*** If yes, then consider whether the verification alone is sufficient to eliminate unacceptable risk and whether it is cost effective. ***Step 3:*** If yes, the process output should be verified and the process should be appropriately controlled. ***Step 4:*** If the process output can't be verified, then validate the process or ***Step 5:*** The product or process can be redesigned to reduce variation and improve the product or process. The risk or cost may also be reduced by redesigning the product or process to a point where simple verification is an acceptable decision [6, 9].

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## PHASES IN PROCESS VALIDATION

Validation related activities are grouped into three phase.

***Phase 1*** (Pre-validation phase or qualification phase): During phase 1, developing and understanding of process takes place. This phase cover 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. Using the accumulated knowledge and in-depth understanding of the process, process control strategies were developed during phase 1 [1, 4, 5, 9].

***Phase 2*** (Process validation phase or Process qualification phase): During this phase, reproducibility of the process is confirmed with all established limits of the critical parameter even under "worst case" conditions. GMP compliant procedures must be followed during this stage. Successful completion of phase 2 is necessary before commercial distribution of a product [1, 4, 5, 9].

***Phase 3*** (Validation maintenance phase): During this phase documents related to all process, including validation reports are reviewed to assure that there are no changes, deviations, failures, modifications to the production process, and all SOPs are followed, including change control procedures. Manufacturer should have full assurance of its performance before any batch is distributed for marketing, For successful validation, in-depth knowledge and the approach to control manufacturing processes are required which include the source of variation, the limitation of the detection of the variation, and the attributes susceptible of the variation. It is the responsibility of the manufacturer for maintaining the degree of assurance accomplished, even if some minor changes occurred due to personnel, material and process changes [1, 4, 5, 9].

## CONDUCT OF A VALIDATION

### VALIDATION TEAM

Multi-functional team required to be set to plan and execute the validation activities. Multi-functional team should comprises expertise from Quality Assurance, Engineering, Manufacturing, Others depending on company organization and product types which may include personnel from Laboratory staff, Technical Services, Research & Development, Regulatory Affairs, Clinical Engineering, Purchasing/Planning. Responsibilities of multi-functional validation team are list in Table 2. [5, 6].

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## VALIDATION PROTOCOL

Detailed protocol to perform the validation is essential to ensure that the process is validated adequately. Validation protocol is prepared and reviewed and the elements the protocol are listed in Table 3 [1, 5, 6].

## PRE-REQUISITES FOR PROCESS VALIDATION

Before start of process validation, manufacturing equipment, control instruments and formulation should be qualified. Compatibility of active ingredients with excipients, and of final drug product, packaging materials, stability studies and other information on a pharmaceutical product should be studied in detail and qualified at the development stage. Proper training and motivation of personnel involved in validation are prerequisites to successful validation [1].

## PROCESS VALIDATION OPTIONS

Options of process validation are (a) Prospective validation, (b) Concurrent Validation, (c) Retrospective validation (d) Process Revalidation. The steps and sequence of events required to perform a process validation are summarized in Table 4.

## PROSPECTIVE VALIDATION

During prospective validation, critical parameters that may affect the quality of the finished product are assessed. Sequence of trial should be designed to determine the criticality of these factors. All equipment, production environment and the analytical testing methods to be used should be fully validated. Preparation of Master batch documentation will be initiated after identification of critical parameters, machine settings, component specifications and environmental conditions of the process. Using this well defined process, a series of batches (generally considered acceptable that three consecutive batches/runs within the finally agreed parameters) should be produced which would give desired quality product and constitute a proper process validation. Detailed testing should also be done on the final product in its package. After review, recommendations should be made on the extent of monitoring and the in-process controls necessary for routine production which should be included in the batch manufacturing and packaging record. Limits, frequencies and actions to be taken in the event of the out of limits should have been specified adequately [4, 5, 7-9].

