White Paper on A Practical Risk-Based Approach to Computerized System Validation
Table of Contents

Overview ........................................................................................................................................................................... 3  
Industry Challenges & CSV Expectations........................................................................................................................... 3  
Need for a Risk-Based Approach to CSV .......................................................................................................................... 3  
Industry Guidance to Risk-Based Approach in CSV .......................................................................................................... 4  
Applying Risk-Based Approach to CSV ........................................................................................................................... 5  
Risk-Based Approaches for Different Categories of Computerized Systems: ...................................................................... 7  
A Practical Risk-Based Approach to CSV .......................................................................................................................... 8  
Summary and Conclusion .................................................................................................................................................. 10  
References ........................................................................................................................................................................ 10  


Overview

Computerized System Validation (CSV) is a process of achieving and maintaining compliance with applicable GxP regulations and fitness for intended use by the adaptation of principles, approaches and life cycle activities within the framework of validation plans and reports & by the application of appropriate operation controls throughout the lifecycle of the system.

Pharmaceutical and Life Sciences industries witness constantly evolving stringent regulations & requirements of CSV by major regulatory authorities such as USFDA, EU, Japan Regulatory Authority & others. Hence, validation services have become an integral part of the business requirements across these industries.

This whitepaper provides an overview of the CSV expectations of industry to overcome the challenges associated with Software Validation & its Compliance. It provides a road map of best practices for practical risk management methods during the CSV process which is gaining wider acceptance across the globe.

Industry Challenges & CSV Expectations

As computer systems are diverse w.r.t. the criticality, complexity, novelty and business impact, the level of risk involved and the validation required for each of the computerized systems varies. At the same time, the industry is prone to face many challenges to adhere to constantly evolving stringent regulations and also, to minimize the risk of system failure due to product innovation & business process integration.

Major practical challenges of a regulated industry are:

- Decentralized CSV governance and uncontrolled CSV execution. CSV execution challenges lead to significant costs, resulting from overlapping SOPs, inconsistent documentation standards and excessive rework.
- Different opinions and styles of project team members are magnified by poor project management, lack of ownership, and a slow escalation and resolution process.
- Lack of metrics to measure the effectiveness and contribution to quality and compliance of their CSV work.
- On-time deployment of qualified & skilled resources across multiple projects

Hence, the current expectation of industry towards CSV activities has exceeded furthermore from the past to overcome the challenges efficiently and minimize the risks associated with computerized systems and to maximize the resource utilization in a productive way. Few such expectations from CSV activities include:

- Efficient Quality Risk Management throughout the project lifecycle
- A good understanding of the product & business processes involved
- Ability to relate the impact of business processes on the related regulations and quality attributes affecting patient safety, product quality & data integrity
- Adopting a framework for evaluating the impact of regulations while allocating adequate effort to mitigate the risk
- Leverage supplier involvement/documentation with scaleable life cycle activities

Need for a Risk-Based Approach to CSV

Increasing costs and the need to reduce unwanted costs; along with the increased focus on regulations have led organizations to adopt the risk-based approach to validation.

The FDA and other regulatory authorities (e.g., EMEA, MHRA, MHLW) are encouraging the industry to adopt a risk-based approach to CSV and compliance with Electronic Record/Electronic Signature (ER/ES) regulations.
However, the business remains unclear wherever a risk-based approach is needed. Often, firms see risk-based compliance as another value, not as a chance to integrate risk management with business method improvement and cut back compliance prices.

In fact, it appears that unclear and overlapping standards, a poorly-structured quality system, many interpretations and opinions, lack of experience, poor execution and failing project management turn compliance efforts to agonizing projects with limited value add to quality.

Most companies agree on the mechanical aspects of risk management (e.g., methodologies, documentation, processes), but are not clear about how to apply risk management to CSV and how to get benefit from it.

Provided a proper input w.r.t. business process, system components along with a skilled resource, a risk-based approach can yield a fruitful result and benefits the business not only in terms of cost but also meets the regulations.

