Processes Validation a Critical Review Why and When

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Abstract

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. It was proposed in direct response to several problems in the sterility of large volume parenteral market. The first validation activities were focused on the processes involved in making these products, but quickly spread to associated processes like environmental control, media fill, equipment sanitization and purified water production. The concept of validation was first developed for equipment and processes and derived from the engineering practices used in delivery of large pieces of equipment that would be manufactured, tested, delivered and accepted according to a contract. The use of validation spread to other areas of industry after several large-scale problems highlighted the potential risks in the design of products. The most notable is the Therac-25® incident. Here, the software for a large radiotherapy device was poorly designed and tested.

Key words: process validation, FDA, cGMP

Introduction:

In use, several interconnected problems led to several devices giving doses of radiation several thousands of times higher than intended, which resulted in the death of three patients and several more being permanently injured.[1]

The primary objective of any pharmaceutical plant is to manufacture products of requisite attribute and quality consistently at the lowest possible cost. Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in validation owing to industry's greater emphasis on quality assurance and productivity improvement. Validation is a necessary part of quality assurance program and is fundamental to an efficient production operation.[2]The word validation simply means assessment of validity or action of proving effectiveness. Validation is a team effort and it will involve people from various disciplines of the plant. 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."** 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

ESSENTIALS OF PHARMACEUTICAL VALIDATION[3]

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 the processes but confirms that the processes have been properly developed and are under control. 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 The CGMP[4] section requires process validation of a finished pharmaceuticals product.

21 CFR part 211.110 of these regulation states: -

1) "To monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in -process materials and the drug product". This means that we must establish in process and finished product controls, such as physical check, chemical and microbiological tests. Identify and study all parts of manufacturing process that may cause variation in the in-process material

or finished product.

2) Validation of process is in accord with good business judgment. The requirements to evaluate a process provide challenge and accumulate and interpret the resulting data all provide a greater understanding of the process and the product.

- The integrity of the manufacturer will be strengthened.
- Higher quality products will be distributed commercially.
- Financial losses will be reduced due to less batch rejection, product returns and complaint recalls.

A generally stated requirement for process validation is contained in the medical device cGMP regulations, section 820.100 (B) (1) states " Where deviations from device specifications could occur as a result of the manufacturing processes itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications."

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 process will yield less 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?[5]

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures. 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 product.
- 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.

HOW VALIDATION IS DONE?[6]

The basic principle is characterized by harmony between the results obtained and requirements, this proposes

- Specified requirements and objectives.
- Available means.
- Choices, which are justified in relation to objectives
- Each stage should begin when the previous stage is over.

Certain dispositions to be taken:

- How restrictions should be defined.
- How norms should be dealt with.
- How modifications should be dealt with.

Control the evaluation will involve:

- Set data for decision-making
- Evaluation before decision-making.
- Justifying the decision.
- Follow up.

The following scheme may be suggested:

- Process as a whole and flow diagram.
- Challenging the critical process variables.
- Validation protocol.
- Protocol versus report: procedures, sampling, testing, reporting and results.
- Evaluation and recommendations including frequency for re-validation.

WHEN TO VALIDATE?

It is accepted that the validation trial be carried out successively on three batches, following standardized conditions. Controls use to be made on finished products, but the concept of validation cannot be reduced to one single process on the end product

PROCESS VALIDATION LIFECYCLE[7]