## MATRIX AND "FAMILY" APPROACHES TO PROSPECTIVE PROCESS VALIDATION

In particular situations, manufacturer can utilize the same process for several related products to develop a scientifically sound validation plan rather than different plans for each product manufactured by that process. The matrix approach is a plan to conduct process validation on different strengths of the same product. However matrix approach has some

limitations and can't be utilized when different manufacturing steps such as compression and coating that involve different tools, equipment, and process conditions for the different dosage strengths. The "family" approach literally means a plan to conduct process validation on different products manufactured with the same processes using the same equipment. The validation process using these approaches must include batches of different strengths or products which should be selected to represent the worst case conditions or scenarios to demonstrate that the process is consistent for all strengths or products involved [5].

**CONCURRENT VALIDATION**

Concurrent validation is a practical approach under certain circumstances which includes (a) When a previously validated process transferred to a third party contract manufacturer or to another manufacturing site, (b) Where the product is a different strength of a previously validated product with the same ratio of active / inactive ingredients, (c) 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, (d) When the number of batches produced are limited (e.g. orphan drugs). When this approach is being used there is always the risk of modifying the process parameters or specifications during the course of time which may leads to questions regarding disposition of the batches that had already been released for sale, subsequently known to have undesired quality characteristics. However, for concurrent validation it is important that the systems and equipment to be used have been fully validated previously. Protocol must be prepared and approved by validation team and the reason for conducting concurrent validation must be documented. A report should be prepared and approved prior to the sale of each batch and a final report should be prepared and approved after the completion of all concurrent batches [4, 5, 8].

**RETROSPECTIVE VALIDATION**

Retrospective validation is applicable to processes that are stable and in routine use which have not undergone a formally documented validation process. Documentary evidence for the validity of the processes can be provided by utilizing the historical data. Retrospective validation require the preparation of a protocol and reporting of the results for the data review, which leads to a conclusion and recommendation. Retrospective validation is only acceptable approach for well established detailed processes that include operational limits for each critical step of the process and will be inappropriate where there is a change in operating procedures, product formulation, equipment and facility. Data from batch documents, process control charts, annual product quality review reports, maintenance log books, process capability studies, finished product test results, including trend analyses, and stability results acts as a source for retrospective validation. Data from a minimum of ten consecutive batches produced will acceptable for retrospective validation. In case if there are less than ten batches, which is not sufficient to demonstrate retrospectively then the retrospective validation should be supplemented with data generated with concurrent or prospective validation. Some of the

essential elements for retrospective validation are (a) Batches manufactured for a defined period (minimum of 10 last consecutive batches), (b) Number of lots released per year, (c) Batch size/strength/manufacturer/year/period, (d) Master manufacturing/packaging documents, (e) Current specifications for active materials/finished products, (f) List of process deviations, corrective actions and changes to manufacturing documents, (g) Data for stability testing for several batches, (h) Trend analyses including those for quality related complaints [4, 5, 7].

**PROCESS RE-VALIDATION**

Process re-validation provides the assurance that changes in a process and /or the process environment that are introduced do not adversely affect process characteristics and product quality. Documentation requirements will be the same as for the initial validation of the process. However, at scheduled intervals periodic review and trend analysis should be carried out. Some planned or unplanned changes that may require re-validation under following situations (a) Changes in raw materials (physical properties such as density, viscosity, particle size distribution, and moisture, etc., that may affect the process or product), (b) Changes in the source of active raw material manufacturer, (c) Changes in packaging material (primary container/closure system). (d) Changes in the process (e.g., mixing time, drying temperatures and batch size), (e) Changes in the equipment (e.g. addition of automatic detection system), (f) Changes of equipment which involve the replacement of equipment on a "like for like" basis would not normally require a re-validation except that this new equipment must be qualified, (g) Changes in the plant/facility, (h) Variations revealed by trend analysis (e.g. process drifts). A decision not to perform re-validation studies must be fully justified and documented adequately [4, 5, 6].

**FINAL REPORT**

At the closure of validation activities, a final report should be prepared. This report should summarize and reference all protocols and results. It should derive conclusions regarding the validation status of the process. The final report should be reviewed and approved by the validation team and appropriate management [1, 4, 6].

**MAINTAINING A STATE OF VALIDATION**

**MONITOR AND CONTROL**

Implement continuous monitoring to ensure the process remains within the established parameters. If monitoring shows a negative result or a deviation on quality characteristics, investigated the cause and implement the corrective action and a revalidation [6].

