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Computer Software Validation: Importance in Pharma Industry

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ABSTRACT:
As quality is an important aspect of any manufacturing process, so is validation to these processes. Validation is one of the most important steps in the development of a quality product. Computer Software Validation (CSV) addresses the scientific correctness of the application software, the business objective of the organization and the concerns of regulatory agencies. This review highlights the importance of Computer Software Validation in the Pharmaceutical industry, its process, common issues faced during the validation and gives a glimpse on the Good Automated Manufacturing Process (GAMP) and its use in computer software validation. The principles outlined in this review is specific to each system and may vary from case to case depending on its scope and complexity.

I. INTRODUCTION:

In the Pharmaceutical industry, validation is one of the most recognized parameters important when related to the Good Manufacturing Process (GMP). The Food and Drug Administration (FDA) is bound to conduct inspections in GMP sites so as to ensure the precision, accuracy and consistency of the batches. A validated system ultimately leads to a high-quality standard product. The concept was first proposed by Food and Drug Administration in the 1970s (1). The pioneers named Ted Byers and Bud Loftus introduced it to improve the quality of the pharmaceutical product. Validation is therefore defined as the process of collecting and evaluating data to draw scientific evidence that an equipment, utility, or facility is capable of consistently delivering quality products (2).

Validation of systems has now been important because of the increasing trends in harmonization of requirements which will in coming years eventually result in a common level of expectation worldwide. It has already become an integral part of the regulatory requirements and everyday life in the global healthcare environment. It has a major role to play as it gives a sense of confidence in the quality of products for human health. This also means that the extend of risk to the patient reduces because of the validation effort and will ultimately determine its continued utility (3).

Pharmaceutical product research, development, manufacturing and distribution require considerable investment in both time and money and computerization has become key to improving these operational efficiencies (4). Validation of such systems therefore has a great impact on the final product. Pharmaceutical industry majorly relies on the four below mentioned types of validation process which ensures that the procedures, process and activities carried out is compliant at all stages.

- Prospective validation/ Premarket validation
- Retrospective validation
- Concurrent validation
- Revalidation

In recent years, the introduction of Computer Software Validation has increased the demand of computerized data handling especially in the pharmaceutical industry. Computerization has helped provide useful data management is all aspects of the industry. Owing to the increase in stringency of the guidelines, it is important that such systems be validated wherever installed (5). A majority of the regulatory authorities has made it a requirement that all GMP based processes as well as medical devices be validated from time to time.

Computer Software Validation (CSV) is basically a documented process which assures that the computer-based system will provide data that meets a set of predefined requirements. This validation helps in improvement of handling complications and adds to overall robustness of the medical device/ system, thus improving the standards of the pharmaceutical company (6). These systems directly control the system or the processes involved with it. It is a tool essential for guaranteeing overall sufficient quality control of any final product. The validation includes qualification of all software and hardware which directly or indirectly has an impact on the product (7).

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Both the European Medicines Agency (EMA) as well as the Food and Drug Administration (FDA) have produced guidelines for Computer Software Validation Practices. The FDA has released guidelines on general principles of software validation, industry computerized systems used in clinical trials and many others. FDA published its general principles on software validation guidelines in 2002. The document contains two major sections:

Section 4.8: This section discusses about the selection of validation activities, the tasks to be done, the work items that should commensurate with the complexity of the software design and the risk associated with the use of the software for the specified intended use. For lower risk devices only baseline activities should be used. As the risk of devices increases additional validation activities should be included to lower the risks associated with it.

Section 6.1: This section addresses a major question that how much validation is needed. The extent of validation evidence needed depends on the device manufacturers documented intended use of that software (8).
Also, the Pharmaceutical Inspection Cooperation scheme has published guidance on good practices for computerized schemes in GXP environments.

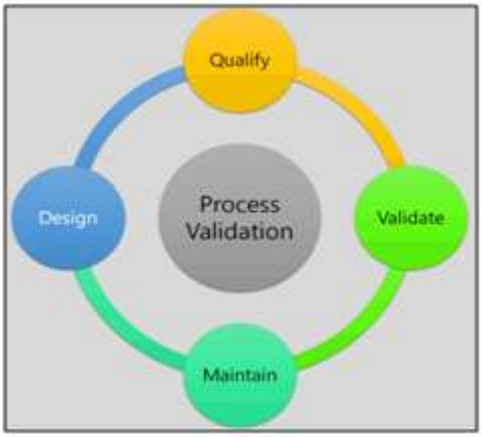

Fig 1: The essential guide to process validation

Importance of CSV:

Computer Software Validation plays an important role in the pharmaceutical industry to improve the quality of the product, to support as well as accelerate the performance of the product. The major benefit of these are evaluation of correctness of the procedure so as to decrease manual error (6). Validation is an important tool which assures that any system in a pharmaceutical company will operate within a specified parameter whenever required (8). Also, the pharmaceutical industry uses various expensive raw materials, processes, sophisticated facilities and machinery to deliver end products (1). To maintain the integrity and quality of such products, it is important to develop a robust system that meets the requirements of company standards. Now-a-days computerized systems are highly involved with the manufacturing and end process of a product. Hence, it is important to assure that these systems are functioning in an appropriate manner. This in turn is related to consistent quality of the final product (9).

