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An Overview on Validation Process in Pharmaceutical Industries

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Abstract **Review Article**

Medicinal products are the prime element in the healthcare and must manufacture with the highest quality, safety & efficacy level. There are multiple principles to obtain such quality are now biggest interest in pharmaceutical industry. One of the important principles that industries follow is Validation. It is the art of designing and practicing the designed steps alongside with the documentation for all processes, methods, computer systems, equipment qualification & revalidation. According to GMP validation studies it is the necessary part of GMP and required to be done as per predefined protocols. Validation master plan (VMP) defines the principles involved in the qualification of a facility, describes the systems to be validated, and provides a updated plan for accomplishing and keeping a qualified facility. The VMP is quite different than validation procedure (SOP), which explains the specific process for performing validation activities.

Keywords: Quality, Validation, Process Validation, Protocol, Validation Master Plan.

INTRODUCTION

The principle aim of the pharmaceutical industry is to consistently deliver a safe, effective & better quality product along with specified standards, at the minimum possible cost. The industry has been established in the development of quality and safety procedures ensuring that the risk related to its procedure is reduced to a minimum. The institution of Good Manufacturing Practices (GMP) in drug industries was a small step in the pharmaceutical work but a giant step in the reduction of risk to patients and operators and financial losses in the pharmaceutical industry. Moreover, to ensure a GMP, one of the most prime means is the validation procedure.

Validation focuses on maintaining the quality step by step of the manufacturing of finished products process. In general, a complete process is validated and every step is verified.

Validation does not take part in the improvement of processes but ensures that these have been properly developed and are under control. It is a prime requirement by the regulatory authorities as well as an opportunity for improvement to the pharmaceutical industry.

To timely perform all required validation activities in the industry without any error or delay every organization prepares Validation Master Plan (VMP) in advance before the new financial year starts. The plan provides an overview of the whole validation activities, its plan of actions, its content, its organizational structure, and planning. The prime elements of VMP are being the list/inventory of the items to be validated and the planning schedule. All validation procedures relating to critical technical operations, relevant to the product and process controls within an organization should be included in the validation master plan.

History of Validation [3]

The validation idea firstly introduces by two FDA officials, Ted Byers and Bud Loftus, in the year of 1970s, to improve the quality of pharmaceuticals industries. Due to problems that occurred in the sterility of large volume parenteral market this concept was introduced. Initially, validation activities were concentrated on this product making processes but later it expanded to other associated processes of pharmaceutical as well. In the year of 1976, the FDA proposed a whole set of current GMP regulations which were amended many times. The pharmaceutical industry follows them as a part of good management and business practice. U.S.F.D.A. was the pioneer in advocating the concept of process validation, & after 29th September 1978, the definition of process validation appeared literature of U.S.F.D.A.

Definitions of Validation [1]

A) US FDA Definition

"Process validation is establishing documented evidence that provides a high degree of assurance that a specified process will consistently produce a product meeting its predetermined specifications and quality characteristics."

B) European commission

"Documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes".

C) WHO Definition

"The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected result."

Validation in pharma, its need & importance [1]

Need of Pharmaceutical Validation

As the definition suggested validation process is a formally approved process that provides a great assurance that consistent batches will produce along with complying with the required specifications. It is part of quality assurance where the systematic study of systems, facilities & processes involved focus on determining whether they perform their intended functions adequately and consistently as specified. Validation assures that the processes are properly developed and are under control.

Significance of the Validation process in pharmaceutical industries:

a. Assurance of Quality

Product quality can be assured by introducing the validation step in the overall pharmaceutical function.

b. Cost Reduction

As each step is validated & controlled constantly there lesser rejects and reworks which would lead to an effective cost reduction.

c. Government Regulation

Validation is mainly coming as an essential part of GMPs. To get the approval to manufacture & introduce a new product in the market organization has to comply with the validation requirements around the globe.

