COMPUTER SYSTEM ASSURANCE (CSA)

Whitepaper for Industry implementation

ISPE Special Interest Group [SIG]

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Contents

1. Purpose

The purpose of this white paper is to provide guidance for the industry on the key concepts of Computer Software Assurance and provide direction to apply rational and critical thinking and commensurate it with risk associated with product quality and patient safety.

This document takes into consideration challenges with the current computerized system validation approach and proposes methods to overcome the obstacles through the Computer Software Assurance.

This document is outcome of deliberations of a special interest group of professionals from ISPE GAMP INDIA steering committee.

2. Scope

Scope of this document is to provide guidance and sample templates that are required for implementation of Computer Software Assurance for the benefit of the industry. This document does not intend to replace or override the current regulatory requirements for Computerized System Validation.

3. Background of CSA

Over the last decade, innovation and technology has emerged with tremendous speed and brought the industrial revolution (Industry 4.0) through smart manufacturing and automations. The Pharmaceutical industry has adopted most of the technological innovations such as Artificial Intelligence and Machine learning, Big Data & Analytics, cloud computing, Robotic Process Automation, 3D Printing, Virtual Reality and Augmented Reality, IoT(Internet of Things) and Tele radiology, etc. which is now known as Pharma 4.0

The traditional computerized system validation process was conceptualized prior to this technology evolution and being updated to some extent but is not able to cope up with industry expectations. The lack of expertise, understanding of the technology and over thinking makes the traditional computerized system validation process as prolonged activity.

In process of addressing this issue, theUS FDA launched Case for Quality Program in 2011 following an in-depth review to understand the barriers for Medical Device quality.

This program mainly focused on Validation of Software in Medical Devices guidance (released in 2002) which is intrinsicpart of Medical Device Quality.

The final report has following key facts including.

- An analysis of root cause data revealed that failures in product design and manufacturing process control caused more than half of all product failures or recalls.
- Companies perceive that the regulatory framework is misaligned with assurance of quality outcomes, in that compliance with regulations does not ensure quality, and that current intervention practices may de-incentivize improved quality.

The "Case for Quality" helps to understand the gaps between the USFDA expectations and industry practices. This report lays down the improvements from the industry and from the USFDA to align with each other to focus on Product quality and Patient safety.

In the Year 2015, USFDA in coordination with Siemens-Fresenius executive exchange identified computerized system validation process as a barrier to implement technologies across the pharmaceutical and health care industries. Later, in the Year 2016, an industry working team was formed for development and establishment of Computer System assurance program across the industries.

In consideration of industry feedback, USFDA included the CSA Guidance release in FDA's list for 2021. This Guidance provides more robust and sophisticated methodologies for implementation of Computer System Assurance.

4. Industry Common CSV Pain Points

USFDA and Industry working group of Computer System Assurance (CSA) identified the common pain points of the industry in implementation of new technologies with traditional CSV methodology.

Table 1 CSV Common Pain Points

S. No	Barrier	Description
I.	Deterrent to pursuing automation	The volume of documentation and complex process of computerized system validation deter the rate of investment (ROI) on implementation of new technologies and automation.
II.	Gathering evidence for auditors	The lack of knowledge and understanding on the regulatory expectations on CSV forced the industry to collect the evidence for each function in the computer system beyond the intended scope to please the auditors. This process of gathering the evidence doubles the CSV process implementation time.
III.	Duplication of vendor efforts at client sites	The failure in exploring the product and supplier maturity and inexperience in communication with vendor results in customer to repeat the activities, during implementation of computerized systems onsite.
IV.	Burdensome and complex Risk Assessments	The traditional risk assessments are applied beyond the scope of intended requirements, shifting the focus to unintended mitigations, burdensome testing, and implementation of unnecessary controls.
V.	Testing documentation and errors	It is observed that high number of deviations in the testing occurs due to the test script errors and the time spent on correction and resolution of these errors does not add any additional value to actual computer system.
VI.	Numerous Post- Go Live Issues	Despite spending huge amount of time on creation of validation documentation and testing, numerous Post-Go live issues are observed.

5. New Approach to Validation

AUTOMATION: USFDA supports and encourages automation as it has the potential to improve productivity and efficiency, help in tracking and trending, plus a host of other benefits. Manufacturers can gain advantages from automation throughout the entire product lifecycle. They can reduce or eliminate human errors, optimize resources, and reduce patient risk. USFDA's position is that using these software products can be an excellent way to enhance product quality and patient safety, which in the end, is the overarching goal.