Fig 2: Importance of Software validation

Not only pharmaceutical companies but recently many pharmaceutical laboratories have accepted computer system validation as an important asset. Computerisation of laboratories has increased since the introduction of these regulations which have struggled to keep up progress in documentation (9).
Benefits of effective computer software validation are listed below:

- Ability to provide all required documents readily to FDA
- Maximize the value of the computer system
- Reduce labor cost by enhancing employee efficiency and effectiveness
- Effective Project Management
- Cost-effective
- Helps in timely submissions
- Discovers defects/ faults at early stage
- Helps in risk reduction
- Promotes continual process improvement

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Apart from the above benefits, CVS can also be used to ensure evidence of testing, training, audit, review, management responsibility, design control and document control (9). Also, a good compliance system will ease the audit process and reduce the risk of non-compliance. Once confidence is gained in such a system, it develops a good foundation for management control in a company and also helps in better communication with the regulators (9).

Good Automated Manufacturing Practices:

GAMP was found in 1991 by the FDA to deal with the stringent regulations for GMP compliance of manufacturing and related systems. Its first guidance was published in 1994. The organization entered in partnership with ISPE and in 2000 became a sub-committee of the group. Today, GAMP is recognized as a regulatory guidance document worldwide (10).

Good Automated Manufacturing Practices (GAMP) is a set of guidleines for manufacturers and users of automated systems in the pharma industry (8). The guidelines provides guidance in risk managements systems as well as contributes to the development of computer systems (11). Also, GAMP is a technical subcommittee of the International Society for Pharmaceutical Engineering (ISPE) which discusses on the matters of life cycle of the product. The guideline of the most important principles of GAMP i.e., quality cannot be tested into a batch of product, it must be built into each stage of manufacturing process. Hence, GAMP covers all aspects of production, from the raw materials, equipment, training to the hygiene of the staff (10).

GAMP aims to deliver a cost-effective framework of good practice to ensure that computerized systems are effective and of high quality, fit for intended use and compliant with applicable regulations (12). The five key concepts to GAMP 5 are as follows:

- Product and Process Understanding
- Lifecycle approach within QMS
- Scalable Lifecycle Activities
- Science based Quality risk management
- Leveraging Supplier involvement (10)

The general principles that should be considered for software validation are listed below:

1. Requirements: A documented software is incomplete without a checklist for validation and verification.

2. Defect prevention: The software system must itself not contain any defect and should assure needs to focus on preventing introduction of defects into the software. Hence, software testing is a necessary activity. However, in most cases software testing by itself is not sufficient to establish confidence that the software is fit for its intended use.

3. Time and effort: For the software to be validated, it requires time and effort. Hence, the preparation of software validation should begin early i.e., during the design and development of the product.

4. Software life cycle: Software life cycle can be termed as a cost-effective and time-efficient process that the development teams use to design and build the software. It contains documentation and software engineering tasks to complete the validation process.

5. Plans: The entire software validation process is developed according to a strategic plan. It plans "what" has to be accomplished through the software validation process.

6. Procedures: After a plan is made, certain procedures are to be followed to complete the software validation process. These procedures establish "how" to conduct the validation effort.

7. Software validation after a change: Due to complexity of the software, even a minor change can have a major impact on the output of the product. In such cases, the validation of the software system needs to be re-established. Whenever software is changed, a validation analysis should be conducted not just for validation of the individual change, but also to determine the extent and impact of that change on the entire software system.

8. Validation coverage: Validation coverage should be based on the software's complexity and safety and risk factors. For low risk products, baseline activities should be carried out. For high risk products, the validation system should provide additional coverage.

9. Independence of review: An independent validation review provides accurate information regarding the product.

10. Flexibility and Responsibility: Specific implementation of all the above principles can vary depending on the product and system to be validated. The device manufacturer has the flexibility of choosing the right principles for its devices at the same time the responsibility that the system has been validated lies with the manufacturer alone. Software is designed,

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developed, validated, and regulated in a wide spectrum of environments, and for a wide variety of devices with varying levels of risk. FDA regulated medical device applications include software that:

· Is a component, part, or accessory of a medical device;

· Is itself a medical device; or

· Is used in manufacturing, design and development, or other parts of the quality system (13).