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## CHANGES IN PROCESSES AND/OR PRODUCT

Evaluate the changes in the process and /or product including changes in procedures, equipment, personnel, etc. to determine the possible impact on quality characteristics and considered the extent of revalidation [6].

## CONTINUED STATE OF CONTROL

Changes undetected and changes considered minor may cumulatively affect the validation status of the process. Hence such process should be considered for periodic [6].

## CHANGE CONTROL

SOP should be available 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 authorised. 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 [4, 5, 9].

**TABLE 1: PHARMACEUTICAL VALIDATION BENEFITS**

| | |
|---|---|
| 1. | Reinforce the understanding of processes which will reduce the risk of problems. |
| 2. | Decreases the defect cost. |
| 3. | Reduce the regulatory noncompliance. |
| 4. | Offers fewer in-process controls and end product testing. |
| 5. | Decrease the product rejections and reworks. |
| 6. | Reduces the utility costs and prevent the capital expenses. |
| 7. | Lesser complaints about process related failures. |
| 8. | More rapid and reliable start up of new equipment. |
| 9. | Easier scale-up from development work. |
| 10. | Easier maintenance of the equipment. |

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**TABLE 2: RESPONSIBILITIES OF VALIDATION TEAM**

| | |
|---|---|
| 1. | Plan the approach and identify the requirements. |
| 2. | Identify the processes. |
| 3. | Identify process parameters and desired process output. |
| 4. | Decide whether verification and/or validation requirement. |
| 5. | Prepare a master validation plan. |
| 6. | Select methods and tools for validation. |
| 7. | Prepare and review validation protocols and the validation report |
| 8. | Carry out IQ, OQ and PQ. |
| 9. | Decide continuous process controls. |

**TABLE 3: ELEMENTS OF THE PROTOCOL**

| | |
|---|---|
| 1. | Objectives and scope of the validation study. |
| 2. | Validation team who are responsible for the validation with their qualifications and responsibilities of each personnel. |
| 3. | Type of validation whether prospective or concurrent or retrospective or re-validation. |
| 4. | Number and selection of batches to be validated, list of all equipment to be used and their normal and worst case operating parameters. |
| 5. | Outcome of IQ and OQ for all critical equipment. |
| 6. | Calibration requirements for all measuring devices. |
| 7. | Critical process parameters with their respective tolerance. |
| 8. | Description of the processing steps (Master documents for the product). |
| 9. | Sampling points, stages of sampling, methods of sampling, sampling plans. |
| 10. | Statistical methods to be used for analysis of data. |
| 11. | Training requirements for the processing operators. |
| 12. | Validated test methods to be used in in-process testing and for the finished product. |
| 13. | Specifications for raw and packaging materials and test methods. |
| 14. | Forms and charts to be used for documenting results. |
| 15. | Format for presentation of results, documenting conclusions and for approval of study results. |

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**TABLE 4: OUTLINE OF A PROCESS VALIDATION PROGRAM**

| | | |
|---|---|---|
| 1. Objective | : | Proving or demonstrating that the process works |
| 2. Type of validation | : | Prospective, concurrent, retrospective, revalidation |
| 3. Type of process | : | Chemical, pharmaceutical, automation, cleaning |
| 4. Definition of process | : | Flow diagram, equipment/components, in-process, finished product |
| 5. Definition of process output | : | Potency, yield, physical parameters |
| 6. Definition of test methods | : | Method, instrumentation, calibration, traceability, precision, accuracy |
| 7. Analysis of process | : | Critical modules and variables defined by process capability design and testing program |
| 8. Control limits of critical variables | : | Defined by process capability design and testing program |
| 9. Preparation of validation protocol | : | Facilities, equipment, process, number of validation trials, sampling frequency, size, type, tests to perform, methods used, criteria for success |
| 10. Organizing for validation | : | Responsibility and authority |
| 11. Planning validation trials | : | Timetable and PERT charting, material availability, and disposal |
| 12. Validation trials | : | Supervision, administration, documentation |
| 13. Validation finding | : | Data summary, analysis, and conclusions |
| 14. Final report and recommendations | : | Process validated, further trials, more process design, and testing |

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