CHANGING THE PARADIGM: Current industry practice as part of CSV program is documentation heavy. Documentation is done at the expense of critical thinking and testing. CSA brings paradigm shift in this approach by encouraging critical thinking over documentation. By using CSA concepts, companies can execute more testing with less documentation based on risk associated with requirement.

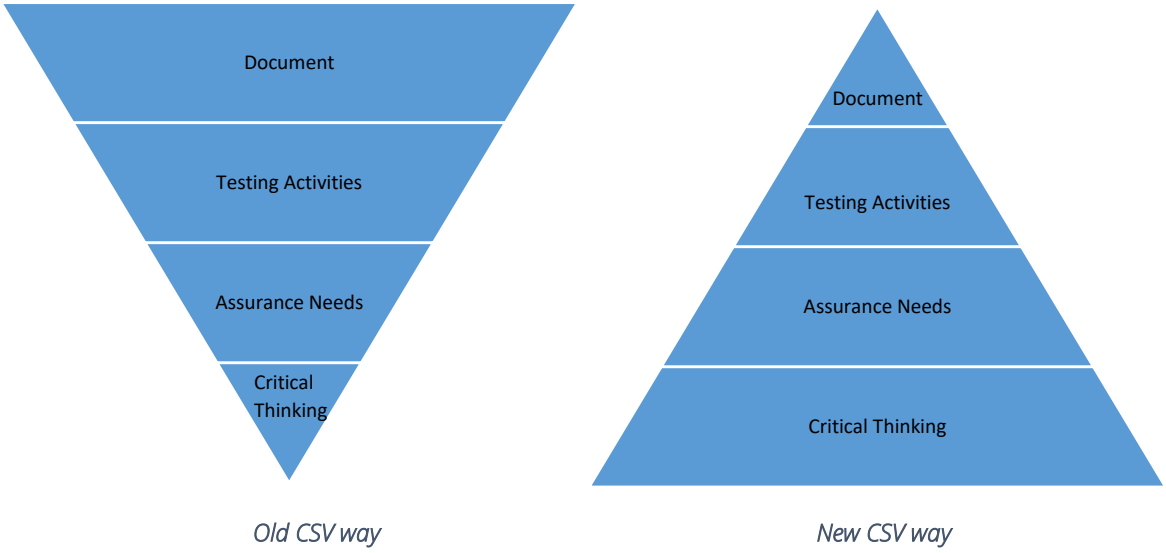

Figure 1 Paradigm Shift from CSV to CSA

LEVERAGE VENDOR DOCUMENTATION: Perform vendor assessment and based on outcome leverage vendor executed testing during designing the validation strategy of the product. If the vendor demonstrates, a strong QMS then the validation strategy can be optimized to validate the delta and high-risk scenarios.

RISK RATING: CSA recommends the following streamlined risk assessment process, which aims to perform risk-based testing at requirement level (refer section 7 for more details)
This simplified approach includes only two variables:

- Requirement's potential impact on product quality and patient safety.
- Implementation method of the Requirement.

UNSCRIPTED TESTING: Unscripted testing liberates a tester from following click-by-click level test script and allows the tester to conduct free-form testing and documenting the results. Unscripted testing includes Ad-hoc and Exploratory Testing (refer section 8 for more details)

6. Computer System Assurance Key Drivers

Regulatory & Industry Initiative: CSA is a collaborative effort to address the issues, developing a joint understanding and providing a path forward, which is efficient & meets the goals of all stakeholder in the pharmaceutical industry. The biggest beneficiary being the patient.

Clarification from Regulators: The Regulators have provided clarification & guidance in many aspects of software qualification. Many areas are now clearly understood. The legacy understanding of the process which was inefficient by the industry now needs to be changed as per the new clarification & guidance to make the process efficient.

Appropriate Records: One of the key drivers of CSA is the appropriate level of testing & supporting records. FDA has clarified that it does not expect huge documents for test execution; appropriate level of test & supporting documents should be created as required. Appropriate level of testing should be performed based on Risk assessed for the computer system functionality.

Optimized Efforts: The CSA necessarily may or may not bring down the time taken to validate but it will optimize the effort of validation to invest time and resources for better quality.

