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COMPUTER SYSTEM VALIDATION: A REVIEW

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ABSTRACT

Pharmaceutical industry regulatory compliance of computerized systems is of ever increasing importance. The regulations require specific record keeping on product safety, efficacy, strength, quality and purity. 21 CFR Part 210 and 211 and others apply to Pharmaceutical Products and 21 CFR Part 820 applies to Medical Devices. Life cycle include the stage of planning, specification, programing, testing, commissioning, documentation, operation, monitoring and modifying. The V-Model supports structured testing which is essential for successful validation. Qualification is the process of establishing appropriately documented verifications and tests that provide a high level of assurance that a computer system will operate in accordance with predefined specifications (DQ, IQ, OQ, PQ).

KEYWORD: Computer system validation, GMP, life cycle model.

INTRODUCTION

Computer are widely used during development and manufacturing of drug and medical device. Proper functioning and performance of software and computer system play a major role in obtaining consistency, reliability, security and accuracy of the data.[8] Computer system application is expected to support the fundamental requirement of minimizing risk to product identity, purity, strength, and efficacy by providing consistent and secure operation and reducing the potential of human error. From the regulatory and business viewpoint, the advantages of utilizing computer systems can only be realized by ensuring that each system does what it purports to do in a reliable and repeatable manner.[5] The good manufacturing practice (GMP) regulations in focus are from the U.S. Code of Federal Regulations (CFRs), as inspected and enforced by the Food and Drug Administration (FDA), and Annex 11 of the

European Community (EC) Guide to Good Manufacturing Practice for Medicinal Products.[2, 3, 7]

Regulatory background

American code of federal regulation has following references, which related to the computer system validation and their validation. Even though these comments are not highly specific but they are very closely related to computer system validation.

a) Current good manufacturing practice for finished pharmaceuticals (21 CFR-part 211.68) specifies.[3,7]

"Automated, mechanical and electronic equipment or other types of equipment, including computer, or related system that will perform a function satisfactorily, may be used in the manufacturer, processing, packaging, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written record of these calibration checks and inspection shall be maintained".

b) Good manufacturing practice for medical devices (21 CFR-part 820) defines.[2]

"All production and quality assurance measurement equipment, such as mechanical, automated and electronics equipment, shall be capable of producing valid result. When computers are used as part of an automated production or quality assurance system, the computer software programs shall be validated by adequate and documented testing"

c) Good laboratory practice for non –clinical laboratory studies (21 CFR-part 58) state,[7]

"In automated data collection system, the individual responsible for the direct data input shall be identified at the time of data input. Any change in automated entries shall be made so as to obscure the original entry, shall indicate the reason for the change, shall be dated and the responsible individual shall be identified"

What is computer system validation (csv)?

Computer System Validation (CSV) provides documented proof that the system (e.g. hardware, software, peripherals and network) will repeatedly and reliably do what it is designed to do, is "fit-for-purpose", and complies with the applicable rules and regulations. CSV must show that the system operates predictably according to its specifications, and that

conclusion is supported by formal, documentary evidence because regulators will not take your word for it. [9]

Requirement

Requirement will determine the scope of the project. The validation and/or qualification should be the first major deliverable for any computer system. Requirements include the following,

Software: how the software is to operate.

Hardware: The hardware including the server.

Controlling system: the operating system on the server and the database used to collect the data from the software.

Equipment: Equipment is other computer system or pieces of manufacturing equipment with which the software may interact

Operating procedures and documentation: These all have requirements that include people who will be doing the work of validation, people who will be trained to utilize the system once it is in place.

Controlled processes: established controlled processes and change control need to be reviewed or addressed to ensure that control is maintained throughout the life of the project and for the ongoing stability of the system once validation and qualification is complete.

Total computerized system: network may be local or wide area, may utilize the web, may be within a corporate intranet or utilize the facilities of the internet.

Operating environment: security will be addressed as both a part of the operating environment, the software and operating system on the hardware, and all interfaced equipment.

