International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 4(5): September-October 2014

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Research Article……!!!**

Received: 01-10-2014; Revised: 15-10-2014; Accepted: 21-10-2014

INDUSTRIAL PROCESS VALIDATION AS A QUALITY ASSURANCE IMPLEMENT: A HYPOTHETICAL APPROACH

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Keywords:

GMP, Process validation, Quality assurance, Statistical tools

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ABSTRACT

Industrial process validation is the skill of designing and enthusiastic the designed steps beside with the documentation. Process validation emphasize on method design elements and maintaining process control during commercialization and communicate that process validation is an current program and align process validation activities with product lifecycle. Process validation also emphasizes the function of objective measures and statistical tools & analyses and emphasizes knowledge, detection, and control of variability and gives assurance on reliable of quality throughout life cycle of product. Quality assurance functions essentially to observe the fact that the quality function is being performed. It may also carry out the statistical evaluation of the test results to show that the process is reproducible. Quality assurance implements the inspection criteria and sets the specification for the product approval or rejection. It analyzes the product complaints to learn how effective its test program has been in preventing rejectable product since reaching to the market place. According to GMP, validation studies are vital part of GMP these are required to be done as per predefined protocols.

INTRODUCTION

VALIDATION

Definitions [1, 2, 3]

Validation is defined as follows by different organizations.

Food and Drug Administration (FDA)

Establishing documentation evidence, which provides a high degree of assurance that specific process, will consistently produce a product meeting its predetermined specification and quality attributes.

World Health Organization (WHO)

Action of providing that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, and equipment sanitization and purified water production. [4]

The principal objective of dosage form design is to achieve a predictable therapeutic response to a drug included in a formulation which is capable of large scale manufacture with reproducible product quality. To ensure product quality, numerous features are required, like chemical and physical stability, suitable preservation against microbial contamination if appropriate, uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labeling, and validation.

Importance of validation [5]

- Assurance of quality
- Easier scale-up form development work
- Time bound
- Reduction in rejections.
- Process optimization
- Reduction of quality cost.
- Nominal mix-ups, and bottle necks
- Increased output.
- Avoidance of capital expenditures Fewer complaints about process related failures.

- Reduced testing in process and in finished goods.
- More rapid and reliable start-up of new equipments.
- Easier maintenance of equipment.
- Minimal batch failures, improved efficiently and productivity.
- Improved employee awareness of processes.
- Government regulation like Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products

Validation principle [6]

The basic principle of quality assurance is that a drug should be produced that is fit for its proposed use. In order to meet this principle, a good understanding of the processes and their performance is significant. Quality cannot be adequately assured by in process and finished product inspection and testing, but it should be built into the manufacturing processes. These processes should be controlled in order that the finished product meets all quality specifications.

So, building of the quality requires careful awareness to a number of factors, such as the selection of quality materials and components, product and process design, control of processes, in-process control, and finished product testing.

Careful design and validation of system and process controls can establish a high degree of confidence that all lots or batches produced will meet their projected specifications.

Responsible authorities for validation [7]

The validation working party is convened to define progress, coordinate and ultimately, approve the whole effort, including all of the documentation generated. The working party would usually consist of the following staff members, preferably those with a good insight into the company's function.

Table 1.1 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 compliance 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

ADVANTAGES OF VALIDATION

- Improved reporting potential.
- Enhanced data and evaluation capabilities and increased assurance about process reproducibility and product quality.
- Improved ability to set target parameters and control limits for routine production, correlating with validation results.
- Superior ability to statistically evaluate process performance and product variables e.g., individuals, mean, range, control limits**.**

Steps in method validation [8]

1. Develop a validation protocol or operating procedure for the validation
2. Define the application, purpose and scope of the method
3. Define the performance parameters and acceptance criteria
4. Define validation experiments
5. Verify relevant performance characteristics of equipment
6. Qualify materials, e.g. standards and reagents
7. Perform pre-validation experiments
8. Adjust method parameters or/and acceptance criteria if necessary
9. Perform full internal (and external) validation experiments
10. Develop SOPs (standard operating procedures) for executing the method in the routine
11. Define criteria for revalidation
12. Define type and frequency of system suitability tests and/or analytical quality control (A QC) checks for the routine
13. Document validation experiments and results in the validation.

