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A BRIEF DESCRIPTION ON VALIDATION: AN OVERVIEW

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ABSTRACT

Validation is the mean 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. Validation is the art of designing and practicing the designed steps alongside with the documentation. Validation and quality assurance will go hand in hand, ensuring the through quality for the products. Hence, an emphasis made on to review that gives a detailed, overview of validation, Validation Documents, and reports. Additionally a view of validation against the elements of process validation and need of validation also describes in this review.

Keywords: Process Validation, Quality Assuarance, Pharmaceutical Validation, Pharmaceutical manufacturing.

INTRODUCTION

The development of a drug product is a lengthy process involving drug discovery, laboratory testing, animal studies, clinical trials and regulatory registration. To further enhance the effectiveness and safety of the drug product after approval, many 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 released for use. For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered[1]. 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 first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes including environmental control, media fill, equipment sanitization and purified water production[2,3]. In a guideline, validation is act of demonstrating and documenting that any procedure, process, and activity will consistently lead to the expected results. It includes the qualification of systems and equipment. 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. In general, an entire process is validated and 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[4]. The CGMP regulations for finished pharmaceuticals, 21 CFR 210 and 211, were promulgated to enforce the requirements of the act. Although these regulations do not include a definition for process validation, the requirement is implicit in the language of 21 CFR 211.100, which states: "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess." 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 required that the drug product be tested for its identity, strength, quality, purity and stability before it can be launched[5,6]. The objective of the present review is to highlight the importance of pharmaceutical validation and process controls in drug development.

VALIDATION

Validation is "Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes" (FDA 1987). A properly designed system will provide a high degree of assurance that every step, process, and change has been properly evaluated before its implementation. Testing a sample of a final product is not considered sufficient evidence that every product within a batch meets the required specification[7].

Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

A) Cleaning validation

B) Process validation

C) Analytical method validation

D) Computer system validation

Sequential Elements of Process Validation [7]

a) Installation Qualification (IQ)

b) Operational Qualification (OQ),

c) Performance Qualification (PQ).

a) Installation Qualification:

The IQ ensures that all equipment has been installed correctly with applicable inputs (e.g., power or compressed air), all environmental conditions have been met (e.g., temperature or humidity or air quality), all required calibrations have been performed (e.g., pressure gauges or temperature gauges), all safety measures have been implemented and the equipment has been entered into the manufacturer's PM (Preventive Maintenance) and calibration systems to ensure proper maintenance.

b) Operational Qualification:

The OQ demonstrates that the process produces conforming product throughout the range of process inputs, which include process parameters (e.g., temperature, pressure or time), raw material specifications, production logistics (e.g., personnel or multiple shifts) and duplicate sets of equipment where appropriate (e.g., multiple production lines). Including worst-case combinations of process parameters is critical to demonstrate that the entire range of process parameters will produce acceptable product. Training of manufacturing operators on the manufacturing procedures is also required. These procedures must be approved either by the validation team as an attachment to the OQ protocol or through the manufacturer's document control system if it allows a controlled-release of procedures prior to completion of the process validation. The OQ should reference the experiments that were performed to understand the process and the PFMEA, if applicable.

c) Performance Qualification:

The PQ demonstrates that the process consistently produces acceptable product. Often this is interpreted as producing three lots at the nominal process parameter(s). This three-lot guidance is based on a statement in the FDA's preamble to the Quality System Regulation. Although this practice has been widely adopted by industry, the minimum number of lots required for a PQ is the responsibility of the manufacturer and should be based on the specific production logistics, such as the number of manufacturing shifts and production lines.

The main reasons for validation are [7,8]

1. Quality assurance: Quality cannot be assured by daily quality control testing because of the limitations of statistical samples and the limited facilities of finished product testing. Validation checks the accuracy and reliability of a system or a process to meet the predetermined criteria. A successful validation provides high degree of assurance that a consistent level of quality is maintained in each unit of the finished product from one batch to another batch.
2. Economics: Due to successful validation, there is a decrease in the sampling and testing procedure
3. Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
4. Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
5. Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.es and there are less number of product rejections and retesting. This lead to cost-saving benefits.
6. Compliance: For compliance to current good manufacturing practices CGMPs, validation is essential.

Essentials of Pharmaceutical Validation

Validation is an integral part of quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control[(a)] . Adequate validation is beneficial to the manufacturer in many ways:

- It deepens the understanding of processes; decreases the risk of preventing problems and thus assures the smooth running of the process.
- It decreases the risk of defect costs.

- It decreases the risk of regulatory noncompliance.
- A fully validated process may require less in-process controls and end product testing.

Pharmaceutical Validation

Validation refers to establishing documented evidence that a process or system, when operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its pre-determined specifications and quality attributes.

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.

Process validation is a requirement of current Good Manufacturing Practices (GMPs) for finished pharmaceuticals (21CFR 211) and of the GMP regulations for medical devices (21 CFR 820) and therefore applies to the manufacture of both drug products and medical devices.