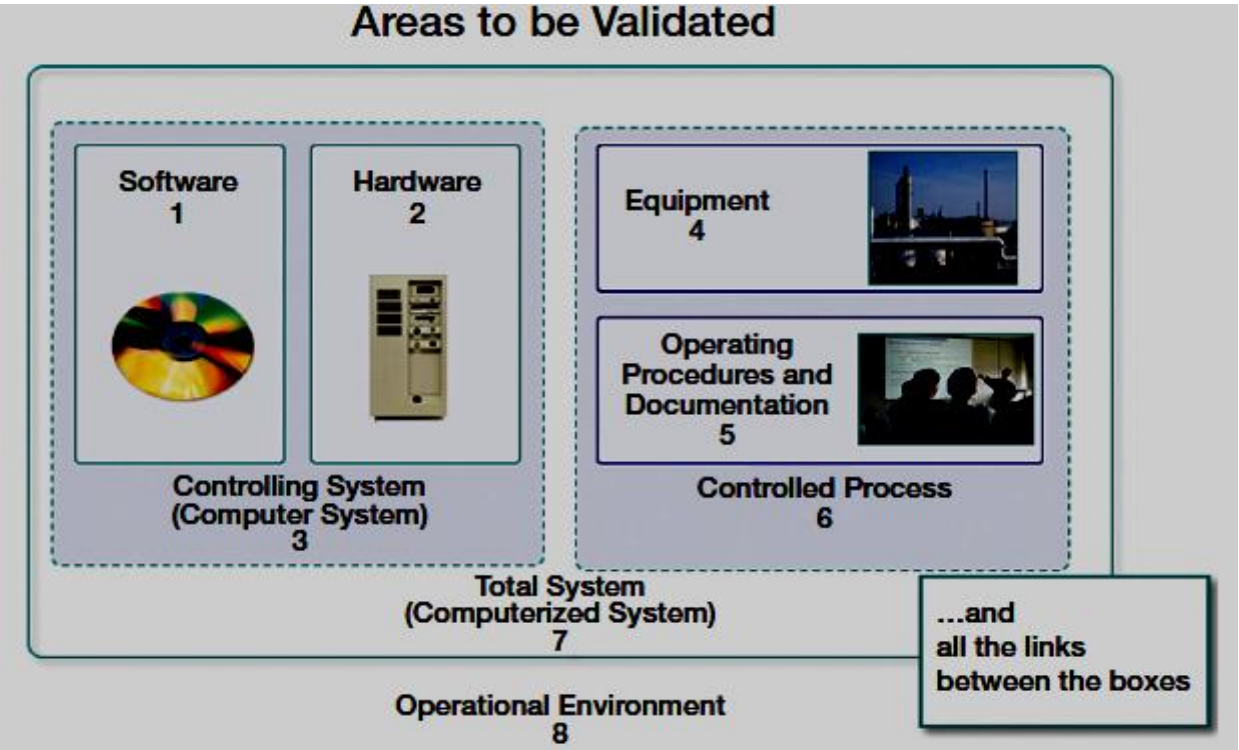

Fig 1: area for validation and qualification [3]

Life-cycle model

Software development uses a life-cycle development model (SDLC). Each step in the software development process can be connected to a step in the computer validation. Therefore, this model can be applied to computer system validation to illustrate each step in the validation process. This enables an efficient documentation of the development process. A brief overview of the model is given by Augsburg et al. (1994).

Each step of this model is described as follows

Requirements and design: A new computerized system may replace an older pharmaceutical process or may start a new process. The functional requirements are determined. While the development life-cycle starts, the group of people, responsible for validation should be selected. The responsibility of the Validation Committee is to define the validation plan, which outlines the tasks and determines the resources required for validation. The system specifications have to be defined. The detailed description of the final computerized system has to be documented.

During this phase the documents to be produced while validating are identified. This covers protocols and reports. The system documentation might be updated due to validation efforts.[1, 6]

Coding

At the beginning of this phase, the validation plan should be finished off. Information about the validation test environment, assumptions, exclusions and limitations about the system as well as installation procedures should be clarified. This phase covers the implementation of software and construction of hardware.

Testing

This complex phase can be divided into several phases. All single modules whether they are hardware or software have to be tested. Afterwards an integration test has to be performed. While the developers conduct unit, system and integration testing, the Validation Committee is in a position to define test cases and data running the acceptance test. Several documents such as, requirement documents, functional specification and system design documents should be available for review and updates.

Installation testing

The end user performs the system's task with his/her own data and procedures. System failure leads to new documentation and re-design.

Production maintenance

The system is released for production. System changes (software or hardware) have to be documented and controlled in a predefined manner. The first and second step can be linked to the earlier mentioned design qualification, step three and four will be validated in installation qualification and the task of performance will be linked to step five of the above life-cycle model.

