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REVIEW ARTICLE

Computerized System Validation: Introduction Implementation and Regulations - A Review

Todkar VS*, Lade MS, Patil KS, D'souza JI

Tatyasaheb Kore College of Pharmacy Warananagar, Maharashtra- 416113, India.

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ABSTRACT

Computerized System validation covers the equipment those are having their own Control systems based Software Systems. It defines the extent of the validation program and lays down broad guideline for the various validation activities to be carried out. This provides a framework and practices for validation and qualification of Computer based software systems. The validation master plan is the basis of individual project validation plans, also called master validation plan. This plan states regulatory expectations for the activities, tasks, and testing to be performed during validation of Software Systems. This document provides broad guidelines to be followed and implements the concept for Software System validation as per the best understanding of Good Automated Manufacturing Practice, Version 5 (GAMP 5) & Part 11 regulation (wherever applicable). Computer system validation provides recognized proof that the systems will repeatedly and consistently do what it is deliberate to do, is "fit-for-purpose", and complies with the applicable rules and regulations. Computer system validations have many advantages like improve quality, reduce other validation outlay and time, improve GMP compliance and 21 CFR part 11 regulation which has impact on product quality, safety, identity or efficacy that subject matter to GxP rules. It is likely that the future will see meeting of computer system validation terminology and techniques as a common technical discipline across other industry sectors as well.

KEYWORDS

Computer System Validation, Good Automated Manufacturing Practices, Quality Assurance, Validation Life Cycle

INTRODUCTION

The speculation of validation was initially premeditated by Food and Drug Administration (FDA) members; viz., Bud Loftus & Ted Byers, in 1970's, categorize to improve the quality of Pharmaceutical products. The development of drug is very time consuming & lengthy process in which numbers it involves drug discovery, testing, clinical trial & regularization. For effectiveness & safety of drug after approval, USFDA also require to be tested before released for use i.e. identity, strength, quality, purity & stability of the drug. Validation is an important part of Quality Assurance to monitor overall process of manufacturing the drug.

***Address for Correspondence:**
Todkar Vaibhav S.
Tatyasaheb Kore College of Pharmacy,
Warananagar- 416113, Maharashtra, India.
E-Mail Id: vstodkar.tkcp@gmail.com

Validation[21]

"Validation is the documented evidence which provides a high degree of assurance that specific process will consistently produce a product meeting its predetermined specifications & quality characteristics".

Introduction

Validation is a very vital part of quality assurance which gives confirmation of the

quality in the equipments, manufacturing process, software & testing. Validation assures that products with specific quality characteristics & attributes can be produced constantly within given limits of manufacturing process. Validation is bridge to move the product from development to commercial production

Principle of Validation

Validation is wide ranging concept which includes analytical, equipment, process and computer system validation. Concern of validation is to design and built quality, safety & efficacy into product. Quality cannot be assured merely by in-process & finished product inspection or testing. Each step of manufacturing process must be controlled to assure that the finished product meets all quality & design specifications. Validation is the prime factor which helps to meet the quality product and the regulatory requirement.

Importance of Validation

- It minimizes the risk of preventing problems & thus assures the smooth running of the process.
- Validated process is more efficient & produces less reworks, rejects & wastage.
- Validated process may require less in-process controls & end product testing.
- It minimizes risk of defect cost & risk of regulatory noncompliance.

Need of Validation

- It would not feasible to use the equipment without knowing result of producing required product or not.
- Now-a-days Pharmaceutical industries are using highly expensive materials, sophisticated facilities & so far the equipments 7 highly qualified personnel.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, complaints are the significant parts of the total production cost.
- Detailed study & control of manufacturing validation is necessary if failure cost is to be reduced & production is to be improved.

Types of Validation[21]

A. Analytical Validation

It is the evaluation of quality of product through testing, to demonstrate reliability is being maintained throughout the product life cycle & that the precision, accuracy, strength, purity.

