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Review Article

PROCESS VALIDATION AS AN INDUSTRIAL PRACTICE

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ABSTRACT

Quality is the primordial intention to any industry and its products manufactured. Recently validation has become one of the pharmaceutical industries' most recognized and discussed subjects. Validation is the means of catering enormous benefits to even more than the acceptable quality level which in the global standard scale lending importance to validation is increasingly profound in recent years. The word validation simply means "Assessment of validation or action of proving effectiveness". The process is developed in such a way that the required parameters are achieved and it ensures that the output of the process will consistently meet the required parameters during routine production, the process is validated. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis is made in this review that gives a detailed, overview of validation concept of designing, organizing and conducting validation trials.

Keywords: Validation, quality assurance, quality.

INTRODUCTION

The main objective of dosage form design is to achieve a predictable and predetermined therapeutic response to a drug included in a formulation that is capable of large scale manufacturing with reproducible product quality. Numerous features are required to ensure product quality like chemical and physical stability, suitable preservation against microbial contamination, uniformity of dose of drug, acceptability to users including prescribers and patient, as well as suitable packing, labeling, and validation[1].

In mid 1970's, in order to improve the quality of pharmaceuticals the concept of validation was first proposed by two Food and Drug Administration (FDA) officials, Ted Byers and Bud Loftus. The first validation activities were focused on process involved in making these products but quickly spread to associated processes involving environmental control, media fill, equipment sanitization and purified water production[2,3].

Validation is the act of demonstrating and documenting that a procedure operates effectively. The U.S Food and Drug Administration (FDA) guidelines state that the process validation is the established documented evidence which provides a high degree of assurance that specific process[3].

The term process validation was quite confusing as the concepts underlying the term are quite old and the use of synonyms such as verification and confirmation appears to predict the use of validation. The first edition of the Orange Guide the British version of GMPs, which was published in 1971 contains a section titled "Verification of Procedures" that states, "Procedures should undergo a regular critical appraisal to ensure that they remain capable of achieving the results which they are intended to achieve". This term now here appeared in the U.S.F.D.A. documentation in the compliance programme entitled "Drug Process Inspections" issued in June 1978 (before publication of the revised cGMP Regulations)[4].

Process validation is defined as the set of data and evaluation of it, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a number of activities in series taking place over the lifecycle of the product and validation process as shown in **Figure 1**. This definition did not appear in any of the earlier revisions of that particular compliance programme until March 29, 1983. It was made official definition of process validation on March 29, 1983 draft on guidelines entitled "Guidelines on General Principles of Process Validation" was made available and the same was finalized in May, 1987[5].

Need of Validation: Although it is mandatory from the government and regulatory bodies but it is also a fact that quality of a pharmaceutical product cannot be adequately controlled solely by pharmacopoeia analysis of the final product.

- Validation gives confidence over the product manufacturing process.
- It gives assurance to the product quality as per customer requirements.
- Validation is mandatory as per regulatory requirements[6].

If we are not going for validation then following problems can be occur

- Low process capability
- Scrap, Rework
- Protracted production cycle times and low capacity utilization
- Resolution of process related problems slow and difficult
- High cost of compliance
- Risk of drug shortages
- Releasing a poor quality product, Recalls
- Delay in approval of new drugs
- Quality problems confounding clinical trial data

So, as to minimize these problems we need to do validation[7].

Importance of Validation

- Assurance of quality
- Process optimisation
- Reduction of quality cost.
- Least batch failures, improved efficiently and productivity.
- Reduction in rejections.
- Increased product output.
- Avoiding of capital expenditures
- Fewer complaints about process related failures.

• Government regulation (Compliance with validation requirements is necessary for obtaining approval to manufacture and to introduce new products)[8].

Planning for Validation

All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents. A validation master plan is a document that summarizes the company's overall philosophy, intentions and approaches to be used for establishing performance adequacy. The validation master plan should be agreed upon and planned by management. The validation master plan should provide an overview of the entire validation operation, its organizational structure, its content and planning. The main elements include the list/inventory of the items to be validated and planning schedule. The validation master plan should be a summary document and should therefore be as simple, brief, concise and clear as possible. It should not repeat information documented elsewhere but should refer to existing documents such as policy documents, SOP's and validation protocols and report.[9,10].