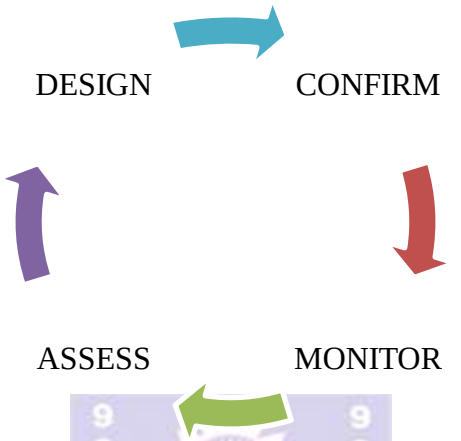

Figure 1: Process validation lifecycle

Design

GMP requirements for process design

- Design of facility
- Design of equipment
- Design of production and control procedures
- Design of laboratory controls
- Propose process steps (unit operations) and process variables (operating parameters) that need to be studied
- Identify sources of variability each unit operation is likely to encounter
- Consider possible range of variability for each input into the operation
- Evaluate process steps and variables for potential criticality
- Select process steps and variables for test in representative models
- Development studies to identify critical operation parameters and operating ranges
- Designed experiments
- Lab scale, pilot scale and or full scale experimental batches to gain process understanding
- Establish mechanisms to limit or control variability based on experimental data
- Aim for robust process, i.e.; one that can tolerate input variability and still produce consistent acceptable output

Confirm:

- Transfer developmental knowledge to production, i.e., technology transfer
- Batch record and operating SOP's in place, equipment and facilities equivalency established
- Raw materials approved
- Measurement systems qualified (QC lab as well as production floor test instrumentation)
- Personnel training completed
- Environment controlled as necessary
- Execution of conformance batches with appropriate sampling points and sampling level
- First evidence that process can function at commercial scale by production personnel

- Demonstrates reproducibility
- Reasonable measure of protection to consumer
- Full sample and data analysis
- Data may confirm process as-is, point to major process design change(s) or suggest major process design change(s) or suggest process improvement(s).
- Implement changes via approved change control procedures
- Assess need for additional conformance batch (es) or limited testing. Amount/degree of additional work commensurate with the significance of the change and its impact on product quality

Monitor:

- Monitor critical operating and performance parameters
- Utilize appropriate tools, e.g; statistical process control
- Monitor product characteristics (e.g; stability, product specifications)
- Monitor state of personnel training and material, facility, equipment and SOP changes
- Investigate OOS for root cause and implement corrective action

Assess:

- ➢ Analyze monitoring data
- Trend data: e.g; real time, monthly, quarterly review
- Evaluate need to increase level of monitoring/sampling, or decreased monitoring based on accumulated data
- ➢ Periodic evaluation (at least manually) per 21CFR211.180(e)
- To determine the need for changes in drug product specifications or manufacturing and control procedures
- ➢ Study OOS and OOT (out of trend) data in the aggregate
- ➢ Assess impact of process and product changes and product changes made over time
- ➢ Feed back into design stage for significant process shifts or changes

PHASES OF VALIDATION [8]

User Requirement Specification (URS) is a document that describes the intended use along with requirements & acceptance criteria considering basic functional and design aspects from which detailed functional & design specifications can be drawn. URS is linked to Performance Qualification, which tests the system in its operating environment with the product.

Functional Specification (FS) is a document that describes the detailed functional attributes along with necessary safety features wherever applicable. FS is linked to Operational Qualification, which tests all functions specified as per the requirements or defined in the FS without product.

Design Specification is a document that describes the design aspects in sufficient detail to enable it to be constructed, installed and qualified. Design Specification is linked to Installation Qualification, which checks the correctness of supply and the installation.

Design Qualification verifies whether the requirements defined in design specification is completely in accordance with the user requirement specifications. This is done by a formal review and approval of functional and design specifications, provided by the supplier.

Installation Qualification verifies and documents evidence that all key aspects of installation meet the approved design specifications as intended and that the installation recommendations derived from in-house / manufacturer / supplier, have been suitably achieved.

Operational Qualification verifies and documents that the installed equipment / system operate within typical or anticipated operating ranges indicated in the Functional specification.

Performance Qualification verifies and documents evidence that the system in its normal operating conditions performs as intended with placebo throughout anticipated operating ranges defined in the User Requirement Specification.

