An Expert Panel Discussion on Best Practices When Transitioning from CSV to CSA

What the upcoming Computer Software Assurance guidance means for life sciences companies

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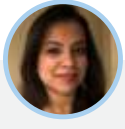

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INTRODUCTION

During a 2011 review of medical device quality data, the US Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) noticed a variety of widespread manufacturing risks that were impacting product quality. A few of these risks included:

- An industry focus on regulatory compliance as opposed to adopting best quality practices;
- Lack of adoption of automation and digital technologies, with manufacturers choosing, instead, to continue running long-outdated versions of software; and
- Virtually no competitive market around medical device quality.

After obtaining feedback from FDA and industry stakeholders, the CDRH launched their Case for Quality initiative. The intent of this initiative was to identify issues withing current manufacturing practices and help medical device manufacturers raise their manufacturing quality level by shifting their focus from being compliance oriented to what really mattered—improving product quality.

One of the key findings of the FDA's Case for Quality initiative was that the burden of Computer Systems Validation (CSV) was deterring technology investments and, as a result, inhibiting quality best practice. To address this, the CDRH, in collaboration with the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER), is planning to release a new guidance document entitled 'Computer Software Assurance for Manufacturing and Quality System Software' (CSA). The guidance was initially expected to be published in 2020 but was delayed due to COVID-19. The FDA is expected to formally release the CSA guidance in 2022.

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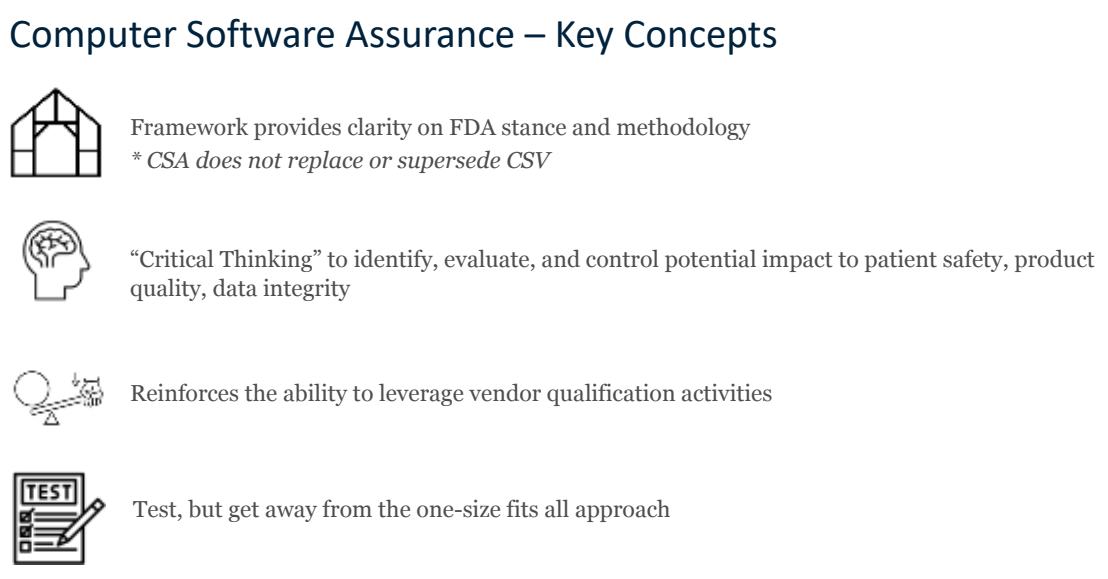
CSV TO CSA: DRIVERS, KEY CONCEPTS, AND BENEFITS

Today, CSV processes typically focus on producing accurate and approved system lifecycle documentation and testing to present information to the FDA and other third-party auditors. Since auditors expect to see this evidence and records, the CSV methodology has resulted in a documentation heavily focused mindset to demonstrate compliance with regulatory expectation rather than an innovative one. The FDA has recognized that too much time is being spent generating documentation that was to be used during audits. It was estimated that roughly 80% of the current CSV efforts are focused on generating documentation, whereas 20% of the efforts are allocated to testing. While documentation will always be a vital part of the CSV process, the FDA recognizes that it is more important to have a safe, high-quality product that meets patient needs.

The intent of the upcoming CSA guidance is to support product quality and patient safety by emphasizing critical thinking in the validation process. The FDA wants manufacturers to utilize critical thinking and spend 80% of their time applying the right level of testing to higher-risk activities, with only 20% of time spent on documentation. The emphasis should be on identifying those critical items that actually impact product quality and are based on the intended use of the system. This frees up both testing and validation resources to allow more value-add activities to occur.

