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Review Article

VALIDATION AND PROCESS DEVELOPMENT: A REVIEW

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ABSTRACT
Total Quality Management and specifications according to regulatory guidelines involved in pharmaceutical production has a great impact significantly on the quality of the products. The validation protocol includes inventory control and equipment inspections in the preliminary steps and in-process controls in the subsequent steps. Process controls are mandatory in good manufacturing practices (GMP). The purpose of setting validation parameters is to monitor the on-line and off-line performance of the manufacturing process, and hence, validate it[1,2]. Thus validation is an integral part of quality assurance. This review critically evaluates the need for pharmaceutical validation, the various approaches and steps involved, and other pertinent considerations.

KEYWORDS: Total Quality Management, Pharmaceutical validation, Pharmaceutical process control.

INTRODUCTION

In Pharmaceutical organizations, validation is a fundamental segment that supports a company commitment to quality assurance. Validation is a tool of quality assurance which provides confirmation of the quality in equipment systems, manufacturing processes, software and testing methods[3].Validation assures that products with pre-determined quality characteristics and attributes can be reproduced consistently/reproducibly within the established limits of the manufacturing process operation at the manufacturing site. Validation is required in order to move a product from development to commercial production in the product life cycle[4]. The development of a drug product is a lengthy and costly process which involves-drug discovery, various *in vitro* and *in vivo* studies, clinical trials and regulatory requirements. For further enhancement of effectiveness and safety of the drug product after approval, 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 launched[5,6] . For this very reason, pharmaceutical validation and process controls are the key areas which have to be addressed in a very judicious manner. Validation is a mark of quality, and it implies that a process is well understood and is in a state of control. GMPs and validation are two concepts that are inseparable and are integral part of quality assurance (QA). Validation is also effective in minimizing the costs of the financial expenditure of an organization, as a validated process is more efficient and produces less reworks, rejects and wastage. Compliance with validation requirements is necessary for obtaining approval of the regulatory authorities[7]. The objective of the present review is to highlight the importance of pharmaceutical validation and process controls in drug development.

VALIDATION IN GENERAL ACCORDING TO DIFFERENT REGULATORY BODIES

FDA-guidelines

Validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

EU-guidelines

Action of proving, in accordance with GMP-principles that any procedure, process, equipment, material, activity or system actually leads to the expected results[9-12].

ESSENTIAL OF PHARMACEUTICAL VALIDATION

The validation process provides the highest degree of assurance of the quality of product and process which ought to meet the predetermined quality specification. Validation in itself does not improve the processes but also confirms that the processes have been properly developed and are meeting the specifications. Validation process is beneficial to the manufacturer in many ways:

- Decreases the risk of preventing problems and thus assures the smooth running of the process
- Decreases the running cost
- Decreases the risk of regulatory non-compliance
- Fully validated process may require less in-process controls and end product testing.

Validation should thus be considered in the following situation

- Totally new process
- New equipment
- Process and equipment which have been altered to suit changing priorities
- Process where the end- product test is poor and an unreliable indication of product quality.

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 condition 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 report, to assure that there have been no changes, deviation, 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 assure that there have been no changes/deviation that should have resulted in requalification and revalidation. The validation steps recommended in GMP guidelines can be summarized as follows:-

- 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 studies 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 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.
- Comprehensive documentation should be available to define support and record the overall validation process.

Protocols should specify the following in details

- The objective and scope of study. There should already be a definition of purpose.
- A clear and precise definition of process equipment system or subsystem, 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 changes and statement of qualification requirements.
- Detailed stepwise statement of actions to be taken in performing the study.
- Assignment of responsibility for performing the study.
- Statement on all test methodology to be employed with a precise statement of the test equipment.
- 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 of the study is to be evaluated.
- 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.

Validation of analytical assays and test methods

Method validation confirms that 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 though laboratory studies. Method should be validated or revalidated.

- Before their introduction and routine use.
- Whenever the condition change for which the method has been validated e.g. instrument with different characteristics.
- Wherever the method is changed and the change is outside the original scope of the method.

