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Process validation: An essential process in pharmaceutical industry

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Abstract

The purpose of this work is to present an introduction and general overview on process validation of pharmaceutical manufacturing process especially tablet manufacturing process with special reference to the requirements stipulated by the US Food and Drug Administration (FDA).Quality is always an imperative prerequisite when we consider any product. Therefore, drugs 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 to build the quality into the product at every step and not just tested for at the end. In pharmaceutical industry, Process Validation performs this task to build the quality into the product because according to ISO 9000:2000, it had proven to be an important tool for quality management of pharmaceuticals.
Keywords: Process validation, Quality Assurance, Quality, Pharmaceutical industry.

1. Introduction

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 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. A process validation protocol is a requirement as stipulated by Current Good Manufacturing Practices Regulations for finished pharmaceutical products [1].

2. Process Validation

The word validation means "assessment of validation or action of proving effectiveness". 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 [2].

Why is validation required?

- It would not be feasible to use the equipment without knowing whether it will produce the product we wanted or not.
- The pharmaceutical industry uses expensive materials, sophisticated facilities & equipment and highly qualified personnel.
- 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.
- Detailed study and control of the manufacturing process- validation is necessary if failure to be reduced and productivity improved.
- The pharmaceutical industries are concerned about validation because of the following reasons.
  - Assurance of quality.
  - Cost reduction.
  - Government regulation[3,4]

3. Types of process validation

3.1 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.

3.2 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.

3.3 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 [5,6].

4. Phases of process validation

4.1 Phase 1:

Pre-Validation Phase or the 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.

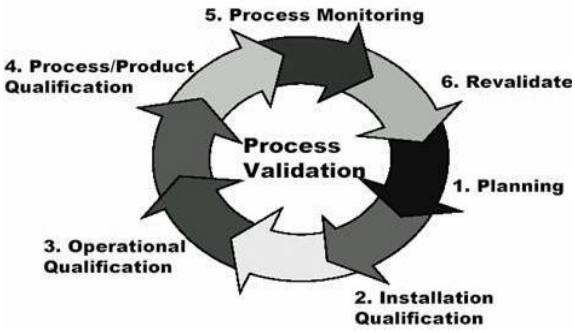
4.2 Phase 2:

Process Validation Phase (Process Qualification phase), designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the "worst case" conditions.

4.3 Phase 3:

Validation Maintenance Phase, requiring frequent review of all process related documents, including validation audit reports to assure that there have been no changes, deviations, failures, modifications to the production process, and that all sops have been followed, including Change Control procedures. At this stage the validation team also assures that there have been no changes/ deviations that should have resulted in requalification and revalidation.

Figure 1: General view of process validation



5. 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.

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.

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.

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.

DQ check items

- Goods manufacturing practices and regulatory requirements.
- Performance criteria.
- Facility air flow, movement flow and pressure engines.
- Reliability and efficiency.
- Commissioning requirements. Construct ability and installation of equipment.
- Maintenance and access to critical equipment and instrumentation.
- Safety and environment impact.

IQ check items [7, 8]

- Installation conditions (wiring, utilities and functionality).
- Calibration, preventive maintenance, cleaning schedules.
- Safety features.
- Supplier documentation, prints, drawings and manuals.
- Software documentation.

- Spare parts list.
- Environmental conditions (such as clean room requirements, temperature and humidity).
- Equipment design features (i.e. materials of construction clean ability).

OQ check items

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

PQ check items

- Actual product and process parameters and procedures established in OQ.
- Acceptability of the product.
- Assurance of process capability as established in OQ.
- Process repeatability, long term process stability [9,10]

6. 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,

- Head of quality assurance.
- Head of engineering.
- Validation manager.
- Production manager.
- Specialist validation discipline: all areas [11,12]

Table 1: Responsible authorities for validation

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.

7. Validation Protocol

The validation protocol should be numbered, signed and dated, and should contain as a minimum the following information:

- Title
- Objective & Scope
- Responsibility
- Protocol Approval
- Validation Team
- Product Composition
- Process Flow Chart
- Manufacturing Process
- Review of Equipments / Utilities
- Review of Raw Materials and Packing Materials Review of Analytical and Batch Manufacturing Records
- Review of Batch Quantities for Validation (Raw Materials)
- Review of Batch Quantities for Validation (Packing Materials)
- HSE Requirements
- Review of Process Parameters Validation Procedure
- Sampling Location
- Documentation
- Acceptance Criteria
- Summary
- Conclusion

8. The validation report

The validation report [13,14,15] should contain the approved validation protocol, tabulated or graphical results, process monitoring (forms) and all analytical results of the validation batches. The validation report should have a conclusion that explains the manufacturing specialist's statement and opinion stability testing on all validation batches must be performed according to the protocol, according to NDA/ANDA stability plan.

9. Importance of validation

Process validation is a key element in the quality assurance of pharmaceutical product as the end product testing is not sufficient to assure quality of finished product. The most compelling reasons to optimize and validate pharmaceutical production and supporting processes are quality assurance and cost reduction [16,17].

10. Conclusions

Quality is always an imperative prerequisite when we consider any product. Therefore, drugs 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 to build the quality into the product at every step and not just tested for at the end. In

pharmaceutical industry, Process Validation performs this task to build the quality into the product because according to ISO 9000:2000, it had proven to be an important tool for quality management of pharmaceuticals.

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