Validation Protocol

A validation protocol is a written plan stating how validation will be conducted, including test parameters, product characteristics, production and packaging equipment, and decision points. These decision points constitutes acceptable test results. Validation protocol should give details of critical steps of the manufacturing process that should be measured, the allowable range of variability and the manner in which the system will be tested. The validation protocol provides a summary of what is hoped to be accomplished. The protocol should list the selected process and control parameters, state the number of batches to be included in the study, and specify how the data, once assembled, will be treated for relevance.

Validation Report

The validation report 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 the NDA/ANDA stability plan[10].

Validation Setup

Each and every step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including in specifications.

- Product selection
- Process design
- Process/ Product characterization
- Process/ Product optimization
- Process validation program
- Product/process certification[11].

Types of Process Validation

Prospective Validation: Prospective Validation is carried out during the development stage as means of a risk analysis of the production process, which is broken down into individual steps; these are the evaluated on the basis of past experience to determine whether they might lead to critical situations.

It can be performed when a new formulation is developed or during critical changes like change in the batch size is done since here multiple parameters are changed like quantities of materials, equipment size, manufacturing process and parameters. The trials are then performed and evaluated and an overall assessment is made on these trials. If at the end the results are acceptable the process is satisfactory[12].

Concurrent Validation: Concurrent Validation 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 nature and specifications of sub sequent in-process and final tests are based on the evaluation of the results of such monitoring. Concurrent validation carried out during normal production, it is together with a trend analysis including stability should be carried out to an appropriate extent throughout the life of the product [13].

Retrospective Validation: Retrospective Validation 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 analyzed to determine the limits of process parameters. A trend analysis may be conducted to determine the extent to which the process parameters are within the permissible range.

Retrospective validation is obviously not a quality assurance measure in itself and should never be applied to new processes or products. It may be considered in special circumstances only e.g., when validation requirements are first introduced in a company, retrospective validation may then be useful in establishing the priorities for the validation programme[14].

Revalidation: Revalidation is needed to ensure that changes in the process and/or in the process environment, whether intentional or unintentional do not adversely affect process characteristics and product quality. Revalidation may be divided into two broad categories:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals.

Revalidation after changes may be based on the performance of the same tests and activities as those used during the original validation, including tests on sub processes and on the equipment concerned with validation. Conditions requiring revalidation study and documentation are listed as follows:

- Changes in the source of active raw material manufacturer.
- Changes in packaging material (primary container/closure system).
- Changes in raw materials (physical properties such as density, viscosity, particle size distribution, moisture etc. that may affect the process or product).
- Changes in the process (e.g., mixing time, drying temperatures and batch size).
- Changes in the equipment (e.g. addition of automatic detection system).
- Changes of Equipment which involve the replacement of equipment on a "like for like" basis would not normally require a re-validation except that this new equipment must be qualified.
- Changes in the plant/facility.
- Variations revealed by trend analysis (e.g. process drifts).

Periodic Revalidation: The decision to introduce periodic revalidation should be based essentially on a review of historical data i.e., data generated during in-process and finished product testing after the latest validation, aimed at verifying that the process is under control[15].

Major Phases in Validation:

Pre-validation Qualification Phase: It 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.

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.

Validation Maintenance Phase: It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes, deviations, failures and modifications to the production process and that all standard operating procedures (SOPs), including change control procedures have been followed. It is assumed that throughout manufacturing and control operations are conducted in accordance with the principle of good manufacturing practice (GMP) both in general and in specific reference to sterile product manufacture[13].

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. It involves document verification of the design of equipment and manufacturing facilities.

Installation Qualification (IQ): It is documented verification that all 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 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 documented verification. It covers all aspects of a facility, utility or equipment perform as intended in meeting predetermined acceptance criteria[16].

Approaches to Validation Process

There are two basic approaches to the validation of the process itself (apart from the qualification of equipment used in production, the calibration of control and measurement instruments, the evaluation of environmental factors, etc). 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[17]

- extensive product testing
- simulation process trials
- challenge/worst case trials, and
- control of process parameters (mostly physical).

