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A review on computer aided instrument validation

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ABSTRACT

As quality is the most important aspect of any manufacturing process, it becomes necessary to validate or examine all the peripherals connected to the manufacturing instruments used in pharmaceutical industries. Among all the peripherals connected to the manufacturing instruments, computer is the main equipment, as it controls and handles all the activities of manufacturing process starting from input to finalized output. This article explains validation processes of any computer systems to avoid any risk to product identity, purity, strength and efficacy by providing consistent and secure operation and reducing the potential of human error.

Key words: Validation, Design Qualification, Installation Qualification, Operational Qualification, Performance Qualification.

INTRODUCTION

Every Computerized System with functions that can directly or indirectly affect product quality or cause product misshipments is to be identified as a New System and Validated. Throughout these proposed validation standards, all references to computerized systems apply to such systems and include Computer-Related Systems.

Pharmaceutical product research, development, manufacturing, and distribution require considerable investment in both time and money, and computerization has become key to improving operational efficiency. To consider the close links with the manufacturing process this article will focus throughout on computer systems and the associated field input/output instrumentation required for the direct control and monitoring of the manufacturing process. Here the traditional demarcation between “real-time” and “information” systems is fast disappearing with process control and automation systems now capable of providing significant levels of data processing and management for pharmaceutical manufacturing. To achieve and

maintain validated computer systems pharmaceutical manufacturers need to include the following as part of their compliance policy. The master validation plan for each site must identify all computer systems operating in a GMP environment.

All validation document preparation and activities must be performed in accordance with predefined and approved procedures. The integrity of quality related critical parameters and data must be maintained throughout each phase of the validation life cycle, including the supplier design and development phases. Sites must operate a validation maintenance regime incorporating change control and revalidation programs. Computerized systems may simplistically be considered to exist as main application types. i.e.: process control systems, data processing systems, (including data collection/capture) and data record/ storage systems. There may be links between these three types of system, described as 'interfaces'. [1, 2]

Validation Life Cycle

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”.

Life-Cycle Models:

1) V-model

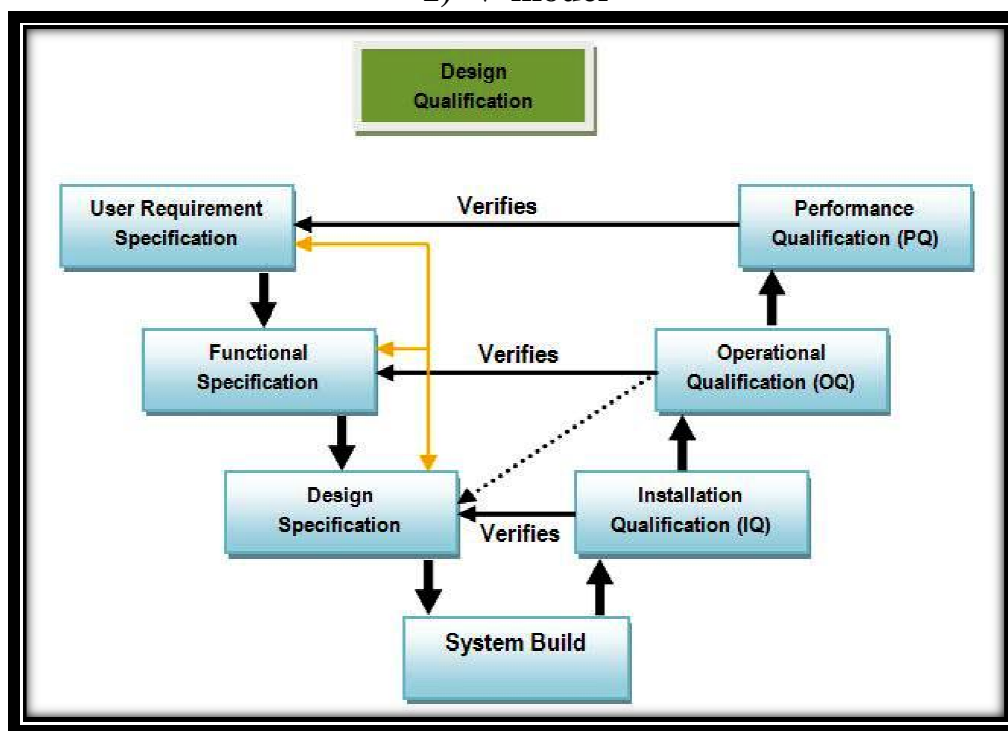


Figure:1

This model comprises of User Requirement Specifications (URS), Functional Specifications (FS), Design Specifications (DS), development and testing of code, Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (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.[2,5]