TYPES OF VALIDATION[9]

The guidelines on general principles of process validation mentions four types of validation:

A) Prospective validation (or premarket validation)

B) Retrospective validation

C) Concurrent validation

D) Revalidation

A) Prospective validation

Establishing documented evidence prior to process implementation that a system does what it proposed to do based on preplanned protocols. This approach to validation is normally undertaken whenever the process for a new formula (or within a new facility) must be validated before routine pharmaceutical production commences. In fact, validation of a process by this approach often leads to transfer of the manufacturing process from the development function to production.

B) 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 because it's very unlikely that any existing product hasn't been subjected to the prospective validation process. It is only used for the audit of a validated process.

C) 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.

D) Revalidation

Revalidation means repeating the original validation effort or any part of it, and includes investigative review of existing performance data. This approach is essential to maintain the validated status of the plant, equipment, manufacturing processes and computer systems. 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.
- Significant (usually 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.

STAGES OF PROCESS VALIDATION[8-9]

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.

Stage 1: Process Design

The commercial process is defined during this stage based on scientific knowledge gained through development and scale-up. Process knowledge is established and the process is defined through laboratory and pilot scale studies. Sources of variability are identified and understood, and their impact on product quality is defined. The degree of management of the

sources of variability is commensurate with the risks to product and patient safety that the variability poses. Potential critical process parameters are identified and evaluated through multivariate analysis and effects of scale are assessed.

Process controls are established to manage critical process parameters and variability of process inputs. Design of experiment (DOE) methodologies is used to perform mechanistic modelling to establish process design and operating spaces. As a part of the establishment of design and operating spaces, "worst case" conditions and parameters are evaluated. The primary objective of the Stage 1 work is to define the process in enough detail such that the control of critical parameters and sources of variability is effective at commercial scale.

Stage 2: Process Qualification

The purpose of the work in this stage is to confirm that the process design is capable of commercial manufacturing. Prerequisites to these activities include completion of activities in Stage 1, qualification of the facility and critical utilities, qualification of process systems and equipment, validation of sampling and analytical methods, and performance of manufacturing operations by trained staff using approved manufacturing instructions and records. The process qualification (PQ) work is documented in a protocol which defines manufacturing condition, operating parameters, processing limits and raw material inputs; the data to be collected and how it will be evaluated; the tests to be performed for each significant process step and acceptance criteria for those tests; a sampling plan including sampling points, number of samples, and frequency of sampling based upon statistical rationale; and criteria to provide rationale to conclude that the process produces a constant product including statistical methods to be used in the evaluation of data and a pre-established plan for addressing deviations and non-conformances.

The work is documented in a report summarizing the testing and results and their conformance with expectations that confirm the consistence of manufacturing operations. Additional in-process material and product testing beyond that for routine manufacturing operations is expected.

Stage 3: Continued Process Verification

The object of this stage is to continuously verify that the process is in a state of control and is performing consistently and in accordance with the process that was tested during the process qualification stage. Detection of deviations or excursions from the operation of the qualified process is essential to effectively perform continued process verification. This is done by collecting and analyzing process information in real time, especially critical process parameter data, to assess process performance and to make process corrections to assure that a consistent product is produced from each manufacturing run. The guidance recommends that a person or persons trained in statistical process control establish sampling plans and methods for statistical evaluation of real time process data for purposes of trend analysis and real time process correction. These statistical data may also be used as a basis for process improvement and assessment of process variability. These analyses are essential elements in the evaluation of process "drift" and they may provide a basis for the need to perform process re-qualification activities.

VALIDATION MASTER PLAN (VMP)[9]

The validation master plan complements the facilities master file and is usually the first document to be reviewed during inspections by a regulatory authority it reinforces the commitment of the company to GMP and should provide a clear over view of the validation program including schedules and responsibilities.

The VMP is also a convenient guide for the validation committee and those performing the qualifications, because new equipment may enter the validation programme from time to time, the VMP is best considered as a live document.

