

Pharmaceutical Validation and Process Controls Approaches: A Review

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Abstract: The overall validation study provides us the accuracy, stability, sensitivity and reproducibility of the test methods results based into the documented forms. The validation is an essential part of the quality assurance as well as quality control in organization. This whole process includes not only equipment but also raw material inspections as well as in process controls parameters. Process controls are mandatory to maintain good manufacturing practice i.e. G.M.P. and according to it validation studies are required to be done as per predefined protocols, the minimum that should be validated. Validation is an integral part of quality assurance, it include process, cleaning and testing as a result such control procedure stablish to monitor the output and validation of manufacturing processes that may be responsible for variability of drug product.

Keywords: Major phases in validation, Strategy for the validation of methods, Environmental considerations- cleaning and clean room standards, Process validation, Validation report.

INTRODUCTION:

Validation is a one of the documented evidence which assure the quality of the process or system. It provides that high degree of assurance of a specific process, equipment, method or we can say system consistently meeting its pre-determined specifications as well as acceptance criteria. The main principle involved in this validation is quality, safety, and efficacy built into the product. Quality in system assured not only by In-process and finished product inspection but also testing each step of a manufacturing process. The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration and we have to maintain quality in each step in this whole process. Process controls include raw materials inspection, in-process controls and targets for final product to build quality in system.

MAJOR PHASES IN VALIDATION: [2, 4, 17]

Pre-validation qualification phase of pharmaceutical validation:

The pre-validation phase occurs during research and development of new drugs. In this phase all potential parts of the manufacturing process must be considered and analysed so we can say that it is a planning phase. This planning phase includes scale-up studies, pilot studies and small-batches. During this phase, we have to focus on material handling protocols, storage procedures for raw ingredients and finished product. We conduct each step carefully like equipment verification, packaging or distribution of final product. Initial planning phase investing time and energy we get into the pay off in the manufacturing process.

Process validation phase of pharmaceutical validation:

Process validation is done throughout the manufacturing process phase. The goal of process validation is to ensure that all products are up to code. This ensures a high quality product and decreases the chance of mistakes or recalls and increases accuracy into our process. The main idea is to only allow trained personnel into manufacture product unit. All materials are handled as similarly as possible from the transportation and storage phase to the manufacturing phase to get results. [3, 4]

Validation maintenance phase of pharmaceutical validation:

The maintenance phase of pharmaceutical validation occurs when the manufacturing process has running smoothly and consistently for some time which we want. The current SOPs are producing reliable product and there are no known problems with the process for us, but it is not time to just relax and let things ride as it is. In this final phase, it is important to regularly review SOPs and document any changes to the process parameters. There are audits to be done and audit reports to file again. Regular inspections and process oversight are useful in this case also additional refresher training for employees is necessary to ensure more quality products.

Method validation is one of the processes that used to confirm that the analytical procedure runs for a specific test is suitable for its intended purpose. Results from method validation are used to analyze the quality, consistency and reliability of analytical results and it is an integral part of any good analytical practice ever.

Analytical methods need to be validated or revalidated in the following case;

- Before their introduction into routine use.
- Whenever the conditions change such that an instrument with different characteristics and samples with a different matrix.

- c. Whenever the method is changed and that new change is outside the original scope of the method.
The USP has published specific eight steps guidelines for method validation for compound evaluation:
- Accuracy
 - Precision
 - Specificity
 - Limit of detection
 - Limit of quantitation
 - Linearity and range
 - Ruggedness
 - Robustness
 - System suitability tests.

The FDA has also published guidance for the validation of bioanalytical methods and the most comprehensive relative document is the conference report of the 1990 Washington conference: Analytical methods validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies, which was sponsored by the American Association of Pharmaceutical Scientists A.A.P.S., the A.O.A.C. and the U.S. FDA. The report presents guiding principles for validating studies of both human and animal subjects as well as the report has also been used as a basis for the FDA industry guidance document. ^[5-7, 8]

STRATEGY FOR THE VALIDATION OF METHODS:

The validity of a specific prescribed method should be demonstrated in laboratory experiments. It should be conducted by using samples or standards that are similar to unknown samples analysed. For preparation procedure we should follow a validation protocol which will have preferably written in a step by step instruction format. This proposed procedure assures that the instrument or equipment has been selected and the method has been developed accurately. It meets criteria such as health and safety requirements, ability to be automated and to be controlled by computer systems, sample throughput, time and environmental and costs per analysis. ^[8, 22, 24]

- Develop a validation protocol with suitable acceptable operating procedure.
- Develop Validation master plan for the validation.
- For a specific validation project define responsibilities.
- Develop a validation project plan.
- Define the application, scope and purpose of the method.
- Define performance parameters.
- Define acceptance criteria.
- Define validation experiments.
- Verify relevant characteristics of equipment.
- Verify Qualify materials such as standards and reagents for purity, accurate amounts and sufficient stability.
- Perform and define pre-validation experiments.
- Adjust method parameters.
- Perform full internal validation experiments.
- Develop SOPs. Define criteria for revalidation.
- Define type and frequency of system suitability tests.
- Define analytical quality control (AQC) checks for the routine.
- Document validation experiments and results in the validation report.