2) 4Q- model

The 4Q model is recommended with just four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The process is illustrated in Figure:2

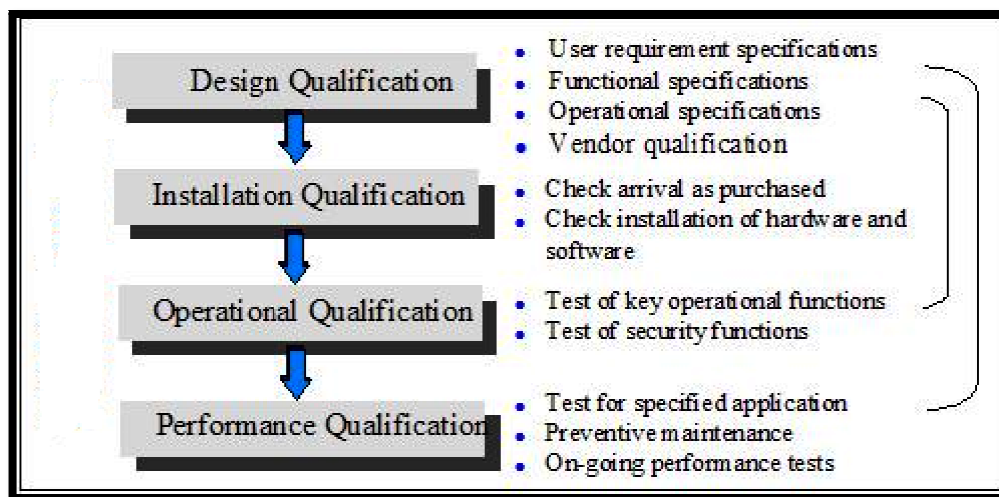


Figure: 2

Both the 4Q and the V-model do not address 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. In this case a life cycle model that combines system development and system integration is preferred. An example is shown in figure: 3. [2, 4]

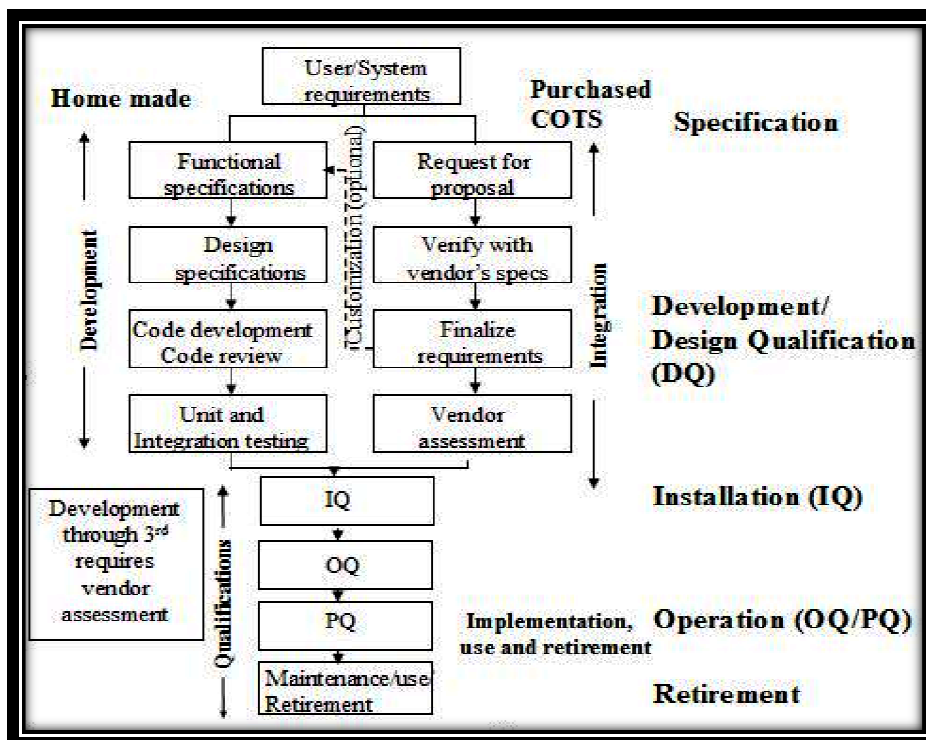


Figure: 3

User representatives define User or System Requirement Specifications (URS, SRS). If there is no vendor that offers a commercial system the software needs to be developed and validated by following the steps on the left side of the diagram. Programmers develop functional specifications, design specifications and the code and perform testing in all development phases under supervision of the quality assurance.