Industry Guidance to Risk-Based Approach in CSV

The ICH guidance for industry, Q9 Quality Risk Management, describes a systematic approach to quality risk management and suggests an organized method for the assessment, control, communication, and review of risks for general application within pharmaceutical industry. International Society of Pharmaceutical Engineers (ISPE) GAMP 5 has also issued guidance on how to adopt a risk-based approach to validation based on the various categories of software in consideration. The industry will focus more on the GAMP 5 guidance on the risk-based approach and its implementation. The ISPE GAMP5 guidance is aligned to the ICH Q9 guidance and both suggest the use of risk assessment as the key input to deciding the extent and effort for validation. GAMP5 suggests the identification and evaluation of risks throughout the life cycle of the software. Key risk areas must be identified, and efforts must be focused only on the point of risk unless like traditional approach of “validate everything”.

Comparison of Traditional and Risk-based Validation Approach:
Applying Risk-Based Approach to CSV

In general, CSV process and the related activities are based on the GAMP5 framework, as it provides an excellent and pragmatic approach for CSV which when followed will ensure the computerized systems are fit for the purpose, meet the needs of business and compliant with current regulations.

The range of activities required to validate a computerized system is determined based on the GAMP5 software and hardware categorization, GxP impact, applicable ER-ES requirements and its risk-based lifecycle approach. Quality risk management is a systematic program starts with the identification of the risks associated with a product or process, its assessment, implementation of appropriate controls, communication and review of risks. It is a strategic process used throughout the life cycle of computerized system from concept to retirement phase to ensure the safety, integrity, quality and compliance. It is an iterative process used throughout the entire computerized system life cycle from concept to retirement.

The primary principles for quality risk management are:

- Identification and evaluation of risk to computer system quality should be based on scientific knowledge which is ultimately link to the patient safety.
- Determination of the effort required to validate the system to efficiently address the risks.

**Step 1: Perform Initial Risk Assessment and Determine System Impact**

An initial risk assessment is performed based on an understanding of business process and business risk assessments, user requirements, regulatory requirements and known functional areas.

The results of this initial risk assessment will include a decision on whether the system is GxP regulated (i.e., GxP assessment). It also includes an overall assessment of system impact. Based on the initial risk assessment and
resulting system impact, the subsequent steps of the process will be performed.

The specific level of effort, formality and documentation of any subsequent steps is determined based on the level of risk and system impact. A relevant regulated ER-ES is also identified in this step.

---

**Step 2: Identify Functions with Impact on Patient Safety, Product Quality and Data Integrity**

Functions which have an impact on patient safety, product quality and data integrity is identified by building on information gathered during step 1 and referring to relevant specifications by considering the project approach, system architecture and categorization of system components.

The risk will be measured against the key Critical Quality Attributes (CQA) of the business process that could impact patient safety, product quality and data integrity and apply adequate risk management techniques based on risk priority.

- **Patient Safety:** E.g., Incorrect amount of active pharmaceutical ingredient present in the finished product due to failure of the CS.
- **Product Quality:** E.g., Inefficient tracking and delayed alert of a product recall due to failure of the CS.
- **Data Integrity:** E.g., 1. Incorrect clinical or laboratory results generated due to CS failure. 2. Confidential data leaked to the public due to security defects of the CS.

---

**Step 3: Perform Functional Risk Assessment and Identify Controls**

Functions identified in step 2 is assessed by considering possible hazards and how the potential harm arising from these hazards will be controlled by following FMEA (Failure Mode Effective Analysis) method.

During this step, a more detailed assessment is performed to further assess the severity of the harm, likelihood of occurrence and probability of detection and find out the risk priority.

The judgment as to whether to perform detailed assessment for specific functions is dealt with a case-by-case basis and the criteria will vary widely. The criteria to be considered include:

- Criticality of the supported process
- Specific impact of the function within the process
- Nature of the system (e.g., complexity and novelty)

Appropriate controls are identified based on the assessment. Following are the few controlling measures to overcome the identified risks:

- Modification to the process design
- Modification to the system design
- Procedural control
- Having more detailed specifications
- Increasing the frequency and quality of design reviews
- Improving the rigour of verification activities
Wherever possible, elimination of risk by its design is the preferred approach.

**Step 4: Implement and Verify Appropriate Controls**

The control measures identified in step 2 is implemented and verified to ensure that they have been successfully implemented. Controls are traced to the relevant identified risks.

