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Review Article

DIFFERENT ASPECTS INVOLVED IN PROCESS VALIDATION

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ABSTRACT

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. Validation of the individualsteps of the processes is called the process validation. Process validation involves the collection and evaluation of data, from the process design stage throughout production, that establish scientific evidence that a process is capable of consistently delivering a quality drug substance. It is internationally recognized that validation is necessary in analyticallaboratories. The use of validated methods is important for an analyticallaboratory to show its qualification and competency.This new approach to process validation encompasses equipmentand utility qualification and is fully science and risk-based. Itprovides the pharmaceutical industry with the opportunity tore-think the whole concept of validation and ensure that theseactivities add real value to our businesses and to patients.It involves prospective validation, retrospective validation and concurrent validation.A life-cycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production

Keywords: Validation, prospective validation, concurrent validation, retrospective validation, quality by design.

INTRODUCTION

Validation, as it is known today, has developed from the need to maintain quality,consistency, and above all, public safety. Validation is a rapidly growing and evolvingsubject. This evolution stems from technology's astonishing growth rate, especially interms of what is available in computer hardware and software.[1,2]

Over the past 15 years,machine automation and process control through the use of a computer has causedadditional concerns relating the validation of the processing system. Today, the computeris used for everything from controlling the process, to automatically provide batchreports, and providing automated quality control.The foundation of validation, the methodology behind validation, and the need forvalidation will likely remain a key aspect of the industry we work in.[2,3]. This session reflectsthe current industry trends and serves as an educational tool in our progressive industry.

Process validation establishes the flexibility andconstraints in the manufacturing process controls in theattainment of desirable attributes in the drug productwhile preventing undesirable properties.[3] This is animportant concept, since it serves to support theunderlying definition of validation, which is a systematicapproach to identifying, measuring, evaluating, documenting, and re-evaluating a series of critical steps inthe manufacturing process that require control to ensurea reproducible final product.[4]

USFDA defined process validation as "establishingdocumented evidence which provides a high degree ofassurance that a specific process will consistently producea product meeting its predetermined specifications andquality characteristics."[1]

The basic principles for validation may be stated as follows:

- Establish that the process equipment has the capability of operating within required parameters;
- Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment; [5]
- Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operating within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and
- Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.[4,6]

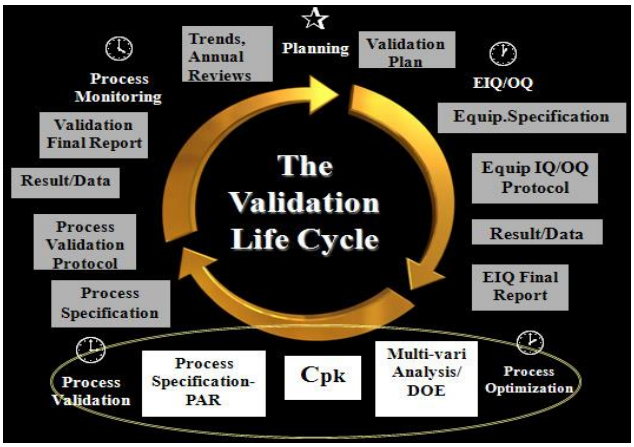

Fig. 1: Flow chart describing validation process [1]

Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control. Adequate validations have been proved beneficial to manufacturer in many ways:

- It deepens the understanding of process
- decreases the risk of defect cost
- decreases risk of regulatory non compliance
- requires less in process control and end product testing.[6,7]

TYPES OF PROCESS VALIDATION

1. Prospective Process Validation. Where anexperimental plan called the validation protocol isexecuted (following completion of the qualification trials) before the process is put to commercial use. Mostvalidation efforts require some degree of prospectiveexperimentation in order to generate validation supportdata.[10]

2. Concurrent Process Validation. Establishingdocumented evidence that the process is in a state ofcontrol during the actual implementation of the process.This is normally performed by conducting in-processtesting and/or monitoring of critical operations during themanufacture of each production batch.Concurrent validation is feasible when nondestructive testing is adequate to verify that products meet predetermined specifications and quality attributes. [8,9]