STRATEGY FOR VALIDATION OF METHOD

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 step by step instruction format as follows.

- 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 equipments.
- Select quality materials, e.g. standards and reagents.
- Perform pre-validation experiments.
- Adjust method parameter and/or acceptance criteria.
- Perform full internal validation experiments.
- Develop SOPs for executing the method routinely.
- Define criteria for revalidation.
- Define type and frequency of system suitability tests and analytical quality control (AQC) checks for the routine and
- Document validation experiments and results in the validation report.

Environmental Consideration: 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.

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

The FDA guide to inspections intended to cover equipment cleaning 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 a acceptable level. Five crucial elements.

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

FUNDAMENTALS ELEMENTS OF VALIDATION

1) Validation plan and procedures
2) Establish acceptance criteria (i.e. testing parameters, limits of acceptability of the components.)
3) Demonstrate equipment systems are calibration and operation properly.
4) Demonstrate that the process meets an established range of operation for multiple runs.
5) Demonstrate that the final product of the process meets pre-determined quality characteristics.
6) Demonstrate the ruggedness of equipment or process performance by challenging the equipment/process at the limits of operating conditions for multiple runs.
7) Demonstrate the accuracy, precision of any analytical test methods.
8) Demonstrate that the validation work has been performed as planned and the outcome meets predetermined specifications and the validation work has been documented, reviewed, approved.

In lieu of validation, routine preventive maintenance programs and routine calibration may be sufficient to establish the reliability and reproducibility of simple equipment performance (i.e. calipers, balances, pH meter, pipettes, conductivity meters)

Prospective Validation means that after a product is developed, the product and its manufacturing process are validated before it is either introduced into the commercial market or used in humans. Ironically, many manufacturers are faced with validating products and processes that have been on the market for many years.

Retrospective validation means the validation of a process, a method, or equipment that has been in use for a long time or a product that has already been on the market.

Validation of Equipment and Equipment Systems

Reliability of equipment operation and performance must be assured. This assurance supports the validation of products produced used these equipment.

The following is a list of equipment requiring validation:

1) Manufacturing equipment (i.e. packaging machine, filling machines)
2) Support processing equipment (i.e. incubators, ovens.)
3) Test equipment (i.e. test stations.)
4) Utility system equipment (i.e. clean rooms, water systems, air systems.)
5) Measuring equipment (i.e. balances, pH meter, pipettes)

In general, Category I equipment are those whose reliability can be assured through calibration and preventive maintenance programs (i.e. balances, pH meter, pipettes) Category III equipment are those that will need validation (i.e. process equipment, test equipment...) Category III equipment validation is commonly performed as a 3 phase process consisting of Installation Qualification (IQ), Operation Qualification (OQ) and Performance Qualification (PQ)[13].

Installation Qualification

It is the documentation of the installation of the equipment that allows for the efficient implementation of calibration and preventive maintenance programs and facilitation of the effective control of changes to the equipment over-time. IQ protocol looks like an equipment specification, listing all of its critical features. An IQ consists of:

1) "As built" drawings
2) Equipment or system requirements
3) A statement declaring the adequacy of the equipment for its intended use
4) Equipment identity characteristics
5) Utility requirements
6) Safety features
7) Reference to operator or maintenance manuals
8) Reference to vendor support services or parts suppliers

Operational Qualification

It is the confirmation of the adequate operation of the equipment as expected under ideal conditions. The protocol must include what will be done, how it will be done, acceptance criteria and information on how raw data is handled or processed. An OQ Protocol consists of the followings:

1) Calibration of sensors and measuring devices on the equipment or on the test equipment used.
2) Qualification of support processing (i.e. equipment cleaning, disinfection)
3) Qualification of monitoring or controlling software
4) A systematic demonstration of equipment electromechanical features and functions.
5) Qualification of test methods
6) A demonstration of cycle performance
7) A demonstration of process consistency (i.e. heat distribution in an oven, fill volume uniformity on a filling machine)
8) A demonstration of safety features and reset procedures after likely events like a power failure.