B. Equipment Validation[21]

Validation of equipment is known as qualification. Equipment validation is divided into IQ, OQ, & PQ. In IQ document specific attributes of a facility or item prove that the installation of the unit has been correctly performed & that installation specifications of the manufacturer have been met. After installation, it must be ensured that equipment can deliver operating ranges as specified in the purchase order. This is said to be as OQ. PQ is concern with proving that the process investigated works as it is supposed to do.

C. Process Validation[21]

A documented program which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification & quality attributes. Process validation is divided into different types:-

- Prospective Validation
- Concurrent Validation
- Retrospective Validation
- Revalidation

D. Computer System Validation[21]

Computer system validation encompasses computers, which directly control process or system or collect analytical data. Computer system validation includes the qualification of all software & hardware, which has impact (Directly/Indirectly) on the quality of a product. Computer system validation provides documented proof that the system will repeatedly and reliably do what it is designed to

do, is "fit-for-purpose", and complies with the applicable rules and regulations. Computer system validations have many advantages like improve quality assurance, reduce other validation cost and time, improve GMP compliance and 21 CFR part 11 regulation which impact on product quality, safety, identity or efficacy that subject to GxP rules. It is likely that the future will see convergence of computer system validation terminology and techniques as a common technical discipline across other industry sectors as well.

It is the technical discipline that Pharmaceutical companies use to ensure that each information technology application fulfills its intended purpose. Stringent quality requirements in FDA regulated industries impose the need for specific controls and procedures throughout the Software Development Life Cycle (SDLC). Evidence that these controls and procedures have been followed and that they have resulted in quality software (software that satisfies its requirements) must be documented correctly and completely. These documents must be capable of standing up to close scrutiny by trained inspectors since the financial penalty for failing an audit can be extremely high. More importantly, a problem in a life science software application that affects the production environment could result in serious adverse consequences, including possible loss of life. Computerized systems are used widely all over all aspects of research and improvement, laboratory testing and analysis, product scrutiny and acceptance, production and process control, environmental controls, packaging, labeling, complaint supervision, and many additional aspects of pharmaceutical companies. In addition, software tools are frequently used to design, build, and test the software of computer systems. All computerized equipment, systems, applications, tools and embedded systems that affect, monitor, or control product safety, quality, efficacy, or purity are subject to one or more of good manufacturing, laboratory, or clinical practice (GxP) and other applicable regulations and hence computer software validation.

Validation Life Cycle[38,39,40,41]

Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and modifying". FDA regulated industries impose the need for specific controls and procedures throughout the Software Development Life Cycle (SDLC).

V-Model

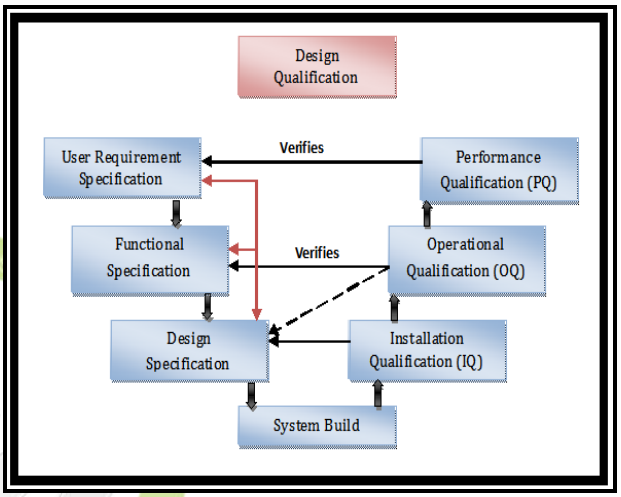

Figure 1: V- Model of Qualification

This model comprises of URS, FS, DS, development and testing of code, IQ, OQ and PQ. The V-Model as described above is quite good if the validation process also includes software development. However, it does not address some very important steps, for example, vendor assessment. It also looks quite complex for true commercial off the shelf system with no code development for customization. Phases like design specification or code development and code testing are not necessary.

4Q- Model

The 4Q model is recommended with just four phases: DQ, IQ, OQ & PQ.

Both the 4Q and the V-model do not highlight the retirement phase. The 4Q model is also not suitable when systems need to be configured for specific applications or when additional software is required that is not included in the

standard product and is developed by the user's firm or by a 3rd party.

