

Review Article

An Overview of Pharmaceutical Validation and Process Controls in Drug Development

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Abstract

It has always been known that facilities and processes involved in pharmaceutical production impact significantly on the quality of the products. The processes include raw material and equipment inspections as well as in-process controls. Process controls are mandatory in good manufacturing practice (GMP). The purpose is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it. Thus validation is an integral part of quality assurance.

This overview examines the need for pharmaceutical validation, the various approaches and steps involved, and other pertinent considerations.

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Introduction

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 in spite of the problems that may be encountered¹. Process controls include raw materials inspection, in-process controls and targets for final product. The purpose is to monitor the on-line and off-line performance of the manufacturing process and then validate it. Even after the manufacturing process is validated, current good manufacturing practice also requires that a well-written procedure for process controls is established to monitor its performance².

This paper provides an overview of pharmaceutical validation and process controls in drug development. The validation concept can be applied to new drugs, new dosage forms and generic drug development.

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 control³. Adequate validation

is beneficial to the manufacturer in many ways³:

- 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 non-compliance.
- A fully validated process may require less in-process controls and end-product testing.

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.

When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process should be shown to yield a product consistent with the required quality. In this phase, the extent to which deviations from chosen parameters can influence product quality should also be evaluated. When certain processes or products have been validated during the development stage, it is not always necessary to revalidate the whole process or product if similar equipment is used or similar products have been produced, provided that the final product conforms to the in-process controls and final product specification. There should be a clear distinction between in-process control and validation. In production, tests are performed each time on a batch to batch basis using specifications and methods devised during the development phase. The objective is to monitor the process continuously⁴.

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 revalidation⁵. 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 follows⁵:

- 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;
- 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;
- All data generated during the course of studies should be formally **reviewed** and **certified** as evaluated against pre-determined criteria;
- Suitable **testing facilities, equipment, instruments** and **methodology** should be available;
- 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**;
- When appropriate attention has been paid to the above, the process, if aseptic, may be validated by means of "**process simulation**" studies;
- The process should be revalidated at intervals; and
- Comprehensive **documentation** should be available to define support and record the overall validation process.

Protocols should specify the following in detail⁶:

- The objective and scope of study. There should already be a definition of purpose;
- A clear and precise definition of process equipment system or sub-system, which is to be the subject of

- study with details of performance characteristics;
- Installation and qualification requirement for new equipment;
 - Any upgrading requirement for existing equipment with justification for the change(s) and statement of qualification requirement;
 - Detailed stepwise statement of actions to be taken in performing the study (or studies);
 - Assignment of responsibility for performing the study;
 - Statement on all test methodology to be employed with a precise statement of the test equipment and/or materials to be used;
 - Test equipment calibration requirements;
 - References to any relevant standard operating procedures (SOP);
 - Requirement for the current format of the report on the study;
 - Acceptance criteria against which the success (or otherwise) of the study is to be evaluated; and
 - 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.

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 evaluated⁵.

Validation of Analytical Assays and Test Methods

Method validation confirms that the analytical procedure employed for a specific test is suitable for its intended use. The validation of an analytical method is the process by which it is established by laboratory studies that the performance characteristics of the method meet the requirement for the intended application. This implies that validity of a method can be demonstrated only through laboratory studies⁷. Methods should be validated or revalidated^{8,9}:

- before their introduction and routine use;
- whenever the conditions change for which the method has been validated, e.g., instrument with different characteristics; and
- wherever the method is changed and the change is outside the original scope of the method.

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 follows¹⁰:

- Develop a validation protocol or operating procedure for the validation;
- Define the application purpose and scope of the method;

- Define the performance parameters and acceptance criteria;
- Define validation experiments;
- Verify relevant performance characteristics 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.

Environmental Considerations: Cleaning and Clean Room Standards

Cleaning validation is documented proof that one can consistently and effectively clean a system or equipment items. The procedure is necessary for the following reasons^{11, 12}:

- It is a customer requirement – it ensures the safety and purity of the product;
- It is a regulatory requirement in active pharmaceutical product manufacture; and
- It also assures from an internal control and compliance point of view the quality of the process.