3. Retrospective Process Validation. Where historic datataken from the records of the completed productionbatches are used to provide documented evidence thatthe process has been in a state of control prior to therequest for such evidence.[5]. This type of validation makes use of historical data and information which may be found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports.[10]

4. Revalidation: Revalidation means repeating the original validation effort or any part of it, and includes an investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. [11]. Possible reasons for starting the revalidation process include:

- The transfer of a product from one plant to another.
- Changes to the product, the plant, the manufacturing process, the cleaning process, or other changes that could affect product quality.
- The necessity of periodic checking of the validation results. [10]
- Significant (usually an order of magnitude) increase or decrease in batch size.
- Sequential batches that fail to meet product and process specifications.
- The scope of revalidation procedures depends on the extent of the changes and the effect upon the product.[3]

THE REGULATORY BASIS FOR PROCESS VALIDATION

The concept of process validation from its beginnings inthe early 1970s through the regulatory aspects associated with current good manufacturing practice (cGMP) regulations and the application thereof to various analytical, quality assurance, pilot plant, production, andsterile product and solid dosage forms considerations. There are several important reasons for validating a product and/or process [12]

First, manufacturers are required by law to conform tocGMP regulations. Second, good business dictates that a manufacturer avoids the possibility of rejected or recalled batches. Third, validation helps to ensure product uniformity, reproducibility, and quality. [13]

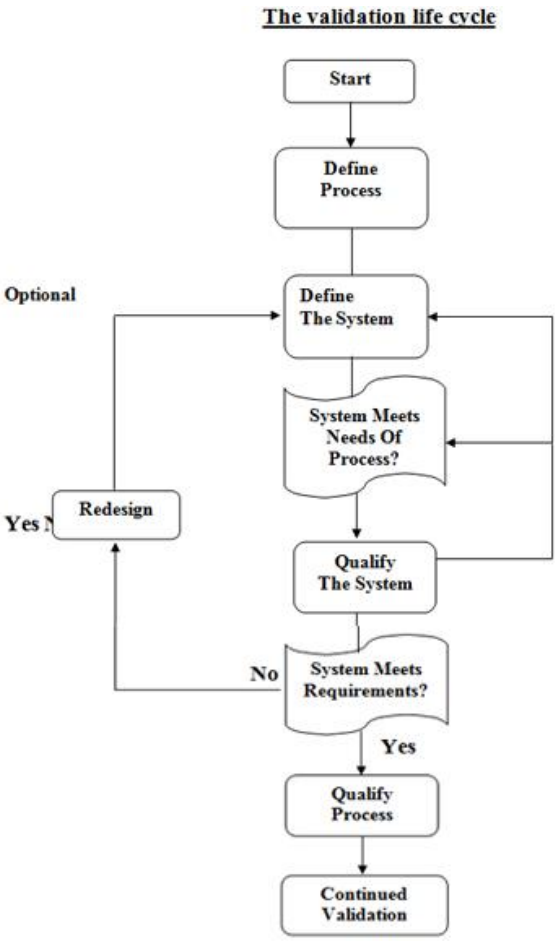

Fig. 2: Validation life cycle [1]

THE STAGES OF PROCESS VALIDATION

1. Process Design: Definition of the process based on knowledge gained throughout development and scale-up activities. Process design involves two important phases:

- Building and capturing process knowledge and understanding
- Establishing a strategy for process control, which may or may not incorporate PAT principles.[14,4]

The process design stage delivers the planned commercial production and control records, which contain the operational limits and overall strategy for process control.

2. Process Qualification:It states that "Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product."[15]

3. Continued Process Verification:Ongoing assurance, gained during routine production thatthe process remains in a state of control. Having confirmed that the process design is capable of reproducible commercial manufacture, the manufacturer must continually assure that the process remains in a state of control throughout commercial manufacture. [16]