The CSA guidance is not aimed at replacing CSV, but on clarifying the FDA's expectations regarding the level and extent of qualification or validation that needs to be completed (**FIGURE 1**). By shifting the focus of CSV processes toward critical thinking, risk management, patient safety, product quality, data integrity, and quality assurance, the CSA approach will create opportunities for streamlining documentation. For example, CSA encourages companies to leverage vendor qualification activities rather than repeating these activities on premise and, wherever possible, to apply the use of automated testing, which minimizes the need for human resources and shortens the timeframe required to validate software systems.

FIGURE 1: Expectations regarding the level and extent of qualification or validation that needs to be completed.



One of the common threads in the industry is that the resources that are involved in the impact assessment activities for a CSV project often are not familiar with the business process and/or the intended use of the system. Critical thinking requires that the validation project team consist of applicable subject matter experts who understand the system being validated and know the points within the process where there is inherent risk. This will ensure that the high-risk aspects of the system functionality and business process are appropriately challenged, rather than applying an unnecessary one-size-fits-all approach.

To further clarify the degree of CSV testing needed, CSA encourages a risk-based approach to CSV for product versus non-product software, and for direct versus indirect systems (**FIGURE 2**). Product software is software used in any of the following: a medical device, Software as a Medical Device (SaMD), a Medical Device as a Service (MDaaS), or an end-product. It includes all software used in manufacturing, operation, and quality system activities that would follow 21 CFR Part 820.70(i). In turn, direct systems have a direct impact on patient safety and/or product quality and may require increased testing based on risk. Indirect systems do not have a direct impact on patient safety or product quality, and therefore require less documentation.

CSA supports a streamlined risk assessment approach. Previously, risk assessments were typically performed using the Failure Mode & Effects Analysis (FMEA) approach. The FMEA approach can be useful for trying to identify risks with a particular feature or function, but there often is some degree of ambiguity within the criteria being evaluated. In particular, there is a large gray area with respect to detectability, which may result in some features or functions being rated a higher risk than they actually are. Risk assessment by FMEA involves determining the overall risk of a particular part of a process according to three variables: severity, probability, and detectability. In contrast, CSA focuses on only two variables: the impact to patient safety and/or product quality, which is paramount to anything involved in the risk

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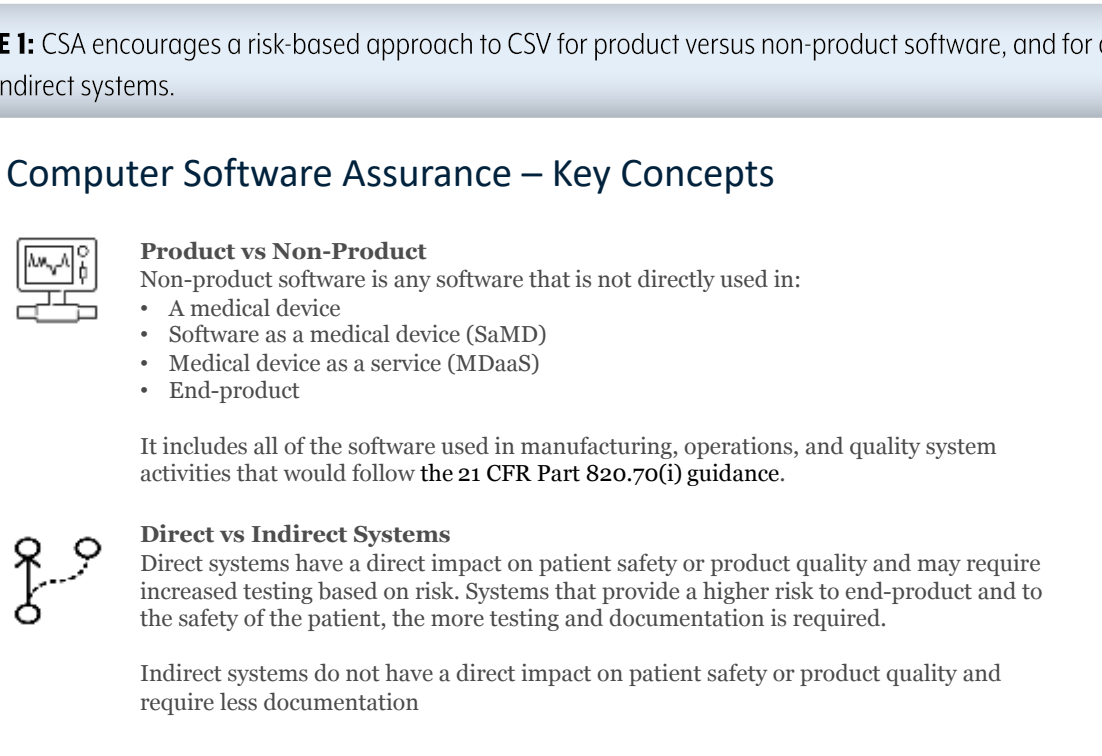

assessment process; and the implementation methodology, which concerns how a given feature or function is being met (i.e., whether the process is out-of-the-box, configured, or customized).