When commercial systems are available either the SRS or a special Request for Proposal (RFP) is sent to one or more vendors (see right side of the diagram). Vendors either respond to each requirement or with a set of functional specifications of a system that is most suitable for the user's requirements. Users compare the vendor's responses with their own requirements. If none of the vendors meet all user requirements, the requirements may be adjusted to the best fit or additional software is written to fulfill the user requirements following the development cycle on the left side of the diagram. The vendor that best meets the user's technical and business requirements is selected and qualified. The extent of validation depends on the complexity of the computer system. The extent of validation at the user's site also depends on the widespread use of the same software product and version. The more standard software is used and the less customization made for such software the less testing is required by individual users. GAMP has developed software categories based on the level of customization. In total there are five categories. Category one and two define operating systems and firmware of automated systems. In the context of this primer only category three to five are of interest [2]. They are described in Table: 1. Each computer system should be associated to one of the three categories.

Category	Description
GAMP 3	Standard software package. No customization. Examples: MS Word (without VBA scripts). Computer controlled spectrophotometers.
GAMP 4	Standard software package. Customization of configuration. Examples: LIMS, Excel spreadsheet application where formulae and/or input data are linked to specific cells. Networked data systems.
GAMP 5	Custom software package. Either all software or a part or the complete package has been developed for a specific user and application. Examples: Add-ons to GAMP Categories 3 and 4, Excel® with VBA scripts.

Table: 1

Validation Master Plan and project Plan

The planning phase is the initial phase of a project. The regulatory impact of the system must be understood, and validation activities must be included in the planning phase for regulated systems. The validation master plan is an ideal tool to communicate this approach both internally and to inspectors. It also ensures consistent implementation of validation practices and makes validation activities much more efficient. In case there are any questions as to why things have been done or not done, the validation master plan should give the answer. If the system is regulated, the system validation plan is typically started in this phase, but cannot be completed until system requirements are fully defined.[1,3]

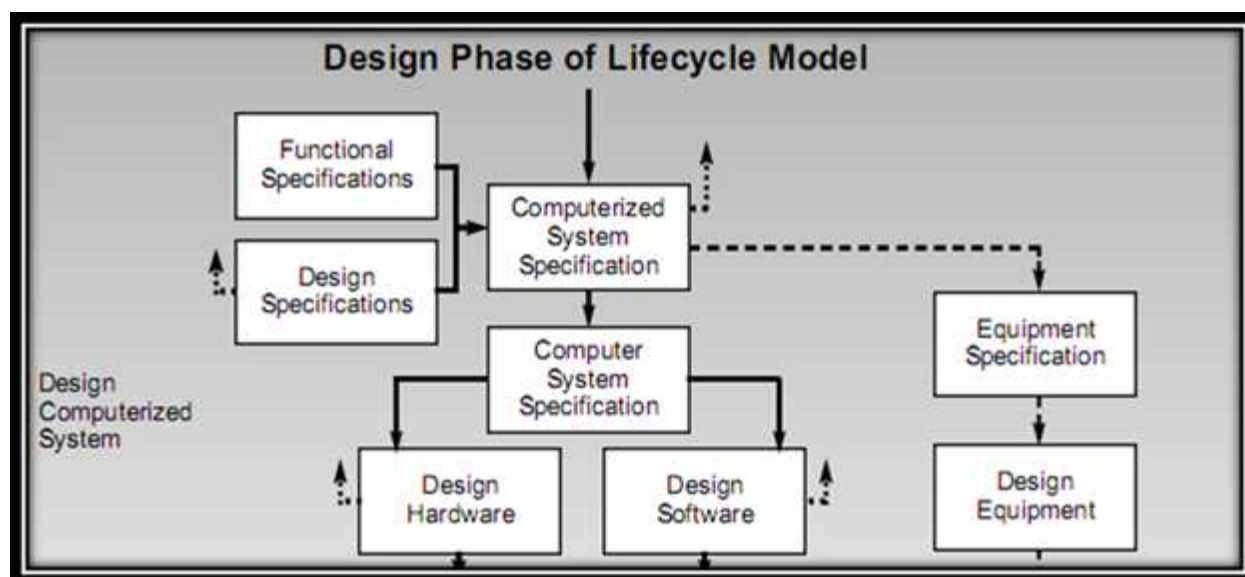
System Qualification

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.

Design Qualification

Design qualification is a formal and systematic verification that the computer system requirements specification is met by succeeding system design specifications and their implementation throughout the development and build (including development testing) activities.