ENVIRONMENTAL CONSIDERATIONS- CLEANING AND CLEAN ROOM STANDARDS: ^[12, 13]

A clean room is a controlled, stabilized and isolated work area that maintains a specified level of air particulates and other contaminants to prevent contamination and maintain stability of products in rooms. Clean rooms are constructed, maintained and used in many industries, such as pharmaceuticals, medical device manufacturing, scientific research, chemical processing, and electronics manufacturing. It helps in minimization of contamination so its design requires careful consideration, construction of its permissible particle concentration, location, intended use, manufacturing process and overall cost. It has a unique design and appearance.

Clean Room Specifications:

In the United States, Federal Standard 209E defines a clean room as, a room in which the concentration of airborne particles is controlled to specified accepted limit. The International Organization for Standardization i.e. I.S.O. prescribes acceptable user standards as well as requirements for clean room construction, function and operation. The ISO 14644-4 document specifies the requirements for the design, operation and construction of the clean room facilities.

For guide to inspections the FDA intended to cover equipment cleaning chemical residues only expects firms to have written standard operating procedure detailing the cleaning processes and also written general procedure on how cleaning processes will be validated and conducted with user acceptable limits. FDA expects a final validation report which states whether or not the cleaning process is valid and which is approved by management team. The data should support a conclusion that residues have passed acceptable level. ¹³

Followings are the Harder cited crucial elements: ^[12, 14]

- A standard operating procedure i.e. S.O.P for cleaning with an acceptable checklist.

- b. A procedure for determining cleanliness by rinse or swab method.
- c. An assay for testing residual drug levels responsible for contaminations.
- d. Pre-set criteria for testing chemical and microbial limit for cleaning.
- e. Protocol for cleaning validation.

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 and meeting a finished product as per predefined parameters or quality. [2, 5]

It is expected that process validation should be completed before the release of the finished product for sale i.e. prospective validation. Process validation is the means of ensuring and providing documentary evidence that processes consistently produce accurate stable quality products. [2, 3, 5]

- a. It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- b. It decreases the risk of defect costs.
- c. It decreases the risk of regulatory non-compliance.
- d. A fully validated process may require less in-process controls and end-product testing.

Prerequisites for process validation:

The formulation, manufacturing equipment and control instruments must be qualified before process validation can be started. The formulation of a pharmaceutical product should be studied in detail and qualified before the application for the marketing authorization has been submitted. This involves studies on the compatibility of active ingredients as well as excipients i.e. Preformulation studies, stability studies and of final drug product and packaging material etc. Other aspects of manufacture must include critical services like water, air, nitrogen, power supply, equipment cleaning and sanitation of premises. Proper personnel training and motivation are keys to successful validation. [8, 10, 14]

The Pharmaceutical Process Equipment: [18, 21]

The key idea of validation is to provide a high level of documented evidence that the equipment, system and process conform to its desired written standard. The validation process must provide the necessary information as well as test procedures required to provide that the system meets its specified requirements.

i) Installation Qualification (IQ):

Installation qualification (IQ) is a documented verification process that the instrument has been properly delivered as well as installed. Also in this qualification we check its specification according to standards set by the manufacturer. Installation qualification requirements include checking for acceptable environmental conditions, proper location and proper energy supply. There is also checking of contents against the recording calibration, validation dates, packing list, verifying software installation, verifying connections with peripherals and among others.

ii) Operational Qualification (OQ):

In quality assurance the operational qualification is the next step. OQ involves testing of equipment and making sure it performs as specified as per its specification as well as within operating ranges as listed by the manufacturer. Operational Qualification is necessary after installation, significant maintenance, calibration requirements and as a feature of scheduled quality assurance testing. Operational qualification includes levelling, fluctuation, repeatability, keyboard controls, deviation reports, calibration and certificates, as well as performance reports.

iii) Performance Qualification (PQ):

The system is installed with design specifications and mainly with manufacturer recommendations. It should be also as per cGMP's recommendations. All instruments are tested together according to a detailed test plan as it should generate reproducible results.

Performance qualification protocols and validation includes following things.

- a. Data summary: A list of data that needs to be recorded during the whole testing procedure.
- b. Manufacturing conditions: It includes component inputs, operating parameters and equipment environment.
- c. Calibration and validation of system.
- d. Sampling plan
- e. Analysis of methodology.
- f. Variability limits.
- g. Non-conformance contingencies.

APPROACHES IN PROCESS VALIDATION:

Process validation is a more reasonable approach it makes validation an integral part of a carefully planned collection which includes evaluation of data, from the process design stage, through commercial production. This establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process and it is described in three stages. [15, 21]

Stage 1 - Process Design
 Stage 2 - Process Qualification
 Stage 3 - Continued Process Verification

THE VALIDATION REPORT:

A written report should be available after completion of the validation process. If we found it acceptable then it should be approved by system and authorized signed and dated by quality officer. The report should include at least the following: ^[4, 8, 22]

- a. Title of study.
- b. Objective of study
- c. Reference to protocol.
- d. Details of material.
- e. Equipment.
- f. Programmes and cycles used.
- g. Details of procedures and test methods.
- h. Results (compared with acceptance criteria).
- i. Recommendations on the limit and criteria to be applied on future basic.

CONCLUSION:

Pharmaceutical validation documentation provides all information related to our quality aspects. It shows our process accuracy regarding aspects to achieve desired quality. Validation plays important role to maintain safety, efficacy and stability of our products which we are developing of manufacturing in our industry. As we know documentation plays important role in all stage in developing drugs and manufacturing process. And validation is one type of the documents used into industry. It has various types according to our need. So overall we can say that it is the heart of quality of products.

CONFLICT OF INTEREST:

The author shows that there is no conflict of interest.

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