The OQ protocol must be supported by SOPs on topics such as operating, cleaning, assembling and calibrating the equipment and perform routine maintenance programs.

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.

Performance Qualification

The PQ is the heart of validation. The PQ is a confirmation that the equipment will continue to operate as expected under routine and challenged conditions of operation and that the outcome is acceptable. It is basically about challenging the equipment to confirm its operation within the established limits of operation. This run must be demonstrated repeatedly in 3 consecutive successful runs. For example, in validation a heat sealing unit with parameters for temperature, pressure and dwell time, the PQ is to demonstrate the two extremes of operation that would most likely result in a poor seal like a set of conditions for the highest acceptable temperature, highest acceptable pressure and the longest acceptable dwell time and a second set of conditions for the lowest of all parameters [14].

Generally, for equipment systems like a clean room, purified water system or compressed air systems, it might be appropriate to perform an IQ/OQ on system components and then a PQ on the system as a whole. **Fig1**

PROCESS VALIDATION

A process is the controlled interaction of components, equipment, environment, software and personnel to produce a product or achieve an acceptable outcome. The validation protocol simply describes a plan that demonstrates consistency in processing and confirms that all component, processing and product specifications are appropriate and attainable under ideal and challenged conditions[15,16].

There are 3 general types of processes in a medical product manufacturing facility:

1) Support process: prepares materials, equipment or environmental areas for the work of manufacturing.
2) Standard manufacturing process: standard events used to process many products.
Equipment dependent, include assembly, formulation, mixing, coating, packaging, labeling and inspection.
3) Product process: a manufacturing process that is product specific.

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.

Process Validation Protocol Format

1. Purpose
2. Scope
3. Responsibility
4. Process History
5. Process Description/Flow
6. Processing Variables/Controls
7. Worst case challenge and Rationale
8. Validation

8.1 Preliminary operation
8.2 Process qualification
8.3 Product qualification
8.4 Validation Acceptance Criteria

9. Process Change Control

Approaches to validation process

There are two basic approaches to the validation of the process itself. 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.

- Extensive product testing,
- Simulation process trials,
- Challenges/ worst case trails and
- Control of process parameters

VALIDATION DOCUMENTS

Validation Master Plan: This document describes the overall company commitment to validation and further defines commitments to equipment, method, and software and process validation.

Validation Protocols: Controlled documents that describe how to perform a Specific validation work/event. They can reference SOPs, specifications and Manufacturing records, acceptance criteria.

Validation Reports: Narrative summaries of a specific validation event referencing the validation protocol document. It summarizes the data and declares the disposition of the item validated[17].

The Validation Report

A written report should be available after completion of the validation. If found acceptable, it should be approved and authorized. The report should include at least the following:

- Title and objective of study;
- Reference to protocol;
- Details of material;
- Equipment;
- Programmes and cycles used;
- Details of procedures and test methods;

- Recommendations on the limit and criteria to be applied on future basis.

CONCLUSION

The goal for the regulators 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 in production. In general, an entire process is validated; 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. 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.

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

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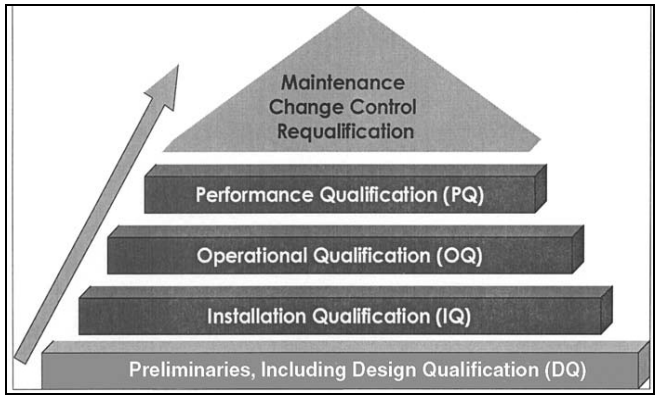

Fig1: steps in qualification