V –model

This V-model by Boehm (Boehm, 1979) is depicted in Fig.3. Each level of the V-model is semantically equivalent to a step in the life-cycle model. The V- model is quite good if the validation process also include 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. This model comprises of User requirement specification (URS), Design qualification (DQ), Installation qualification (IQ), Operational qualification (OQ), Performance qualification (PQ)

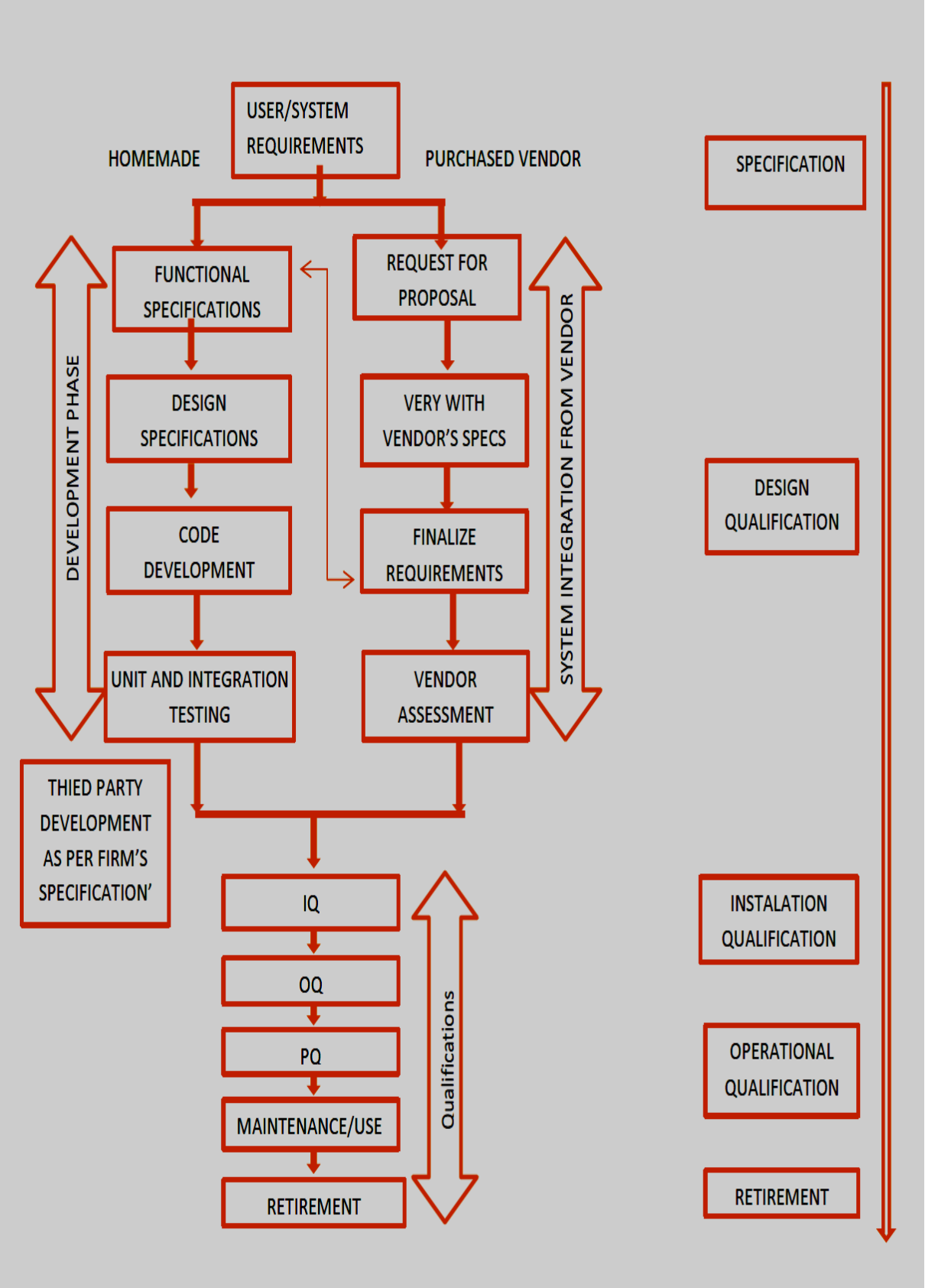

Fig. 2: System integration combined with system development. [6]