Benefits of process validation

1) Reduction of quality cost

Through appropriate validation, the cost of the following process can be optimized

- Preventive costs are costs incurred in order to avoid failures and reduce appraisal costs.
- Appraisal costs of inspection, testing and quality evaluation.
- Internal and External failure costs that associated with a non conformance condition after the product has left the company's ownership.

2) Process optimization

The optimization of the facility, equipment system and closures etc results in a product that meets quality requirements at the lowest costs. Trained, qualified people are the key elements in process optimization that results in improving effectiveness and productivity.

3) Assurance of quality

Validation and process control are the heart of GMPs. Without validated and controlled process it is impossible to achieve quality products. Hence, validation is a key element in assuring the quality of the product.

4) Safety

Validation can also result in increased operator safety. Properly calibrated, validated instruments and gauges used to reduce accident and results in safety.

5) Better customer quality

Through proper validation, market recall is avoided which result in better customer care and quality of the product.

Types of process validation

Depending on when it is performed in relation to production, validation can be prospective, concurrent, and retrospective or revalidation.

Prospective validation

The potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated and an overall estimation. It is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps: these are then evaluated on the basis of past experience to determine whether they might lead to critical situations.

Where possible critical situations are identified, the risk is made. If, at the end, must be modified and improved until a validation exercise proves them to be satisfactory. This form of validation is essential in order to limit the risk of errors occurring on the production scale, e.g. in the preparation of injectable products.

Concurrent validation

It is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. The nature and requirements of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

This careful monitoring of the first three production batches is sometimes regarded as prospective validation.

Concurrent validation together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product.

Retrospective validation

It involves the examination of past experience of production on the assumption that composition, procedures and equipment remain unchanged; such experience and the results of in-process and final control tests are then evaluated. Recorded difficulties and failures in production are analysed to determine the limits of process parameters.

Retrospective validation is obviously not a quality assurance measure in itself and should never be applied to new processes or products.

If the results of a retrospective validation are positive, this indicates that the process is not in need of immediate attention and may be validated in accordance with the normal schedule.

Revalidation

Re-validation is usually performed to the confirmation of initial validation for a Periodic review. Re-validation provides the evidence 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.

Elements of validation

Qualification

The detail and scope of a qualification exercise is in many respects related to the complexity of the equipment involved and the critical nature of that equipment with respect to the quality of the final product.

Installation, design and operational qualification exercises assure that, through appropriate performance tests and related documentation, equipment, ancillary systems and sub-systems have been commissioned correctly.

At various stages in a validation/qualification exercise there is need for protocols, documentation, procedures, equipment, specifications and acceptance criteria for test results.

All these need to be reviewed, checked and authorised. It would be expected that representatives from the appropriate professional disciplines , be actively involved in these undertakings with the final authorisation given by a validation team or the Quality Assurance representative.

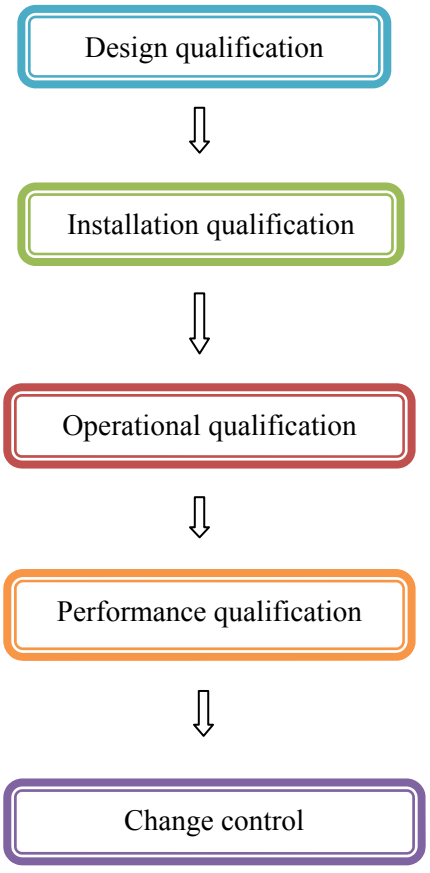

Figure 1.1 Elements of validation

Design Qualification (DQ)

It is documented review of the design, at an appropriate stage of stages in the project, for conformance to operational and regulatory expectations.