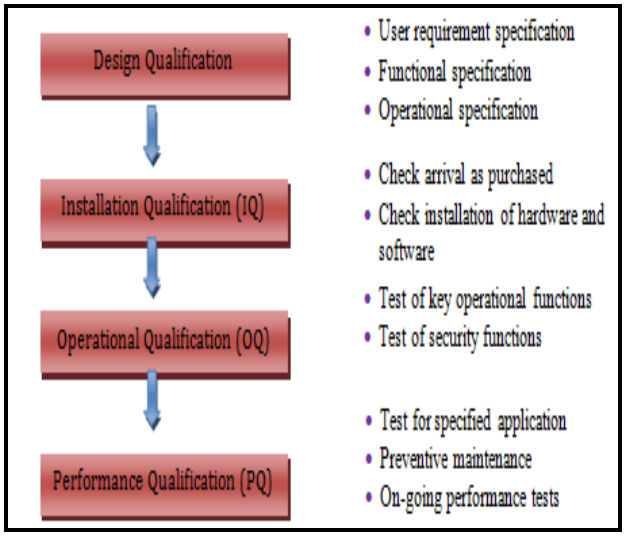

Figure 2: 4Q Model of Qualification

In this case a life cycle model that combines system development and system integration is preferred. An example is shown below in the figure 3.

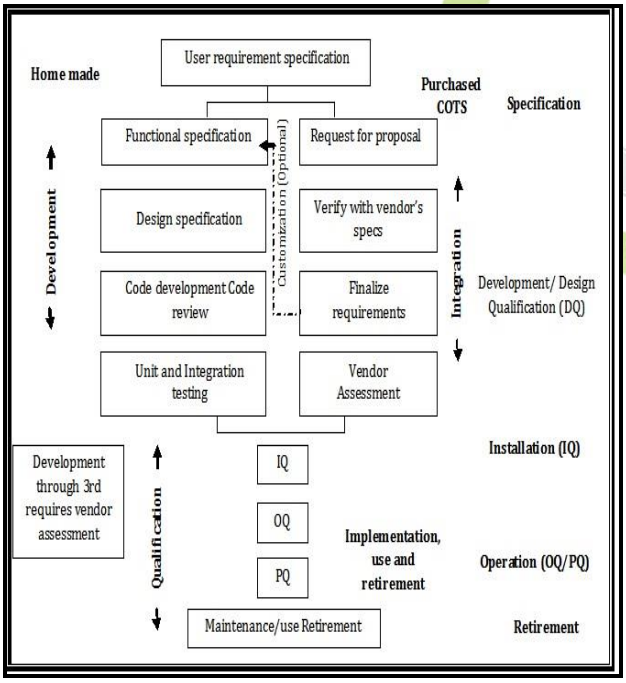

Figure 3: Life Cycle of Computer System Validation

Methodology[5]

1) Validation master plan preparation & approval (Prospective/Retrospective validation approach is followed)
2) Execution & preparation of system assessment report
3) Closure of gaps identified during system assessment
4) Preparation & approval of risk assessment report
5) Preparation & approval of IQ (Installation Qualification) & OQ (Operation Qualification) or IOQ (Installation/ Operation Qualification)protocols
6) Execution of IQ
7) Preparation IQ report
8) Execution of OQ
9) Preparation OQ report
10) Preparation of Validation summary report
11) System maintenance as per the computer based system's harmonized SOPs like deviation, change control management, Audit trail review, User Administration & access control & System backup etc.

1) Validation Master Plan (VMP)

- Validation master plan covers the equipment with computerized control/ data acquisition system (i.e. SCADA/DAS) having GxP impact.
- It defines the level of validation program & lays down wide guideline for various validation activities conceded out in line with validation strategy as per the GAMP 5 & 21 CFR part 11.
- VMP ensures that validations are done efficiently & consistently throughout organization & meets regulatory, quality & business requirements.

