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REVIEW ARTICLE

INDUSTRIAL PROCESS VALIDATION: A REVIEW

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ABSTRACT

Validation is defined in the supplementary information section of the Federal Register as "a QA function that helps ensure drug product quality by providing documented evidence that the manufacturing process consistently does what it purports to do [1]. Process validation provides a higher degree of assurance that the manufacturing process consistently meets the pre-determined specifications and the quality products output can be used to increase purity. . It often includes the qualification of systems and equipment. It is a requirement for good manufacturing practice and other regulatory requirements.

KEY WORDS: Validation, **Process Qualification**, process design, validation master plan.

INTRODUCTION:

Process validation has been widely discussed and criticized by the pharmaceutical industry during the past 20-30 years. Regulatory guidelines in the US and Europe have slowly been modernized; in autumn 2001 for example, new guidelines for process validation came into force in Europe. The advantages and disadvantages of process validation have never been systematically evaluated, and validation is frequently performed without a real understanding of the work involved [1]. The challenge for the pharmaceutical industry is to simplify validation without sacrificing product quality [2].

To successfully fulfill the challenge, those practicing validation need to be aware of the best way to perform validations and the real aim of these. This reviews how pharmaceutical process validation has evolved, the attitudes towards it and how it has been accepted by the industry[1].

CURRENT DEFINITIONS:

The three most often referred to definitions of pharmaceutical process validation are those presented by the European Agency for the Evaluation of Medicinal Products (EMEA), the US Food and Drug Administration (FDA) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The latest versions of their definitions are described in the sidebar "Current definitions of pharmaceutical process validation."[1]

The three definitions are very similar; the only difference is that FDA expresses a minor uncertainty of the concept, despite the efforts of validation, by stating that process validation only provides a high degree of assurance that the process will produce the intended product [2].Even when approaching process validation as scientifically as possible, by incorporating elements of validation during each stage of product evaluating the influence of different process parameters on the final product with statistical principles [3].

The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications. It often includes the qualification of systems and equipment [4]. It is a requirement for good manufacturing practice and other regulatory requirements. . 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:

1. Equipment validation
2. Facilities validation
3. HVAC system validation
4. Cleaning validation
5. Process validation
6. Analytical method validation
7. Computer system validation[5]

Process validation is defined in the supplementary information section of the Federal Register as "a QA function that helps ensure drug product quality by providing documented evidence that the manufacturing process consistently does what it purports to do". 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

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sample of a final product is not considered sufficient evidence that every product within a batch meets the required specification.

In process validation one of the most important is validation master plan. Even though it is not mandatory, it is the document that outlines the principles involved in the qualification of a facility, defines the areas and systems to be validated and provides a written program for achieving and maintaining a qualified facility with validated processes. It is the foundation for the validation program .Results from method validation can be used to judge the quality, reliability, and consistency of analytical results. When extended to an analytical procedure, depending upon the application, it means that a method works reproducibly, when carried out by same or different persons, in same or different laboratories, different reagents, different equipment etc.

OBJECTIVES OF PROCESS VALIDATION:

Validation is done for controlling the process. Process control is demonstrated by satisfactory repeatability, for this reason three successive successful process runs are required to demonstrate reproducibility. Also minimum batch size using the same facilities needs to be validated whenever possible [6].

SCOPE:

To validate the process of the master formula for a particular manufacturing procedure of product and for revalidation in case of any change in the manufacturing process, packing material, ingredient or any change in the composition of any ingredient.

THE METHOD DEVELOPMENT AND PROCESS VALIDATION:

The steps of process validation depend upon the type of method being developed. However, the following steps are common to most types of projects

- Method development plan definition
- Background information gathering
- Laboratory method development
- Generation of test procedure
- Methods validation protocol definition
- Laboratory methods validation
- Validated test method generation
- Validation reports [11]

PROCESS VALIDATION ACTIVITIES:

These can be described in three stages

PROCESS DESIGN:

The commercial process is defined during this stage based on 100 knowledge gained through development and scale-up activities.

PROCESS QUALIFICATION:

During this stage, the process design is confirmed as 103 being capable of reproducible commercial manufacturing.

CONTINUED PROCESS VERIFICATION:

Ongoing assurance is gained during routine production that the process remains in a state of control [10].

TYPES OF PROCESS VALIDATION:

Depending on when it is performed in relation to production, validation can be prospective, concurrent, retrospective or revalidation[5].

PROSPECTIVE VALIDATION:

Prospective validation 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. 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. Careful monitoring of the first three production batches is sometimes regarded as prospective validation. It is acceptable when the three consecutive batches runs within the finally selected parameters, that gives the product of the desired quality would constitute a proper validation of the process.

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 first three production-scale batches must be monitored as comprehensively as possible. The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring. 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:

Retrospective validation involves the examination of past experience, such experience and the results of in-process and final control tests are then evaluated. 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. . Retrospective validation may then be useful when validation requirements are first introduced in a company. If the results of a retrospective validation are positive, then the process is not in need of immediate attention and may be validated in accordance with the normal schedule.

For tablets which have been compressed under individual pressure-sensitive cells, and with qualified equipment, retrospective validation is the most comprehensive test of the overall manufacturing process of this dosage form. On the other hand, it should not be applied in the manufacture of sterile products.

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 IS FURTHER OF TWO TYPES:

- Revalidation after any change having a bearing on product quality.
- Periodic revalidation carried out at scheduled intervals [7].

VALIDATION PROTOCOL :

A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results [11].

CONCLUSION:

The efficient process validation is critical elements in the development of pharmaceuticals. Success in these areas can be attributed to several important factors, which in turn will contribute to regulatory compliance. Experience is one of these factors both the experience level of the individual scientists and the collective experience level of the development and validation department. A strong mentoring and training program is another important factor for ensuring successful methods development and validation[7]. Companies must maintain an appropriate level of expertise in this important dimension of developing safe and effective drugs.

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