. Design Qualification (DQ) defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier.

DQ should ensure that instruments have all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet business requirements.

Safety & environment impact

Installation Qualification (IQ)

IQ is the method of establishing with confidence that all major processing, packaging equipment and ancillary systems are in conformance with installation specifications, equipment manuals, schematics and engineering drawings.

This stage of validation includes examination of equipment design, determination of calibration, maintenance and adjustment requirements.

For complicated or large pieces of equipment, a pharmaceutical manufacturer may elect to undertake a pre-delivery check of the equipment at the supplier's assembly facility. This pre-delivery check cannot substitute for the Installation Qualification.

Operational Qualification (OQ)

The conduct of an Operational Qualification should follow an authorized protocol. The critical operating parameters for the equipment and systems should be identified at the OQ stage.

The plans for the OQ should identify the studies to be undertaken on the critical variables, the sequence of those studies and the measuring equipment to be used and the acceptance criteria to be met. Studies on the critical variables should include a condition or a set of conditions. Encompassing upper and lower processing and operating limits referred to as "worst case" conditions.

Performance Qualification (PQ)

It is documented verification that all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria. Performance Qualification is the last of the qualification processes and should only commence after successful completion of

Operational Qualification (OQ). Performance Qualification is best performed by the personnel who will be responsible for the routine operation of the system; the users must have received full training on the correct operation of the equipment or system prior to conducting PQ. Standard Operating Procedure (SOP) must be written prior to start of PQ and followed at all times during the operation of the equipment or system.

Phases of process validation

The activities relating to validation studies may be classified into three phase

Phase 1: Pre-validation phase or the qualification phase 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, storage and handling of in-process and finished dosage forms, equipment qualification, installation qualification, master production documents, operational qualification, process capability.

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. Process validation of raw material, analytical method, equipment and process validation is carried out under this phase of process validation.

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 assures that there have been no changes/ deviations that should have resulted in requalification & revalidation.

Validation of pharmaceutical dosage form

Validation of raw materials

The validation process of a dosage form begins with a validation of the raw materials, both active pharmaceutical ingredients (APIs) and excipients. Factors to be considered are

(1) The grade and source of the excipients

(2) Particle size and shape characteristics

(3) Lot-to-lot variability

Analytical method validation

Validation of an analytical method which is used during drug development and drug manufacturing is required to demonstrate that the methods are fit for their intended purpose. Additionally, the pharmaceutical industry around the world is subject to extensive regulations due to the nature of its products. [9] 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 though laboratory studies.

1. **Accuracy of method:** The ability of a method to measure the true value of a sample.

2. **Precision of method:** The ability of a method to estimate reproducibility of any given value, but not necessarily the true value.

3. Specificity: The ability to accurately measure the analyte in the presence of other components.

4. In-day/out-of-day variation: Does the precision and accuracy of the method change when conducted numerous times on the same day and repeated on a subsequent day?

5. Between-operator variation: Repeat of the precision and accuracy studies within the same laboratory using same instrument but different analysts to challenge reproducibility of method.

6. Between-instrument variation: How will different instruments within the same laboratory run by the same analyst affect the accuracy and precision of the method?

7. Between-laboratory variation: A collaborative study between various analytical methods chemists who developed the analytical method and the analytical chemists in the quality control laboratory who must routinely run the method will help to ensure the validity and ruggedness of the analytical method.

3. Equipment / Facility validation: Process equipment used in the development phase is assessed relative to its suitability for large-scale manufacture. Alternate equipment is identified and evaluated and a final decision rendered. Existing or new equipment to be used to manufacture the new pharmaceutical product must then undergo a comprehensive evaluation called a validation protocol. This protocol can be divided into a number of components, but usually has design qualification, installation qualification, operation qualification, performance qualification, maintenance (calibration, cleaning, and repair) qualification.

CONCLUSION

From the study it can be stated that pharmaceutical Process Validation is the most important and recognized parameters of cGMP. The cGMP regulation require that Manufacturing processes be designed and controlled to assure that in-process materials and finished product meet predetermined quality requirements and do so consistently and reliably. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Process validation involves a series of activities taking place over the lifecycle of the product and process.

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