The verification activity will demonstrate that the controls are effective in performing the required risk reduction.

**Step 5: Review Risks and Monitor Controls**

During periodic review of systems or at other defined points, the risks are reviewed. The review will verify that the controls are still effective and corrective actions are taken under change management if the deficiencies are found. Other points to be considered during the review are whether:

- previously unrecognized hazards are present
- previously identified hazards are no longer applicable
- the estimated risk associated with a hazard is no longer acceptable
- the original assessment is otherwise invalidated (e.g., following changes to applicable regulations or change of system use)

Where necessary, the results of the evaluation are fed back into the risk management process. If there is a potential that the residual risk or its acceptableness has modified, the impact on formerly implemented risk control measures will be considered, and results of the evaluation is documented.

The frequency and extent of any periodic review is based on the level of risk.

**Risk-Based Approaches for Different Categories of Computerized Systems:**

Risk-Based Approach for Non-configured product (Category 3):

Risk-Based Approach for Configured product (Category 4):
A Practical Risk-Based Approach to CSV

If we look at CSV efforts in most of the life science companies, they are reasonably compliant; they provide limited business value relative to the amount of investment in CSV activities; they concentrate on CSV and testing; the focus is on GxP and ER/ES regulations; their scope is limited to a project or application; and they are based on a checklist-driven process.

A mature CSV process should be based on a harmonized and integrated quality and compliance management system that is not only compliant but also lean. It must provide a value to the business by contributing to quality and control. The quality and compliance management system must address all applicable regulations and business needs. The validation efforts must be optimized by focusing on the key and critical functionalities to ensure that the key business risks are addressed.
By following a detailed risk-based approach as outlined in the below diagram, one can optimize the efforts based on the risks associated with the system at different phases of validation life cycle.

A single risk-assessment methodology for all types computerized system validation is not applicable in all situations. Therefore, the best, most prudent and cost-effective approach is to be selected with appropriate methodology rather than adopting a one size fits all approach.

Therefore, the following approach to risk assessment and risk management are advocated:

- **The non-configurable (COTS) applications and configurable COTS applications should use a simplified risk analysis methodology and focus only on testing the system against its intended use, rather than the entire functionality it could offer while leveraging the vendor validation/testing documents.**

- **The highly configurable and customized applications should use FMEA as the best risk analysis methodology. But, the configurable applications focus only on testing the correctness of the configuration and test the intended use of the system whereas customized applications focus on both functional and design level testing.**

Any identified risks that cannot be verified through testing or the system controls in place should be addressed by means of process controls through standard operating procedures. Any gaps identified in the validated state of the system must be reviewed and closed during reporting.

A metrics must be maintained in which the measurements of resources and costs invested in CSV activities are considered and it must also reflect the gains in quality, shorter review cycles, fewer critical change controls and less rework after the audits. All such measurements will contribute to monitor and drive the improvements.
Summary and Conclusion

The implementation of best practices is likely to vary from one company to another due to differences in the severity of the problems, organizational challenges, priorities associated with on-going projects, and skill sets of the individuals involved. Whether looking at CSV from a compliance management characteristic or Software Lifecycle perspective, the adoption of a practical risk-based validation approach offers good opportunities for increasing the levels of quality and regulatory compliance while reducing CSV costs with optimal utilization of resources.

References

- Guidance for Industry – Part 11, Electronic Records; Electronic Signatures – Scope and Application (August 2003 Pharmaceutical CGMPs)
- http://www.pharmacompliancemonitor.com
- https://www.gxp-cc.com/it-embedded-systems.html
- https://www.fda.gov/downloads/medicaldevices
- https://www.fda.gov/RegulatoryInformation/Guidances/ucm125067.htm
- https://www.fda.gov/iceci/inspections/inspectionguides/ucm074869.htm

About the Author:

Lavanya G, Associate Manager – CSV at iMEDGlobal Solutions India Pvt. Ltd. an FMD K&L Company. With a professional career of 13+ years, she is being providing CSV services to Life Science & Pharma Industries with a domain knowledge of Validation & Compliance. She is proficient in CSV process, Risk & Issue Management, Implementation of QMS methodologies & maintaining the Quality related attributes in-line with GxP guidelines and regulations.