Process of Computer System Validation:

The validation system should primarily address the scientific correctness of the installed software, the business objective of the organization and the concerns of the regulatory authorities. It is a balance between all the three systems which ensures that the system is practical, cost-effective and must develop confidence that the system is under control (9).

Effective process validation contributes significantly to assure drug quality. The principles relies that the drug product produced should be fit for its intended use. Hence, the understanding of the following conditions to incorporate into the product is a must:

- Quality, safety and efficiency are designed or build into the product.
- Quality can be fully assured by in-process and finished-product inspection.
- Each step of manufacturing need to be controlled to assure that the finished product meets all quality requirements (14).

The validation of a product along with its process demonstrates that the end consumer is satisfies with the product and has assurance that the process has taken place within the intended operational environments with validation performed by the concerned person whenever applicable,

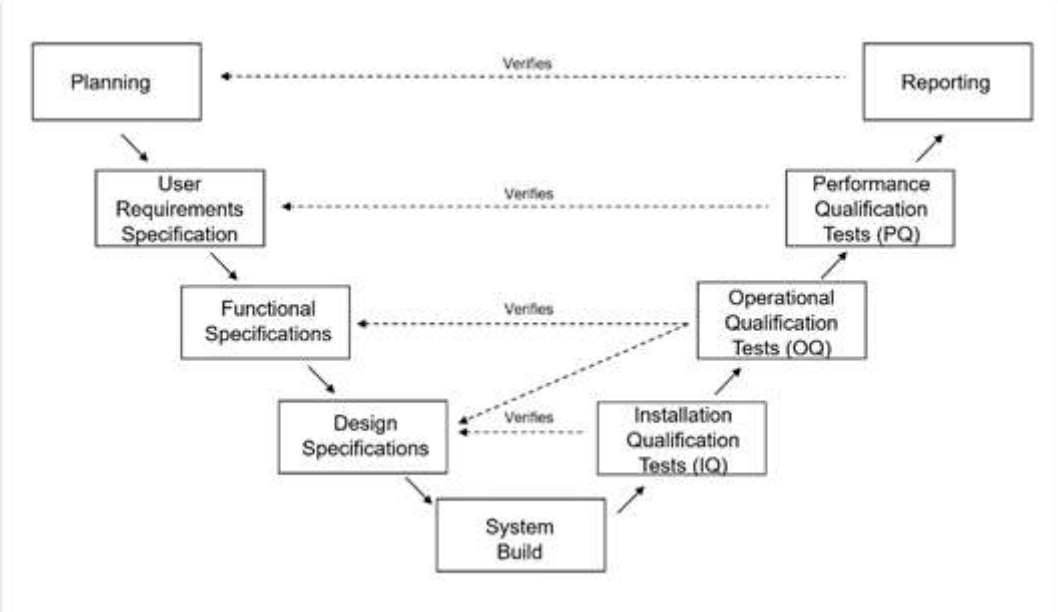

Fig 3: Generalized Process (V model) of Computer Software Validation

The GAMP guidance document outlines activities in a typical software life cycle model including the following:

1. Quality planning: During the design and development phase of a product, it is necessary to have a quality plan ready for the required software so as to identify risks and take necessary actions at an early stage. The quality plan should include:

- The specific tasks for each life cycle activity
- Enumeration of important quality factors
- Methods and procedures for each task
- Task acceptance criteria
- Criteria for defining and documenting outputs
- Inputs for each task
- Output from each task
- Roles, resources and responsibilities for each task

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- Risks and assumptions
- Documentation of user needs

The quality planning must also include typical tasks such as Risk Management Plan, Configuration Management Plan, Software quality assurance plan, Problem reporting and resolution procedures and other support activities.

2. System and software requirements specification: Requirements development include identification, analysis and documentation of information about the device and its intended use. Typical system and software requirements are specified below:

- All software system inputs
- All software system outputs
- All functions that the software system will perform
- All performance requirements that the software system will meet
- The definition of all external and user interfaces, as well as any internal software-to-system interfaces
- How users will interact with the system
- What constitutes an error and how errors should be handled
- Required response times
- The intended operating environment for the software
- All ranges, limits, defaults, and specific values that the software will accept
- All safety related requirements, specifications, features, or functions that will be implemented in software

The typical tasks should include Preliminary Risk Analysis, Traceability Analysis, Description of User Characteristics, Listing of Characteristics and Limitations of Primary and Secondary Memory, Software Requirements Evaluation, Software User Interface Requirements Analysis, System Test Plan Generation, Acceptance Test Plan Generation, Ambiguity Review or Analysis.