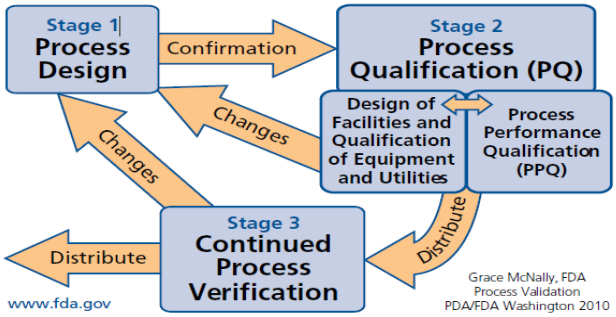

Fig. 3: Stages of Process Validation [7]

MANUFACTURING PROCESS VALIDATION

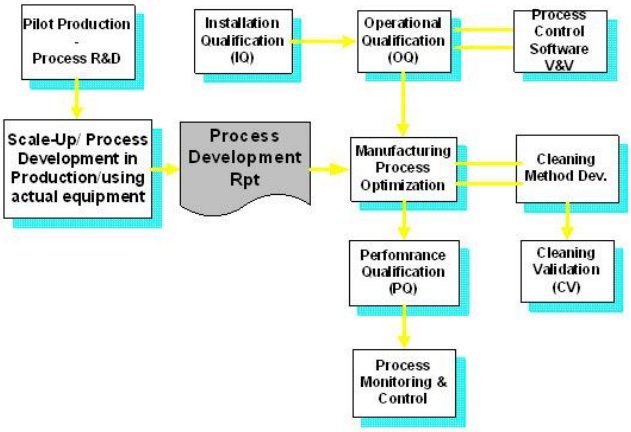

Fig. 4:Manufacturing Process Validation Workflow [4]

(1) Installation Qualification: Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the approved design criteria and that the recommendations of the manufacturer of the equipment are suitably considered. [14]

(2) Operational Qualification: Establishing by objective evidence parameters which result in production that meets all predetermination requirements. [14]

(3) Performance Qualification: Establishing by objective evidence that the process, under anticipated conditions, including worst case conditions, consistently produces a product which meets all predetermined requirements. [14,2]

QUALITY BY DESIGN: AN ALTERNATIVE APPROACH TO PROCESS VALIDATION

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. [17]

Quality by Design (QbD)–"Means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches."[20]

Traditional approach in process validation focuses on three validation lots at commercial scale. Process validation is considered complete when the results of these lots are within acceptance criteria as defined in the validation protocol. [18, 20]

Fig. 5:Quality by Design Model [21]

An alternative approach to traditional process validation is the continuous process verification, which adopts the concept of Quality by Design (QbD). It emphasizes on a life cycle approach where the process is continued to be verified even after the validation lots.[19]

QbD is related to about having a Control Strategy, about Knowing and Controlling Variation, having Quality Built In and Continuing Validation beyond the three batches.[20]

BENEFITS OF APPLICATION OF QBD APPROACH TO ANALYTICAL METHODS

- Development of a robust method
- Applicable throughout the life cycle of the product [22]
- Regulatory flexibility
- Movements within "Design Space" are not considered a change in method [21]

Table 1:Comparison of the current state to the future desired QbD state.[21]

Aspect	Current state	Desired QbD state
Pharmaceutical development	Empirical; typically univariate Experiments	Systematic; multivariate experiments
Manufacturing process	Locked down; validation on three batches; focus on reproducibility	Adjustable within design space; continuous verification within design space; focus on control strategy
Process control	In-process testing for go/no-go; offline analysis	PAT utilized for feedback and feed forward in real time
Product specification	Primary means of quality control; based on batch data	Part of an overall quality control strategy; based on product performance
Control strategy	Mainly by intermediate and end product testing	Risk-based; controls shifted upstream; real-time release
Lifecycle management	Reactive to problems and OOS; post approval changes Needed	Continual improvement enabled within design space

CHARACTERISTICS OF A SUCCESSFUL QBD PROGRAM

1. Involves product design and process development
2. Risk-based, science based
3. Primary focus is patient safety and product efficacy
4. Business benefits are also drivers [23]
5. Results in improved process understanding
6. Results in improved process capability/robustness
7. Systematic development[24]
8. Holistic – applies to all aspects of development
9. Multivariate – interactions are modeled
10. Provides PAR, design space, or suitable equivalent
11. Requires a significant reduction in regulatory oversight post approval[25, 26]

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