Validation Steps [2]

The proposed validation steps in GMP guidelines can be outlined as follows,

- At first, all studies should be conducted according to a detailed, pre-accepted protocol or series of protocols, which in turn is subject to formal – change control procedures.
- The personnel who will conduct the studies and who will run the process should be appropriately trained and qualified and be suitable and competent to perform the assigned work.
- All created data during the period of studies should be formally reviewed and certified as evaluated against pre-determined criteria.
- Suitable testing facilities, laboratories, equipment, instruments and methodology should be available.
- Suitable cleanroom facilities should be made available in the specified as well as background area.
- When appropriate attention should be 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 a record of the overall validation of the process should be maintained.

Scope of Validation

Pharmaceutical Validation is an extensive part of work that practically covers every aspect of pharmaceutical processing activities. A systematic look at the pharmaceutical operations clarifies the following areas for pharmaceutical validation.

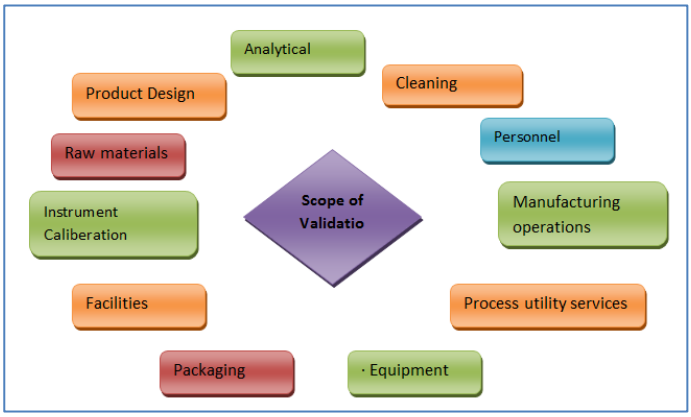

Fig 1 – Scope of validation

Principle for validation [1]

A) Design qualification (DQ):

The very first part of the validation of any new site or facilities, systems or equipment could be the design qualification (DQ). It comprises the documented verification of the design of equipment and manufacturing facilities.

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The compliance of the developed design with GMP requirements should be elaborated and documented.

General considerations of DQ are:

Fig-2: DQ considerations

B) Installation Qualification (IQ)

The objective of this qualification is to establish evidence that all key factors of the process equipment and supporting system installation coherent to the manufacturers approved specification along with the recommendation of the supplier of the equipment.

General considerations of IQ are:

Fig-3: IQ considerations are

C) Operational Qualification (OQ):

The objective of this qualification is to establish the evidence that process control limits and action levels are as per predetermined requirements which result in a product.

General considerations of OQ are:

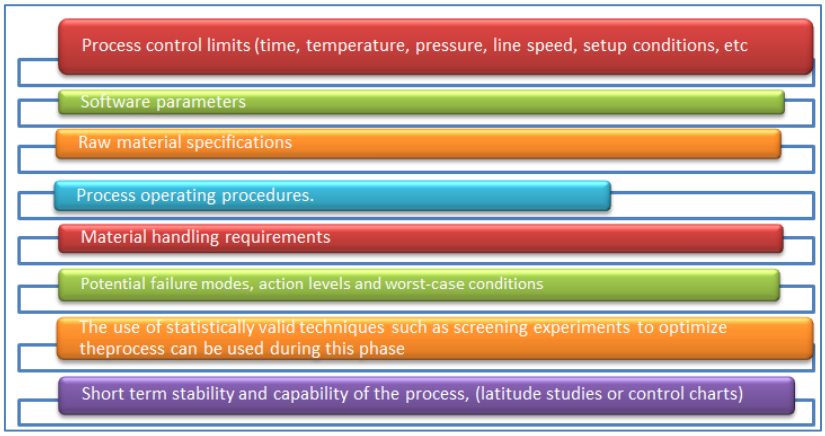

Fig-4: OQ considerations

D) Performance Qualification (PQ):

The objective of this qualification is to establish evidence that the process, under anticipated conditions, consistently produces a product that meets all specified requirements.