3. Software design specifications: In the design process, the specifications need to be translated into a logical and physical representation of the software. It is basically a representation of what the software should do and how it should do. The software design specification should include the following:

- Software requirement specifications
- Software risk analysis
- Development procedures
- Systems documentation
- Hardware to be used
- Parameters to be measured
- Logical structure and logical processing steps
- Data structures and data flow diagrams
- Definition of variables
- Error, alarm and warning messages
- Supporting software
- Communication links
- Security measures
- Any additional constraints not identified in the above elements.

Apart from these the typical tasks include Updated Software Risk Analysis, Traceability Analysis, Software Design Evaluation, Design Communication Link Analysis, Module Test Plan Generation, Integration Test Plan Generation and test design generation

4. Construction or coding: Software can be constructed either by coding or by assembling parts of previously coded software for use in a new application. Coding involves the detailed design specification implemented as a source code. After the source code is developed its traceability analysis should be done and documented to verify the following:

- Each element of the software design specification has been implemented in code
- Modules and functions implemented in the code can be traced back to an element in the software design
- Test for modules and functions can be traced back to the source code.

The typical tasks involve traceability analyses, test cases to source code and to design specification, source code and source code documentation evaluation, source code interface analysis, test procedure and test case generation.

5. Testing: Software testing involves running software products under known conditions with predefined inputs and documented outcomes that can be compared further. Software testing involves time, and is difficult to perform. The principles for software testing includes:

- The expected test outcome is predefined
- A good test case has a high probability of exposing an error
- A successful test is one that finds an error
- There is independence from coding
- Both application and software testing is employed
- Testers use different tools from coders
- Examining only the usual case is insufficient

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- Test documentation permits its reuse and an independent confirmation of the pass/fail status of a test outcome during subsequent review.

Typical tasks in testing software by the developer includes Test Planning, Structural and functional test case identification, traceability analysis, Unit test execution, Integration and functional test execution, system test execution, acceptance test execution, test results evaluation, error evaluation/resolution and final test report.

6. Maintenance: The term maintenance differs when used for both software and hardware. This is because their error mechanisms are different. Hardware maintenance typically includes preventive hardware maintenance actions, component replacement, and corrective changes. Software maintenance includes corrective, perfective, and adaptive maintenance but does not include preventive maintenance actions or software component replacement. Maintenance tasks includes the following:

- Software validation plan revision
- Anomaly evaluation
- Problem identification and resolution tracking
- Proposed change assessment
- Task iteration
- Documentation updating (13).

Common Computer Software Validation problems:

The validation of Computer systems has a lot of problems associated with it. Some of the common problems are listed below:

1. Standard: Each organization works as per its own standard operating procedure. Even policies, procedures, work instructions and templates vary as per business, department or site. These overlapping SOPs and inconsistent standards make it difficult to maintain a standard for Computer Software Validation.

2. Interpretation: A significant cost to validation projects is caused primarily by inconsistent interpretation of standards and requirements by various authors and reviewers. Most regulations include very stringent guidelines but do know mention the procedures to follow them.

3. Organization and Governance: Many companies still have decentralized governance and uncontrolled execution. Thus, the validation tasks vary from project to project and one department to the other. Also, it depends on the team handling the projects.

4. Efficiency across sites and departments: Site-to-site and from one department to other, the efficiencies have been seen to differ. There are many cases where multiple sites using the same system and procedures have been differed as there is no sharing of inventory and project information.

5. Execution: Most of the times excessive rework is done by the validation team in order to get consistent results. This leads to inconsistent quality of work as different opinions and styles are involved. Also, junior as well as well experienced senior reviewers bring a lot of change in the style of execution of a project.

6. Tools: System life cycle asset such as documents, templates, outlines, forms, etc are often inconsistent across departments, sites and organization. Differences in these systems are majorly because these tools are not targeted to drive value.

7. Training: Training in the pharmaceutical company regarding the approaches to the validation is usually conducted in a timely manner. But the standard and processes regarding the procedure requires coaching and guidance which is minimal. The short training provided is rarely enough to qualify individuals without coaching until they get hands on training.

8. Personnel: Many pharmaceutical companies have capable, knowledgeable central validation groups but weaker decentralized execution groups. Organization believes that simply reading the Standard Operating Procedures and receiving a few hours of training can build the gap to a consistent approach (2).

II. CONCLUSION:

This paper discusses the importance of Computer Software Validation, its generalized process, the common problems associated with it, and the Good Automated Manufacturing Process. Successful regulatory inspection of a pharma industry is a crucial process. Success of these inspections depends on the quality and integrity of data provided to auditors during inspection. Computer system validation and qualification of equipment is an important tool to establish and maintain data integrity controls though out the data life cycle.

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