Pilot studies have shown desired results: The CSA process as discussed and agreed by the stakeholders has been executed at a pilot level and the results are encouraging in line with the expectations.

Supports Digitalization Drive: CSA approach encourages the use of automation tools for the qualification activities. Many products are available in the market & these tools make the process of record capturing efficient but also furthers the company's digitization efforts.

7. CSA Risk Management Approach

CSA approach recommends specific testing types for each risk rating. Detailed step wise process is explained below. In section#9, Risk Rating template has been provided which can be used.

Step 1: Determine potential impact on product quality and patient safety from functionality failure for each user requirement point. This should be done by a group of SMEs involved in the project & should have representation from appropriate departments.

Table 2: Potential Impact

Impact on Product Quality/Patient Safety	Description
HIGH	• Severe impact on product quality • A failure with potential to cause irreversible damage to patient
MEDIUM	• Moderate impact on product quality • A failure with potential to cause temporary harm/ reversible damage
LOW	• Minor Impact on product quality • A failure with potential to cause indirect impact or minor harm
NONE	• No impact on product quality • No consequences on patient health

Step 2: Determine the functionality's Implementation method for each requirement point.

Table 3: Implementation Method

Implementation Method	Description
CUSTOM	Bespoke / custom developed or programmed to meet URS
CONFIGURED	Configured using out of box features to meet URS
OUT OF BOX	Out of box features meet URS

Step 3: Determine functionality's Risk Rating, based on the product quality/patient safety & Implementation method for each requirement.

Table 4: Risk Rating

Impact on Product Quality/Patient Safety	Implementation Method		
	OUT OF BOX	CONFIGURE	CUSTOM
HIGH	3	4	5
MEDIUM	2	3	4
LOW	1	2	3
NONE	1	1	1

Step 4: Follow recommended testing activities

Table 5: Testing Activities

Risk Rating	Testing Activities Functionality Validated by
5	Requirement validated through Robust scripted testing
4	Requirement validated through Limited scripted testing
3	Requirement validated through Unscripted testing
2	Requirement validated through Ad-hoc testing
1	Relies on vendor audit and base line assurance

8. Types of Testing

The main intent of CSA is to shift focus from more documentation to testing of software and early detection of system issues especially those having impact to product quality and patient safety. In this regard, CSA suggests executing following different types of testing during system validation:

a. Testing Types

Specific types of testing will be required based upon the requirements risk rating (impact and implementation method of each requirement):

- Intensive Testing: includes normal testing and in addition challenges the system's ability with respect to various factors as below.
- Repeatability Testing challenges the system's ability to repeatedly do what it should.
- Performance Testing challenges the system's ability to do what it should as fast and effectively as it should, according to specifications.
- Volume/Load Testing challenges the system's ability to manage high loads as it should. Volume/Load testing is required when system resources are critical.
- Structural/Path Testing challenges a computerized system's internal structure by exercising detailed program code.
- Regression Testing challenges the system's ability to still do what it should after being modified according to specified requirements, and also verifies that portions of the computerized system not involved in the change were not adversely affected.

- Normal Testing covers Positive Testing and Negative Testing. This type of testing challenges the system's ability to do what it should do according to specifications and prevent what it should not do according to specifications.
- Exploratory Testing is unscripted testing. Tester will test the system to achieve the defined goal and will use critical thinking, common software behaviors and types of failures
- Ad hoc Testing is an unscripted testing performed without any planning or pre-defined documentation and will be done based on experience and knowledge of the system by SMEs.

b. Recommended testing activities

Table 6: Testing Type

Risk Rating	Testing Activities Functionality Validated by	Testing Type
5	Requirement validated through robust scripted testing	Intensive Testing
4	Requirement validated through limited scripted testing	Normal Testing
3	Requirement validated through unscripted testing	Exploratory Testing
2	Requirement validated through unscripted testing	Ad hoc Testing
1	Relies on vendor audit and base line assurance	Leverage vendor documents

Note: If vendor management is not in place, requirements determined as Risk Rating 1 should be considered as Risk Rating 2 and Ad-hoc testing can be followed

c. Assurance approach and acceptable record of results

Following table explains the assurance approach as per the risk rating and the acceptable forms of evidence.