The FDA guide to inspections¹³ intended to cover equipment cleaning (chemical residues only) expects firms to have written procedure (SOPs) detailing the cleaning processes and also written general procedure on how cleaning processes will be validated. FDA expects a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data should support a

conclusion that residues have been reduced to an “acceptable level”¹⁴. Harder¹⁴ cited five crucial elements:

1. A standard operating procedure (SOP) for cleaning with a checklist;
2. A procedure for determining cleanliness (rinse or swab);
3. An assay for testing residual drug levels;
4. Pre-set criteria for testing chemical and microbial limit to which to equipment must be cleaned; and
5. Protocol for cleaning validation.

Harder¹⁴ recommended that the procedure be tested for, requiring it to be successful on three successive cleanings and there should be periodic revalidation as well as revalidation after significant changes. Jenkins and Vanderwielen¹⁵ presented an overview of cleaning validation covering strategy and determination of residue limits, method of sampling and analysis noting that “increased use of multi-purpose equipment” has produced increased interest in cleaning validation. The cleaning protocol must be thorough and must be checked. Training is essential. A validation program requires

- criteria for acceptance after cleaning,
- appropriate methods of sampling,
- a maximum limit set for residues, and
- test methods that must themselves be tested.

Products to be tested may be put into groups rather than testing all of them¹⁶. The most important may not be the highest volume product but those capable of causing the largest possible problems if contaminated or if they contaminate the products (solubility of the drug is an important issue). Equipment may also be tested in groups.

Process Validation

Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design

parameters) are capable of repeatedly and reliably producing a finished product of the required quality⁵. It would normally be expected that process validation be completed prior to the release of the finished product for sale (prospective validation). Where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes, which have been in use for some time without any significant changes, may also be validated according to an approved protocol (retrospective validation)¹⁰⁻¹⁷.

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 pre-requisites to successful validation¹⁸⁻²⁰.

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 requirements²¹. Validation of pharmaceutical process equipment involves the following¹⁰:

- **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 product¹⁴.

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 representative²².

Approaches to Validation Process

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 involve²³

- extensive product testing,
- simulation process trials,
- challenge/worst case trials, and
- control of process parameters (mostly physical).

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 compendial specifications²⁴.

In the approach based on analysis of historical data, no experiments are performed in retrospective validation, but instead all available historical data concerning a number of batches are combined and jointly analysed, if production is proceeding smoothly during the period preceding validation and the data in process inspection and final testing of the

product are combined and treated statistically. The results including the outcome of process capability studies, trend analysis, etc., will indicate whether the process is under control or not.

Expert Evaluation

This is an evaluation of the entire study against the protocol requirements as outlined above. It should be prepared and the conclusion drawn at each stage stated. The final conclusions should reflect whether the protocol requirements were met. The evaluation should include an assessment of the planned calibration and maintenance programmes for the equipment and instrumentation to maintain the validated conditions. In addition, all process monitoring and control procedures required to routinely ensure that the validated conditions are maintained should be reported. The evaluation should be signed by authorized officers of the organization who were members of the team establishing the protocol and who have appropriate expertise in the area assigned to them. Overall approval of the study should be authorized by the head of the validation team and the head of the quality control department²¹.

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 following⁴:

- Title and objective of study;
- Reference to protocol;
- Details of material;
- Equipment;
- Programmes and cycles used;
- Details of procedures and test methods;
- Results (compared with acceptance criteria); and
- Recommendations on the limit and criteria to be applied on future basis.

Conclusion

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. Pharmaceutical validation which includes assay validation, cleaning validation, equipment validation as well as the overall process validation is crucial in stability analysis, animal studies and early phases of clinical development such as bioavailability/bioequivalence studies. After the drug is approved, pharmaceutical validation and process control are necessary to ensure that the drug product will meet/set pharmaceutical standards for identity, strength, quality, purity, stability, evaluation safety and efficacy.

In general, pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.

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