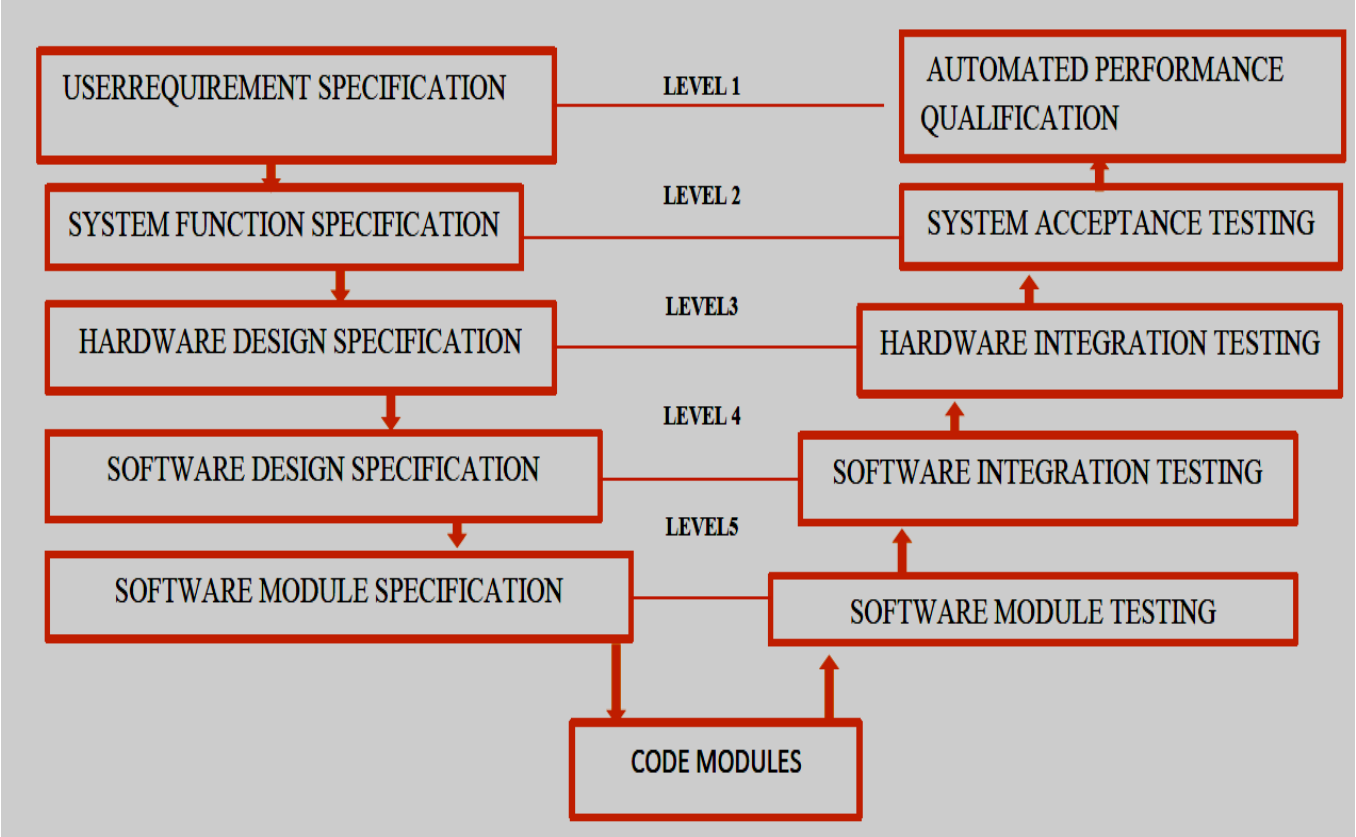

Fig.3: The V- model

How the various stages in the computer system validation are performed?

Computer system validation begin at the beginning of the system design.it begins and goes through a complete SDLC. Various stages in computer system validation as follow

Master Validation Plan.[7]

- ✓ Identification of the parties' responsibility for different parts of the program.
- ✓ Description of the equipment, system, processes, and assays to be validated.
- ✓ Determination of acceptance criteria for each system, process to be validated.
- ✓ Defining all the SOP's.

User Requirement Specification.[5,7]

- ✓ Process control and determining the requirement of the system
- ✓ Programing standard and test procedure, are developed.
- ✓ Integral groups are assigned Project responsibility/schedule.
- ✓ Provide sufficient detail to the supplier to produce a cost, resource, and time estimate to engineer and document the computer system within a validation life cycle.
- ✓ Provide information for the system supplier's functional design specification (FDS).