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to the extent greater than required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the normality of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are within compendia specifications[18].

In the approach based on analysis of historical data, no experiments are performed in retrospective validation, but instead all available historical data concerning a number of batches are combined and jointly analysed, if production is proceeding smoothly during the period preceding validation and the data in process inspection and final testing of the product are combined and treated statistically. The results including the outcome of process capability studies, trend analysis, etc., will indicate whether the process is under control or not.

Expert Evaluation

Expert evaluation is the entire study against the protocol requirements as outlined above. It should be prepared and the conclusion drawn at each stage stated. The final conclusions should reflect whether the protocol requirements were met. The evaluation includes an assessment of the planned calibration and maintenance programmes for the equipment and instrumentation to maintain the validated conditions. In addition, all process monitoring and control procedures required to routinely ensure that the validated conditions are maintained should be reported. The evaluation should be signed by authorized officers of the organization who were members of the team establishing the protocol and who have appropriate expertise in the area assigned to them. Overall approval of the study should be authorized by the head of the validation team and the head of the quality control department[19].

Significance and applications of Quality Assurance in Pharmaceutical Industry:

Quality assurance is a broad range concept which covers all matters that individually or collectively influence quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, such as product design and development.

The system of quality assurance appropriates the manufacture of pharmaceutical products & should ensure that;

a) Medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP).

b) Production and control operations are clearly specified in a written form and GMP requirements are adopted.

c) Managerial responsibilities are clearly specified in job descriptions.

d) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials.

e) All necessary controls of starting materials, intermediate products, bulk products and other in-process controls, calibrations, and validations are carried out.

f) The finished products are correctly processed and checked according to the defined procedures.

g) Pharmaceutical products are not sold or supplied until the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products.

h) Satisfactory arrangements exist to ensure as far as possible, that the pharmaceutical products are stored by the

manufacturer, distributed and subsequently handled so that the quality is maintained throughout their shelf life.

i) There is a procedure for self-inspection and/or quality audit and it regularly appraises the effectiveness and applicability of the quality assurance system.

j) Deviations, incidents, change control, market complaints can be reported, investigated and recorded.

k) There is a system for approving changes that may have an impact on product quality.

l) Periodic evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement[20].

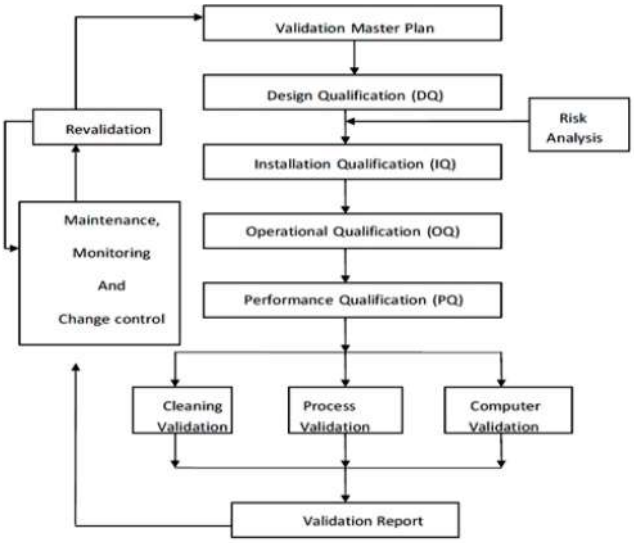

Figure 1: Validation Life Cycle

CONCLUSION

It can be concluded that process validation is a key element in a quality assurance of the pharmaceutical product as the end product testing is not sufficient to assure quality of product. It also renders reduction in the cost linked with process monitoring, sampling and testing. Apart from all the consistency and reliability of a validated process to produce a quality product is the very important for an industry. Validation is the commonest word in the areas of drug development, manufacturing and specification of finished products. It also renders reduction in the cost linked with process monitoring, sampling and testing.

From the review study it is concluded that pharmaceutical validation and process controls are important to assure that the drug product can meet standards for the identity, strength, quality, purity and stability.

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