General considerations of PQ are:

Fig-5: PQ considerations

Re-Qualification

Any alteration to, or relocation of equipment accompanies the satisfactory review and authorized documented change proposal through the change control procedure. This formal review includes the consideration of the re-qualification of the equipment. Change that doesn't cause a direct impact on final or in-process product quality is handled through the documentation system of the preventive maintenance program.

Validations conducted in Pharmaceutical Industries –

A) Process Validation

In the manufacturing process, the used methods and systems which may have an impact on the quality of the products should be defined and validated.

Process validation is a function of quality assurance that helps to receive a high degree of assurance, that a specific process will consistently deliver a product, which meets its predetermined specifications and quality characteristics through documented evidence. Production process validation assures that process performance is constantly monitored and evaluated. To maintain the validated status of a process inadequate state, steps must be taken to recognize and address if any significant process changes made. Such measures can apply to equipment, standard operating procedures, manufacturing instructions, environmental conditions or any other aspect of the processing system.

Types of Process Validation: [4]

Different types of pharmaceutical process validation includes24-26:

a) Prospective Validation

This type of validation usually performed during the product development stage on a minimum of three consecutive production-size batches. Before the process is put into commercial use, the validation protocol is executed. In the product development stage, the production process is divided into individual steps. Each & every step is evaluated on the basis of actual or theoretical considerations to determine the critical parameters that may affect the quality of the finished product.

A series of trials are designed to discover the criticality of these factors. Each trial is planned and documented fully in an authorized protocol. All equipment, production facilities and the analytical testing methods used should be fully validated. To sell or supply validation batches, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, along with the satisfactory outcome of the validation exercise and the marketing authorization.

b) Concurrent Validation:

In this type of validation process, the company will sell the product during the qualification runs, to the public at its market price, similar to prospective & retrospective validation.

This validation constitutes in-process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the manufacturing process is in a control state.

In unusual situations, it may be allowable not to complete a validation programme before routine commercial batches start.

Reasons to carry out concurrent validation must be explained in brief, documented and approved by authorized personnel.

The need for documentation for concurrent validation is the same as specified for prospective validation.

c) Retrospective Validation:

This validation generally dedicated to a product that is already in distribution. Process validation is based upon the already established production, testing and control data. It also proves that the process always remained in a control state & does what it is assigned to do.

Retrospective validation is mainly allowable for well-established processes and will be inadequate if any recent changes in the composition of the product or operating procedures or equipment have done.

Validation of such processes is usually based on past historical data.

d) Revalidation

Revalidation usually performed in the system when some changes introduced in the process environment or facility or equipment or in an existing product or due to incorporating a new product. It ensures that these changes do not unfavourably affect the process characteristics and product quality.

Documentation requirements for this type of validation shall be the same as for the initial validation of the process.

Periodically evaluation conducted to assure that manufacturing facility, systems, equipment and processes, including cleaning, remain in an invalid state.

Following some of the changes that require validation are as follows:

- Changes in raw materials
- Changes in the supplier of active raw material.
- Changes in packaging material or its supplier (primary /secondary)
- Changes in the process or methods (e.g., mixing time, drying temperatures and batch size)
- Changes in the equipment (e.g., the addition of an automatic detection system).
- Changes in the plant site/facility.

A decision not to perform the revalidation studies must be fully justified and documented.

B) Validation of Analytical methods

Validation of analytics is related to methods used for in-process, stability testing, and final control. For pharmaceutical product or for the specific ingredient of the product the analytical monitoring, is necessary to ensure that its safety and efficacy is maintained throughout all phases of its shelf life, including storage, distribution, and use.

Monitoring should be carried out according to the specifications mentioned and validated during product development.