- ✓ Provide an unambiguous and commonly understood operational and interface listing of functional and system requirements, which can be tested during PQ.
- ✓ Identify all manufacturing design data, including quality-related critical parameters and data for system design and testing.
- ✓ Identify the project documentation (and task responsibilities) to support the validation program.

Design Qualification.[7]

DQ is prepared for hardware and software.

The hardware portion of the system description is prepared in text and chart formats. These documents provide signal, data, and process flow details. Some are the hardware component

- ✓ Controller.
- ✓ Peripheral device.
- ✓ Input/output modules.
- ✓ Network modules and cabling.
- ✓ Power requirements.
- ✓ Enclosures etc.

For software there are three level identified as,

- ✓ Operating system software.
- ✓ Configuration system software.
- ✓ Application specification system software.

Installation Qualification.[5,7]

I.Q protocol contains instructions for verification of installation of hardware and software component. The operator who check, dates and sign, all sections attaches to the protocol. Normally the following items are cheeked during I.Q.

- ✓ Power supply, electrical distribution, and fusing.
- ✓ Uninterrupted power supply and emergency power system.
- ✓ Grounding, termination and tagging.
- ✓ Control cabinets and environmental condition.
- ✓ Instrument and equipment indices and identification tags.
- ✓ Device tubing and writing continuity.

- ✓ Drawing (P and ID, loop sheet, wiring schematics and termination, network schematics).
- ✓ Purchase order.
- ✓ Specification.
- ✓ Manuals.
- ✓ Spare part lists.

Operational Qualification [5,7]

O.Q testing verifies functionally of the computer system and acceptance of the I.Q protocol. it involves conducting a series of static and dynamic tests, which verify and document the correct operation of all continuous, sequential control parameter and graphical display elements. The following items should be evaluated:

- ✓ Signal range testing.
- ✓ Valve and motor actuation.
- ✓ PID control loop tuning.
- ✓ Interlock and timer.
- ✓ Alarm points and priorities.
- ✓ Network communication.
- ✓ Security system.
- ✓ Signal and integrated sequence
- ✓ Automatic, semi-automatic, manual operation.
- ✓ Display text, trend, and icon, link to configured device.
- ✓ Recipe parameter and values.
- ✓ Report and data achieve format.

Performance qualification.[5]

Performance qualification involves performing a number of production runs (traditionally, at least three) that are considered to be representative batch sizes for the operation. These are to be conducted using pharmaceutical product and utilizing the computer system and services of production operatives as stipulated in the URS and plant SOPs. Performance qualification testing for the computer system will include a subset of the tests performed during the IQ and OQ phases in order to demonstrate in conjunction with the plant equipment and operating procedures that the system can perform correctly and reliably to specification. Focus will be on documenting how the computer system performs in controlling, monitoring, and recording critical parameters, data, and functions, and how effective and reproducible the system is

under varying process conditions and data loading. As relevant, OQ test procedures can therefore be used for PQ testing. In particular, consideration should be given to tests directly related to data integrity and system repeatability with focus on critical parameters; for example

- ✓ System access security
- ✓ Diagnostic checks
- ✓ Operator interfaces
- ✓ Software installation verification
- ✓ Software backup and restoration
- ✓ Control and monitoring loop operation
- ✓ Alarm, event, and message handling
- ✓ Safety and operational interlocks
- ✓ Software logic functions and automatic process sequence operation
- ✓ Standard operating procedures verification
- ✓ Data records and reports.
- ✓ Power loss and recovery

CONCLUSIONS

Successful computer system validation (CSV) is highly dependent upon a quality management or quality assurance system, a formal System Development Life Cycle (SDLC), and the qualification tasks performed throughout the SDLC. CSV must establish a "level of confidence" that the system consistently meets all requirements and user expectations. From the description of the SDLC and the Qualification Phases of Validation, and the diagram on the following page, it is clear that there is a good match between the V Model SDLC and the requirements of computer system validation. As most methodologies require that specifications and test protocols are written, approved, and acted upon, it is possible to adapt the validation methodology to most situations, provided that the system requirements and functionality can be shown to be tested and proven, and that the system development, implementation, and operation is under control. Above all the system must be shown to operate correctly, consistently, and according to its specifications.

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