VMP should be concise so that it can be easily read in one sitting and may typically include the following;

- Introduction and objectives
- Description of the facilities, including plans
- Constitution of validation committee

- Glossary of terms
- Construction of the documentation
- Description and listing of protocols
- List of standard operating procedures
- Preventative maintenance procedures
- Preventative maintenance programme
- Personal training programme
- Storage documentation
- Example of the protocols

Recent Advances in Regulations Related to Process Validation

FDA guidelines

Table 1: Comparison between old and revised FDA guidelines.

1987 GUIDE	2011 GUIDE
"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics"	"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"
Emphasised on collecting large quantities of data from validation batches, leading to a perception of process validation as a largely documentation exercise.	Tells the manufacturer to collect data throughout the product life cycle and evaluate it scientifically and assess if it supports a quality process.
No emphasis on product lifecycle	The new guidance has aligned the concept of 'product lifecycle', giving the three-stage approach to process validation.
Describes "Installation Qualification" which, in practical terms, refers to IQ, OQ and arguably equipment PQ. The 1987 guide does not mention OQ or equipment PQ.	Describes "Equipment Qualification" which, in practical terms, refers to IQ, OQ and equipment PQ.
Describes "Process Performance Qualification" which, in practical terms, refers to equipment PQ (if not previously covered) and prospective process validation batches.	Describes "Process Performance Qualification" which, in practical terms, refers to prospective process validation batches.
Although not expressly stated in the old guidance, manufacture of three batches for process validation has become industry standard.	The new guidance makes it clear that it is the manufacturer's responsibility to provide assurance that the process is adequately qualified. The use of statistical methods to provide objective evidence is strongly recommended.
The concept of worst-case conditions for process validation was a key theme of the 1987 guidance. The 1987 guidance defines worst-case as: "A set of conditions encompassing upper and lower limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions."	The 2011 guidance has removed the concept of worst-case conditions, it has redefined the expectation as follows: "The commercial manufacturing process and routine procedures must be followed. The PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process."

The 1987 guidance included the concept of revalidation of processes when changes to a process are introduced (e.g. changes in formulation, raw material, equipment), or when process variation is detected.	The 2011 guidance has revised this concept with the introduction of Continued Process Verification. This involves the ongoing assessment of process data (in-process, finished product, equipment parameters, etc.) against variability limits established during the first two stages of process validation.
The 1987 guidance expressly discouraged matrix approaches to process validation. Where multiple similar products, presentations or equipments are grouped together within the one validation exercise to reduce the overall testing requirements.	Conversely, the 2011 guidance provides specific acceptance of the matrix practice, stating: "Previous credible experience with sufficiently similar products and processes can also be considered".
The concept of concurrent validation was not included in the 1987 guidance. Retrospective validation is not mentioned in the guidance.	The new guidance provides information on the precise circumstances under which concurrent release of validation batches is acceptable. Retrospective validation is not mentioned in the guidance and should not be considered an acceptable approach for planned validation.
No acknowledgment on concepts such as integrated team approach and Process analytical technology.	Includes the acknowledgement of some concepts which have gained wide acceptance in industry including: Integrated team approach – the guidance strongly recommends input in the validation process from a wide range of disciplines, as well as the full support of senior management. Process Analytical Technologies (PAT) – the guidance introduces PAT concepts and gives guidance on the role it can play in process validation.

Results:

The pharmaceutical industry today is to manufacture products of the right quality at the lowest possible cost and to supply quality products to the customers. In order to achieve the objective, the industries must validate all the operations of the business. Validation is attaining and documentation of sufficient evidence to give reasonable assurance that the process under consideration does what it purports to do. Validation Team - To prepare, review & approve the process validation protocol and report. To execute the validation activity. Manufacturing Department - Execution of manufacturing process during validation. Review and approval of process validation protocol and report. Quality Assurance - To monitor the validation activity & sampling as per the sampling plan of protocol. Review and approval of process validation protocol and report Quality Control - To analyze validation samples and review of analytical report. Regulatory Affairs - To review the protocol and report from regulatory perspective.

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