2) System Assessment/Gap Analysis

Gap analysis/ system assessment is performed as per the designed checklist based on system documentation (Operational/ technical manual, qualification documents & SOPs etc.) & regulatory requirement.

Following points would be checked during the gap analysis-

Categories of Software

Category number	Software type	Validation approach
1	Infrastructure software (e.g. Operating System)	Record version number
3	Non-Configured (e.g. COTS, firmware, Spreadsheet etc.)	• Abbreviated life cycle approach URS • Record version number & verify correct installation. • Risk based tests against required as dictated by use
4	Configured software (E.g. Data Acquisition system, Supervisory control and Data Acquisition, PLC/HMI & SAP etc.)	• Abbreviated life cycle approach • URS. • Record version number & verify correct installation & configuration. • Risk based testing to demonstrate application works as designed in a test environment within business process. • Procedure in place for maintaining compliance & fitness for intended use.
5	Custom software (e.g. Internally/ externally developed IT/ Process control application, custom ladder logic, custom firmware & Spreadsheet)	Same as configured & plus: • More rigorous supplier assessment with possible supplier audit. • Possession of full life cycle document (Functional Specification, Design Specification, structural testing etc.) • Design & source code review

Categories of Hardware

Category number	Hardware type	Validation approach
1	Standard	• Document details & verification of installation & connection
2	Custom	• Design & acceptance testing • Supplier audit may be required

- Qualification documents
- System related SOPs
- Access control & security setting related documents (i.e. Policy/SOP)
- Design documents (User Requirement Specification, Design Specification, & Functional Specification).
- Engineering documents (Wiring diagram, BOM, Input/ Output list, Technical manuals)

If any gap found in to the system, either of following action would be taken to close GAP or to reduce it's severity.

- Retire the system & return to paper
- Implement procedural controls
- Upgrade existing system
- Replace the system with a new solution.

3) Risk Assessment

- Risk assessment is performed to identify the risk associated with critical process parameters & its control functions that have high potential impact on product quality/ patient safety/ data integrity.
- Risk assessment is done to identify & minimize the errors that may occur during normal operation of the system.
- Risk assessment of identified risk scenario is done with the help of three factors like severity, occurrence & detection. Overall risk ranking is done by two methods viz. RPR (Risk Prioritization Ranking) & RPN (Risk Prioritization Number).
- Severity of risk is identified, frequency of occurrence is identified & depending on that the probability of detection of risk is raised to minimize the occurrence of risk.
- After risk ranking, if risk is acceptable no further action is required. If risk is not acceptable, suitable mitigation action plan is initiated, risk is again assessed & ranking is done to verify it's acceptance.
- These identified risk scenario are challenged during qualification to prove that it is mitigating as per the expected result/designed interlock.

4) Preparation & Approval of IQ/OQ/IOQ Protocol

- Installation Qualification (IQ) protocol is prepared with reference to the design specification (hardware & software design specification)
- Operation qualification (OQ) protocol is prepared with reference to functional specification and URS.
- IOQ protocol contains test related to Installation & Operation qualification.
- Generally IOQ is performed for simple application. For complex application, IQ & OQ is performed.

Tests Performed in Installation Qualification (IQ)

1. System identification
2. Verification of Master documents (like URS, DQ, Operation Manual, Calibration report & schematic diagram etc.)
3. Verification of Hardware & Software configuration
4. Verification of power supply utility
5. Verification of system drawing/ diagram.

After IQ execution completion, IQ report is prepared. If any discrepancy is found during IQ execution, suitable corrective action is suggested.

If discrepancy is critical, operation qualification can be initiated only after compliance/closure of discrepancy. If discrepancy is not critical, suitable corrective action is suggested & compliance of the same can be done immediately or can be closed later.

Operation qualification is performed after the completion of Installation qualification.

Tests Performed in Operational Qualification (OQ)

1) SOP's verification
2) System access control & security policy configuration testing
3) Testing of Application software Programmable function keys (PFK's)/ icons/ buttons & set parameters range.
4) Testing of alarms & interlock, if configured.
5) Power failure & Communication failure testing
6) Environmental condition verification
7) Audit trail & Database integrity test.
8) Operational sequence testing

After completion of OQ execution, OQ report is prepared.