Table 7: Assurance Approach

Assurance Approach	Test Plan	Test Results	Testing Evidence
Intensive Testing(Scripted)	• Test objectives • Detailed test cases (Step by step) Expected results	• Pass/fail for test case • Details regarding any defects/ deviations found and their disposition	• Detailed report of assurance activity • Result for each test case - only indication of pass/fail • A screen capture or other printed evidence that makes clear the result of execution • Defects found and disposition • Conclusion statement • Tester name and date of testing
Normal Testing(Scripted)	• Limited test cases (Step by step) • Expected results	• Pass/fail for test case • Details regarding any defects/ deviations found and their disposition	• Detailed report of assurance activity • Result for each test case - only indication of pass/fail • A screen capture or other printed evidence that makes clear the result of execution • Defects found and disposition • Conclusion statement • Tester name and date of testing • Signature and date of appropriate signatory authority
Exploratory Testing(Unscripted)	• Establishing high level goals to	• Pass/fail for test case	• Summary description of features and functions tested

Assurance Approach	Test Plan	Test Results	Testing Evidence
	meet requirements • (Step by step procedure not required)	• Details regarding any failures/ deviations found	• Result for each test plan objective –only indication of pass/fail • Defects found and disposition • Conclusion statement • Tester name and date of testing • Additional evidence such as screen shots or detailed recording of actual outcomes during testing is not required for systems having an audit trail facility
Ad-hoc Testing(Unscripted)	• Testing of features and functions without any test goal(Plan)	• Details regarding any failures/ deviations found	• Summary description of features and functions tested • Defects found and disposition • Conclusion statement • Tester name and date of testing • Additional evidence such as screen shots or reports not required if systems has Audit trail functionality.

Note1: Above testing strategies can be adopted for Installation Qualification, Operational Qualification and performance qualification or PQ can be done following limited scripted testing approach, it is important that the adopted approach is documented by the organization in Project Validation plan or SOP.

Note2: If new change is having additional requirements, testing strategy shall be determined based risk rating approach

9. Model Templates

a. Risk Rating template

Table 8: Risk Rating Template

S. No	Requirement Description	Impact on Product Quality/ Patient Safety	Implementation Method	Risk Rating	Test Specification

b. Exploratory testing template

Table 9: Exploratory Testing Template

Functional Requirement	Update the functional requirement based on Risk assessment E.g. : Access Management
Assurance Testing Type	Update the assurance testing type based on Risk rating
Requirement number	Map the requirements covered in this test case
Goal	Ensure goal must cover all requirements mapped in RTM
Testing Activity	Ensure testing activity must cover all the requirements mentioned in the Goal
Conclusion	Issues found and disposition /Update the defects identified during Testing
Test Pass/Fail	If all requirements met mentioned as pass
Tested by (Sign & Date)	Sign/Date

c. Ad-hoc testing template

Table 10: Ad-hoc Testing Template

Requirement number	Map the requirements covered in this test case
Testing Activity	Testing activity is summary of testing
Conclusion	Issues found and disposition /Update the defects identified during Testing
Tested by (Sign & Date)	Sign/Date

d. Scripted Testing Template

Table 11: Scripted Testing Template

Test ID:		**ENVIRONMENT:**	QUALITY: ☐	PRODUCTION: ☐
TEST TITLE: User Access and privileges				
TEST OBJECTIVE: To verify user access and privileges functionality of the system				
REQUIREMENT NUMBER: XXXXX				
PREREQUISITES: IQ installation must be completed and approved Authorized user setup must be completed				
ACCEPTANCE CRITERIA: Actual results should match with expected results				

Step	Procedure	Expected Results	Actual Results	Pass/ Fail	Initials/ Date
1.				☐ Pass ☐ Fail	
2.				☐ Pass ☐ Fail	

Note: Above mentioned Ad-hoc, exploratory and scripted testing templates are for test cases and can be include in IQ/OQ/PQ protocols and need pre and post approvals.

10. Changes from Existing Validation Approach

Every company needs to evaluate their existing SOPs & make the required changes to adopt the CSA approach. At a very high level the boxes highlighted in orange colour below are the one that will be impacted in terms of procedure & templates. A company can also do a pilot to implement CSA by taking the protocol approach defining the process to be followed and update the SOPs/Templates at a later stage post success of the pilot project.