Figure: 4



Documents generated for consideration in the DQ include:

- Requirements review documentation
- System design specifications
- Software design methods
- Software review(s)
- System flow diagrams
- Test procedures and records
- Software release/replication procedure
- Instrument data sheets
- System and installation drawings
- Deviation status list
- Requirements traceability matrix
- Configuration management records
- Change control records
- User operating manual
- System manager manual
- Factory Acceptance Test report
- Instrument calibration certificates
- Site Acceptance Test report

On completion of the DQ process the pharmaceutical manufacturer's qualification summary report must record the completion of the DQ and acceptance of the system at site for the in situ qualifications required by the validation lifecycle.[1,4,10]

Vendor Assessment

Validation of software and computerized systems covers the complete lifecycle of the products which includes validation during design and development. When software and computer systems are purchased from vendors, the user is still responsible for the overall validation. The objective of vendor qualification is to get assurance that the vendor's products development and manufacturing practices meet the requirements of the user's firm for quality. For software development this usually means that the software is developed and validated following documented procedures. Vendor assessment should answer the questions: "What type of assurance do you have that the software has been validated during development" or "How can you be sure that the software vendor did follow a quality assurance program?" Depending on the risk and impact on (drug) product quality answers can be derived from:

1. Documentation of experience with the vendor

Experience may come from the product under consideration or from other products.

2. External references

Useful if there is no experience within the vendor within your company

3. Assessment checklists (mail audits)

Use checklists available within your company, through public organizations, e.g., PDA and from private authors.

4. 3rd party audits

Gives an independent assessment of the quality system and/or product development

5. Direct vendor audits

Gives a good picture on the vendors quality system and software development and validation practices.[2]

Installation Qualification

Installation qualification is documented verification that the computer system (including all required software) is installed satisfactorily and is compliant with appropriate engineering codes, manufacturer recommendations, and approved specifications, and that the instrumentation is calibrated and all services are available and of adequate quality.

Documents generated for consideration in the IQ include:

- Validation file
- Security access (area and system user)
- Environmental Condition
- System diagnostics
- Hardware component
- Instrument installation and calibration
- Electrical power and circuit protection
- Loop wiring/tubing and cabling
- Hardware configuration
- Software installation
- Software backup and restoration

On issue of a satisfactory and approved IQ summary report the computer system can proceed to OQ.[1,2]

Operational Qualification

Operational Qualification is documented verification that the installed computer system operates within established limits and tolerance.

Documents generated for consideration in the OQ include:

- Operator interface and screen displays
- Input/output signals (including interfaces)
- Data storage, backup, and restore
- Electronic records and signatures, archive and retrieval
- System report printout
- Alarms, events, and messages
- Process and safety interlocks
- Control and monitoring loop operation
- Software process logic and sequence operation
- SOPs
- Power loss and recovery

Operation qualification generally represents the first opportunity for plantoperatives to use the computerized system in an operational condition and canbe used as part of production personnel’s training program on the system, plantequipment, and manufacturing process.On issue of a satisfactory and approved OQ summary report the computersystem can proceed to PQ.[2]

Performance Qualification

Performance qualification is documented verification that the computerized operation comprising the controlled process and the computer system consistently performs as intended in the user requirement specification throughout all anticipated operating ranges.

Documents generated for consideration in the PQ include:

- System access security
- Operator interfaces
- Software installation verification
- Software backup and restoration
- Control and monitoring loop operation
- Alarm, event, and message handling
- Safety and operational interlocks
- Standard operating procedures verification
- Data records and reports
- Power loss and recovery

On issue of a satisfactory and approved PQ summary report, it is demonstrated that the computer system supports the computerized operation, and conditional on satisfactory process validation is available for use in the GMP operating environment.[2]

Validation Report

When the validation project is completed a validation summary report should be generated by the system owner. The report documents the outcome of the validation project. The validation report should mirror the validation project plan and should include:

- A brief description of the system
- Identification of the system and all software versions that were tested
- Description of hardware used

Major project activities
Listing of test protocols, test results and conclusions
Statement on system status prior to release
List of all critical issues and deviations with risk assessment and corrective actions
Statement that validation has been performed according to the documented procedures
Final approval or rejection statement
The validation report should be approved by QA and the system owner. [1]

Implementation

The implementation phase comprises the activities required to coordinate the controlled and successful roll-out of the system into the production computing environment. Training takes place for technical support personnel, as well as the users of the system. Service level agreements are established with technical infrastructure personnel with respect to system availability, backup, and restoration, etc. Installation and data migration/conversion plans are developed. The implementation takes place, and a post-implementation review is conducted. Key deliverables yielded from the implementation phase typically include a production version of the application code, implementation instructions, training materials and records, service level agreements, system release authorization, and finalized user and operations manuals.[6,9]

Ongoing Evaluation

This phase of the computerized operation is usually the longest phase of the validation life-cycle, covering the operational period of the computer system in pharmaceutical manufacturing. During this period, and as relevant, the validation file must be updated with current and approved validation documentation that continues to provide evidence of a controlled and satisfactory validation life cycle and that will enable inspection readiness.