The primary purpose of analytical validation is to ensure that the adopted analytical procedure will give consistent, reproducible and reliable results adequate with the intended purpose.

C) Cleaning Validation

Validation of cleaning processes ensures that specified facility, production sites, equipment, quality control premises etc are cleaned as per specified standards. This validation for production equipment should demonstrate that contamination from the previous product; detergent or microbial sources have been reduced to a pre-determined level.

A documentation system, which clearly identifies the previous batch and shows that the equipment was properly cleaned, must be established.

D) Computer System Validation

In this validation, a system that includes the input data, electronic processing, and the output information to be used for automatic control or for reporting are validated.

Suitable installation qualification and operational qualification has illustrated the suitability of computer hardware and software to perform the specified task. The functions were computerized systems are used to control a GMP-related processor to store and retrieve data that have GMP implications, they are validated.

Computerized system validation ensures adequate control to prevent unauthorized access or changes to data. In case computerized systems breakdown or failure may result in a permanent loss of critical record, then a backup system and a recovery plan are provided.

If changes to computerized systems are required then it supposed made according to the "change control" system, & have to be formally authorized, documented, tested and subjected to the re-validation process.

Departments Responsible for Validation: The primary departments those are responsible for validation are:

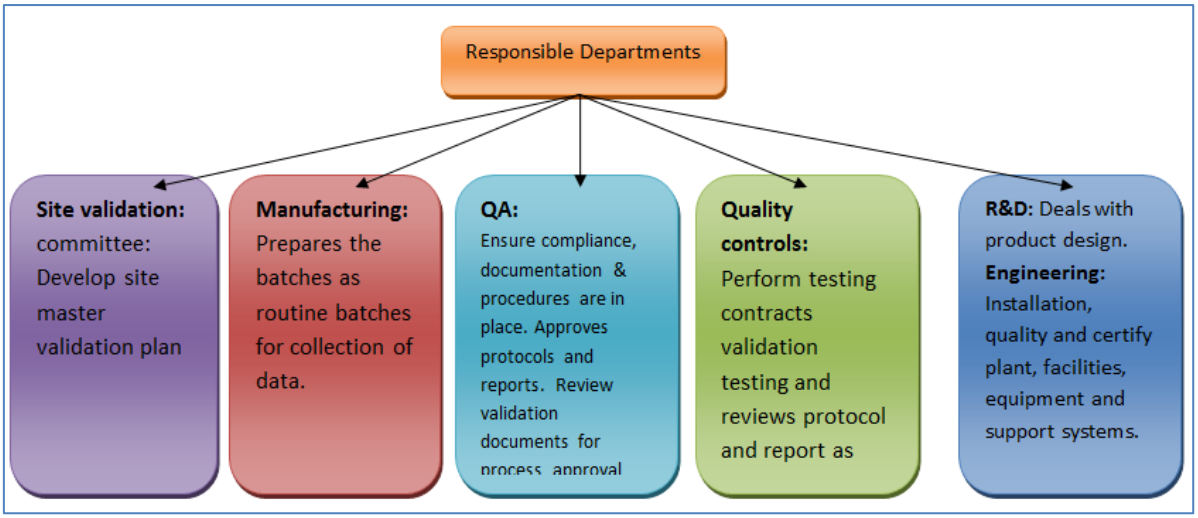

Fig-6: Validation Team and Its Responsibilities

A Validation team is mainly responsible for conducting and supervising validation studies.

Trained & experienced personnel in a relevant discipline may conduct such studies.

Following are some responsibilities of the validation team are

- Creates updates and reviews/approves validation master plan, individual project validation plans and validation deliverables.
- Make sure validation compliance with the company validation master plan and project validation plan.
- Harmonize, apply & verify elements of VMP.
- Consults evaluates and approves changes in validation scope within the system. Reviews and approves IQ/OQ/PQ process validation procedures and plans.
- Reviews test results and give comments related to release.
- Assess risks and develops contingency plan.