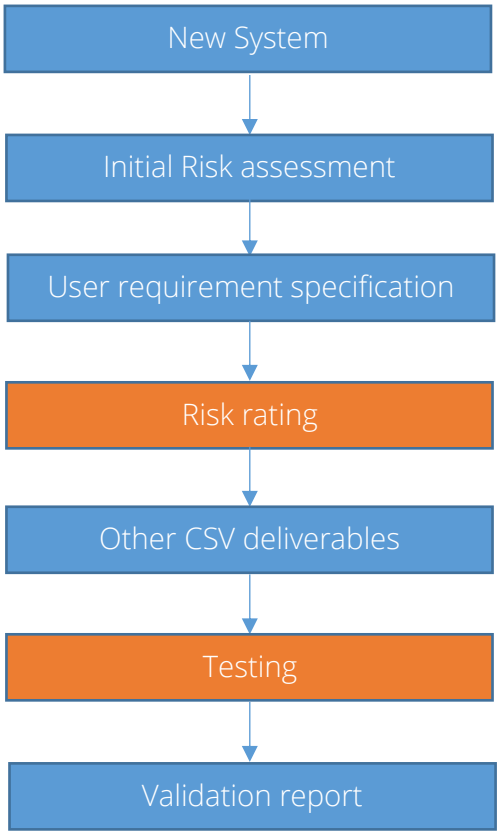

Figure 2: Changes from CSV to CSA

11. Summary

The foundation of CSA is the application of critical thinking by knowledge and experience. The assurance activities within the quality system should be meaningful and add value. This white paper provides detailed knowledge on CSA concepts and it encourages organizations to move towards automation with least burdensome Validation assurance approach to ensuring product quality and patient safety.

12. Examples

a. Electronic Document Management System

CSA approach was applied for all requirements to identify the type of testing, some are mentioned below

Table 12: Examples

Req. IDs	Requirement Description	Impact on Product Quality/Patient Safety	Implementation Method	Risk Rating	Testing Type
UR-01	System should maintain all drafts related to a Document for future reference	None	Out of Box	1	Leverage vendor documents
UR-02	System only displays latest version of document (Eg. SOP) in learning management system to users, during training	None	Configured	1	Leverage vendor documents
UR-03	System should send notification for SOPs, due for periodic review to author	None	Configured	1	Leverage vendor documents
UR-04	The 'status' of the document should be marked diagonally across as 'watermark' on all pages. E.g. Draft/ approved	None	Customized	1	Leverage vendor documents

b. SCADA system for product filtration tank:

CSA approach was applied for all requirements to identify the type of testing and some are mentioned below

Table 13: Examples

Req. IDs	Requirement Description	Impact on Product Quality/Patient Safety	Implementation Method	Risk Rating	Testing Type
UR-01	System controls the equipment parameters such as temperature/ pressure, etc as per the monitored values/ feedback.	Medium	Out of Box	2	Unscripted - Ad-hoc Testing
UR-02	System should raise alarm with notification any deviation in actual parameters from set point out of tolerance limits	Medium	Configured	3	Unscripted Testing- Exploratory Testing
UR-03	System should display the status of all equipment in dashboard view	Low	Configured	2	Unscripted - Ad-hoc Testing
UR-04	System should be able to export the parameter value data for selected interval in non-editable format	Low	Configured	2	Unscripted - Ad-hoc Testing
UR-05	System must have ability to provide multiple access levels and assign user rights and privileges.	Low	Configured	2	Unscripted - Ad-hoc Testing
UR-06	System must allow the administrator to add, modify and deactivate user access.	None	Out of the box	1	Leverage vendor documents

c. Particle Size Analysis with Instrument

CSA approach was applied for all requirements to identify the type of testing and some mentioned below

Table 14: Examples

Req. IDs	Requirement Description	Impact on Product Quality/Patient Safety	Implementation Method	Risk Rating	Testing Type
UR-01	System should measure particle size of sample within accuracy limits	High	Configured	4	Scripted – Limited Testing
UR-02	System should allow the user to edit the permissible range of particle size for each batch	Low	Configured	2	Unscripted - Ad-hoc Testing
UR-03	System should display the testing	Low	Out of Box	1	Leverage vendor documents
UR-04	System should be able to export the particle analysis report	Low	Out of Box	1	Leverage vendor documents

13. References

- GAMP5 A Risk-Based Approach to Compliant GxP Computerized Systems
- ISPE GAMP ROI Good Practice Guide, Data Integrity by Design, Appendix S2- Computer Software Assurance
- FDA Power Point Presentation and Knowledge Sharing Webinars

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