If any critical discrepancy is found, next qualification stage (PQ) can be initiated only after compliance of discrepancy.

Tests Performed in Installation/ Operation Qualification (IOQ)

A. Verification plan

- System identification
- Verification on Master documents (URS, DQ, Operation Manual, Calibration report, Schematic diagram, etc.)
- Verification of Hardware & Software configuration
- Verification of power supply utility
- Verification of system drawing/ diagram.

B. Functional test plan

- SOP's verification
- System access control & security policy configuration testing
- Testing of Application software Programmable function keys (PFK's)/ icons/ buttons & set parameters ranges.
- Power failure & Communication failure testing
- Environmental condition verification
- Audit trail & Database integrity test
- Operational sequence testing.

After completion of OQ execution /IOQ report summary report is prepared. If any critical discrepancy is found, next qualification stage (PQ) can be initiated only after compliance of discrepancy.

5) Validation Summary Report

Summary report is prepared to verify status (pass/fail) of qualification tests performed in the IQ/OQ/IOQ.

6) Periodic Review

Periodic review activity is performed to verify validation status integrity of computer based system.

Points to be covered under periodic review:

- Verification of system related Change control
- Review of system related Deviations
- Verification of System software & hardware configuration
- Verification of system security configuration
- Audit trial review
- System response time (application launch time, data archival time etc)
- Review of system related calibration/PM/AMC report.
- Verification of installation of antivirus software & it's updates.
- Any pending observation related to system with reference to internal audit/external audit/last periodic review.

CONCLUSION

Validation Master Plan defines computerized system validation strategy. System Assessment represents the actual documentation quality status of the system. Risk Assessment recognizes and evaluates the potential failure of a product/ process and its effects identify

actions which could eliminate or reduce the chance of potential failure & document the process. Software & Hardware verification is also done to ensure the capacity of computer hardware which supports to the software. Security configuration/Access control of the system is performed which ensures that no one except the authorized person will operate the system. Audit trail highlights the all process record in one log. Operational testing is carried out to know that the process is carried as per user requirement & design specification. Power & Communication failure test is done to ensure the process remains continued & stored values remains unchanged after the power & communication failure. Alarms test concludes, if the process runs out of the specified/set value & interlock take cares of all possible error before process starts.

Regulatory Requirement for Computerized System Validation

Study of FDA of 3140 medical device recalls which was conducted within 1992 and 1998 states that 242 of them were facing software failures. Those software related recalls, 192 were caused by software defects, introduced when changes were made to software after receiving & distributing. Software validation and other allied good quality software engineering practices discussed in this to avoid such defects and resultant recalls. Software validation is an obligation of quality system regulation, which was published in Federal register on October 7, 1996 and took effect on June 1, 1997. Validation chuck to software worn as mechanism in medical devices, to software that itself is a medical device and to software used in production of the device for manufacturing quality system.

Validation is considered as a vital part of GMPs essentially worldwide, compliances with validation requirements is necessary for obtaining approval to manufacture & to introduce new products. The FDAs cGMP refer to concepts of validation in sections like 21 CFR 210 & 211.21 CFR 211.100 states that : There shall be written procedure for production & process control designed to assure that the drug products have identity, strength, quality & purity.

The Code of federal regulation states the electronic records and electronic signature. The sub-parts of 21 CFR play an important role in maintaining and regulating the electronic records and electronic signature records. It also enforces to maintain the audit trail record of computer based system software. In audit trail all log related to the system is captured. It helps to know all the process related activities, from start to end.

Before emerging of 21 CFR part 11 there was lack in data maintaining and retrieving. Data manipulation was done to meet the required results. Maintenance of all the record for long time was becoming inconvenient, due which the files were missing or the data was getting lost. To have stringent action on this type of paper legacy system electronic record and electronic signature was emerged.

International Society of Pharmaceutical Engineering (ISPE) and many other regulatory agencies describe the methodology of Computer System Validation, from start to retirement of the system.

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