The U.S. Food and Drug Administration (FDA) have proposed guidelines with the following definition for process validation: – "PROCESS VALIDATION" is establishing documented evidence which provides a high degree of assurance that a specific process consistently produces a product meeting its predetermined specifications and quality attributes.

The Process validation activities can be described in three stages.

Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.

Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.

Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

WHY VALIDATE PROCESSES

There are many reasons, in addition to the regulatory requirements, for validating processes. A manufacturer can assure through careful design of the device and packaging, careful design and validation of processes, and process controls, that there is a high

probability that all manufactured units will meet specifications and have uniform quality. The dependence on intensive in-process and finished device testing can be reduced. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework, resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process.

WHAT PROCESSES SHOULD BE VALIDATED

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures [820.75(a)]. When any of the conditions listed below exist, process validation is the only practical means for assuring that processes will consistently produce devices that meet their predetermined specifications:

Routine end-product tests have insufficient sensitivity to verify the desired safety and efficacy of the finished devices;

Clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product.

Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices.

The process capability is unknown, or it is suspected that the process is barely capable of meeting the device specifications.

1. Types of process validation [9,10, 11]

a. **Analytical validation:** Analytical validation is the evaluation of product quality attributes through testing, to demonstrate reliability is being maintained throughout the product life cycle and that the precision, accuracy, strength, purity and specification has not been compromised.

b. **Equipment Validation:** Validation of equipment is known as qualification. Equipment validation is divided into installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ). An IQ documents specific static attributes of a faculty or item to prove that the installation of the unit has

been correctly performed and that the installation specifications of the manufacturer have been met. After installation it must be ensure that the equipment can deliver operating ranges as specified in the purchase order. This is called OQ. The PQ's are concerned with proving that process being investigated works as it is supposed to do.

c. **Process Validation:** Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of prospective, concurrent or retrospective validation and process qualification or re-validation.

Prospective validation:

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 evaluated, 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 assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes 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: Concurrent validation is used for establishing documented evidence that a facility and processes do what they purport to do, based on information generated during actual imputation of the process. This approach involves monitoring of critical processing steps and end product testing of current production, to show that the manufacturing process is in a state of control.

Retrospective validation: Retrospective validation is used for facilities, processes, and process controls in operation use that have not undergone a formally documented validation process. Validation of these facilities, processes, and process controls is possible using historical data to provide the necessary documentary evidence that the

process is doing what it is believed to do. Therefore, this type of validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of product, operating processes, or equipment.

This approach is rarely been used today because it's very unlikely that any existing product hasn't been subjected to the Prospective validation process. It is used only for the audit of a validated process.

Revalidation:

It 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.

a) Revalidation after changes. Revalidation must be performed on introduction of any changes affecting a manufacturing and/or standard procedure having a bearing on the established product performance characteristics. Such changes may include those in starting material, packaging material, manufacturing processes, equipment, in-process controls, manufacturing areas, or support systems (water, steam, etc.). Every such change requested should be reviewed by a qualified validation group, which will decide whether it is significant enough to justify revalidation and, if so, its extent.

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 subprocesses and on the equipment concerned. Some typical changes which require revalidation include the following:

• Changes in the starting material(s). Changes in the physical properties, such as density, viscosity, particle size distribution, and crystal type and modification, of the active ingredients or excipients may affect the mechanical properties of the material; as a consequence, they may adversely affect the process or the product.

• Changes in the packaging material, e.g. replacing plastics by glass, may require changes in the packaging procedure and therefore affect product stability.

• Changes in the process, e.g. changes in mixing time, drying temperature and cooling regime, may affect subsequent process steps and product quality.

• Changes in equipment, including measuring instruments, may affect both the process and the product; repair and maintenance work, such as the replacement of major equipment components, may affect the process.

• Changes in the production area and support system, e.g. the rearrangement of manufacturing areas and/or support systems, may result in changes in the process. The repair and maintenance of support systems, such as ventilation, may change the environmental conditions and, as a consequence, revalidation/requalification may be necessary, mainly in the manufacture of sterile products.

b) Periodic revalidation. It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. 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. During the review of such historical data, any trend in the data collected should be evaluated.

VALIDATION DOCUMENTS

Validation Master Plan: This documents 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.[12]

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;
- Recommendation on the limit and criteria to be applied on further basis.

CONCLUSION

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. Pharmaceutical validation which includes assay validation, cleaning validation, equipment validation as well as the overall process validation is crucial in stability analysis and early phases of clinical development such asprocess bioavailability/bioequivalence studies. After the drug is approved, pharmaceutical validation and control are necessary to ensure that the drug product will meet/set pharmaceutical standards for identity, strength, quality, purity, stability, evaluation safety and efficacy. In general, pharmaceutical validation and process control provide a certain assurance of batch uniformity and integrity of the product manufactured.

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