Validation Protocol [4]

To ensure that the process is adequately validated the detailed protocol is performed.

It should include the following elements

- Objectives and, the scope of the validation process.
- Validation of team membership, their qualifications and responsibilities.
- Type of validation: prospective, concurrent, retrospective, re-validation.
- Number and selection of batches for the validation study.
- A list of all required equipment along with their normal and worst-case operating parameters.
- Outcome of IQ, OQ for critical equipment.
- Requirements for calibration of all measuring devices.
- Critical process parameters and their respective tolerances.
- In process variables and attributes with risk and its prevention measures are mentioned.
- Processing steps description.
- Sampling plans, their points, stages, methods.
- Statistical tools to be used in the analysis of data.
- Training requirements for the processing operators.
- Validated test methods for the process as well as for finished product testings.
- Raw material & packaging materials specifications and test methods.
- Forms and charts for documenting results & remarks.
- Format for documenting the results, conclusions and approval of study results.

What Is Validation Master Plan VMP [5]

A Validation Master Plan is a document that provides the details about the way a company will operate, who is the responsible person over the various aspects of the validation activities, and how the production, quality control and personnel management will be directed. The VMP allows manufacturers to show that they are in control of their overall quality system within the company.

The VMP contains the following data but not limited to:

Title page and authorization – It includes the title, document number, and version. It also contains necessary management approval signatures.

Table of contents – It contains all the major areas of the VMP and where to find them within the document. Abbreviations and glossary – It is to define technical or organizational terms.

Validation plan – The VMP serves to identify what should be validated, and where, when, how, and why the validation is necessary. The validation plan must identify the processes which are critical to the quality of the product and therefore require validation.

Purpose and approach to validation – The purpose gives a summary of each process and describes the validation approach along with supporting grounds to estimate what the document addresses.

Scope of validation – The scope of the VMP addresses all activities at the manufacturing facility related to equipment, utilities, processes, systems, and procedures that may impact product quality.

Roles and responsibilities – It defines the prime responsibilities of the validation department personnel for developing validation protocols, change control documents, task reports and validation Standard Operating Procedures, and for maintenance and storage of all validation-related documents.

Manufacturing and engineering departments will examine & approve the VMP and all other documents like validation protocols, protocol deviations, change control documents, and reports.

QA department will review and approve the VMP, validation protocols, task reports, protocol deviations, change control documents, and SOPs for consistency with cGMPs, consistency with policies and procedures, and approval to implement.

Outsourced services – This section covers the supplier who performs the qualification activities or calibrations. Deviation management invalidation – The VMP addresses the procedure for documenting deviations along with investigation as defined in validation protocols, its corrective actions or corrective action plans shall be reviewed and approved by authorized personnel before or with the approval of the validation report.

Change control invalidation – The VMP states all changes with potential impact on validated systems and/or processes should be addressed by established change management procedures.

Risk management principles in validation – Risk management principles are the critical part of the validation process & should be stated in the validation master plan as they apply to process validation, from the design and development stage to the entire life cycle of the process.

Training – The VMP states that all personnel who will perform the qualification & validation activities should be trained.All validations – These include premises, central plant, manufacturing areas, material storage, along with utilities, processes, qualification, analytical method, cleaning, equipment, revalidation, and computer validation.

Validation matrix – The validation matrix enlists the required validations throughout the facility in order of criticality. References – The VMP should enlist documents that are providing guidance for the writing and execution of validation and qualifications activities in the industries.

Validation Report [1]

A written report should be obtained after the validation process completion.

The report should include at least the following

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

CONCLUSION

Validation is the most commonly used method in the pharmaceutical industries to achieve consistently highest quality in the end product as per the cGMP principles. The product should be manufactured in all validated systems, facilities, methods & manufacturing process should be effective to continue to producing safe products consistently. The adequate validation Master Plan should be prepared prior to 1st quarter of every year to perform the activities timely throughout the year.

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