Validation File

The pharmaceutical manufacturer is responsible for maintaining the validation file and must ensure the computer system supplier(s) documentation is also up to date.

The validation file should have a file reference name and number and contain a document schedule or index with individual document titles, reference numbers, and version numbers. The file may also include electronic copies of documents (e.g., floppy discs, CD-ROM).[1]

Periodic Review

The periodic reviews will be event-based or time-based exercises. Event based reviews will normally be carried out if there is a controlled change made to the computerized operation that is outside the scope of the original validation and could impact on process or product quality attributes. This will normally be conducted in conjunction with the change control procedure and should include a review of all relevant validation documentation to determine the extent of revalidation that may be required. Time-based reviews should be planned for at defined intervals to check adherence to procedures and the currency of validation records. The frequency of reviews can vary, depending on the application, and at a minimum are generally undertaken annually. Such reviews can be supplemented by internal audits to spot-check correct use of procedures and control of validation support documentation.

For the life-cycle validation documents and any associated support documents that make up the validation file the periodic review must verify that these are approved and auditable, and maintain traceability between related documents.[1,7]

Change Evaluation

For any changes an impact assessment must be performed as defined in the change control procedure. This assessment will consider:

- Scope and rationale for the change
- Impact on product quality
- Impact on system validation status
- Requalification/revalidation actions
- Documentation to be generated
- Authorization level required

For changes to the computer system, appropriate representation from both the pharmaceutical manufacturer and the computer system supplier should be considered. The pharmaceutical manufacturer remains responsible for ensuring that the validation status of the system is maintained.[7,8]

Maintenance

The maintenance phase spans the duration of time between the initial production implementation and the retirement of the system. The validated state of the system is preserved during this phase via use of good change control and configuration management practice, as well as a robust problem reporting and resolution process.

A change history is maintained for the system and revalidation/requalification takes place when required. Key deliverables yielded from the maintenance phase typically include the system change history and associated documentation, problem logs, maintenance logs, security logs, and system logs.[9]

Retirement

The retirement phase addresses the retirement of a system from active use by the firm. When a system is retired, consideration must be given to the application source code concerning how it will be phased out, how data will be converted if applicable, how it will be stored, and how it will be available for retrieval if required.

Key deliverables yielded from the retirement phase typically include documentation covering the storage requirements for application source code and data, the retrieval process to be followed, and any hardware or other software dependencies, as well as the process by which the application will be removed from operational status including any data conversion activity, along with a schedule of execution dates and approval.[10]

Future Aspects

Increasing the efficiency of validation activities is a key factor for success in the future of computer validation. Many other methods and concepts are available when trying to increase the efficiency of performing computer validation, but they are too numerous to be included in this article. For example, consolidating the IQ, OQ, and PQ into one document can help expedite the validation exercise by decreasing the number of signatures needed for review and approval. Another example is the development of a checklist for reviewing and accepting a vendor-provided validation document. In some cases, the use of automated test tools may also help when expediting the completion of validation, although it must be carefully considered because this practice also introduces significant complexity to the process of test scripting. Another success factor is to stay abreast of developments in the areas of regulations, technology, and computer validation by joining professional organizations such as GAMP and PDA.[13,14]

CONCLUSION

Successful CSV is highly dependent upon a quality management or quality assurance system, and the qualification tasks performed throughout the lifecycle. CSV must establish a “level of confidence” that the system consistently meets all requirements and user expectations. 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.

The following Quality Management, lifecycle and Validation actions go a long way to validating a system:

- Both the lifecycle and Validation process should begin when a decision is made to proceed with high-level requirements definitions and feasibility studies, and ends when the system is implemented (accepted and live).
- Implement a quality system to control the system implementation that references the lifecycle. Adhere as closely as possible to the defined life-cycle model, supported by procedures and standards controlling system design, build, configuration and test.
- Ensure that the lifecycle activities and deliverables are fully documented, and the documentation is properly reviewed, approved, version controlled, and managed.

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