The risk assessment is a key opportunity to leverage the vendor qualification documentation. As part of that assessment, it is essential to complete a vendor risk assessment, which includes examining the vendor's software development lifecycle, validation documentation process, and adherence to quality management system procedures. If adequate controls are in place, as demonstrated by documented evidence, there is no reason to duplicate the operational qualification testing for the out-of-the-box, base level functionality of a system.

Test scripts present another opportunity for streamlining when following the CSA approach. For higher risk (direct) systems, scripted testing has been the traditional approach. This entails identifying a specific objective, providing detailed step-by-step instructions for challenging the objective, and identifying expected results. The tester needs to record actual results and to generate objective evidence (e.g., screenshots or reports) showing that the system meets its intended use. For lower risk (indirect) systems or features, where software does not directly impact the product or patient safety but does impact the quality system, CSA allows for the use of unscripted testing. Testing is executed without the use of detailed test scripts. When using this approach, there needs to be test objectives and pass/fail criteria, but a step-by-step test procedure is not required. There may only be indication within the steps in the script for a particular tester to carry out certain actions or to verify certain items within the system. By decreasing the level of documentation for unscripted testing, the project team will be able to complete the testing more quickly (**FIGURE 3**).

PREPARING FOR CSA

In order to prepare for the transition to CSA, companies should develop a change management strategy to plan for revisions that will be needed to policies and procedures to

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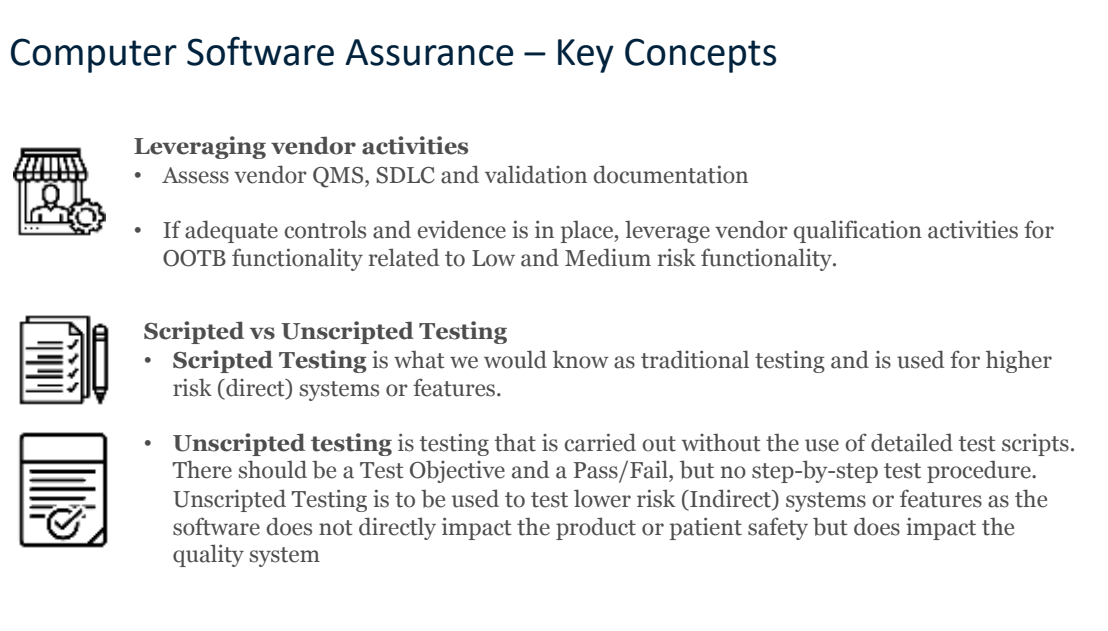

close any gaps between the current CSV approach and CSA. The change management strategy should address how updated roles and responsibilities will be communicated to key stakeholders and it should ensure that stakeholders who own the business processes are included in the user acceptance testing to ensure the systems meet their intended use. In addition, it will be important to enhance the supplier qualification and external auditing processes to enable leveraging of vendor validation packages in lieu of duplicate testing.

The biggest challenge for transitioning to the CSA approach is that old habits die hard. It usually takes time for employees to adopt a new way to computer system validation and testing. Even though many organizations believe that the CSV testing they employ is risk-based, the approach they actually use for testing is often risk averse. This translates into authoring, reviewing, approving, and executing a large volume of formal test scripts, when there may not be a need for formal test scripts for all requirements and functionality. Effective adoption of CSA across the organization will require a significant cultural shift which can be achieved through education, communication and training. In addition, it will be critical to ensure that there is top-down senior management awareness and endorsement of the change.

To further ensure that the CSA process is fully implemented, the CSA approach needs to be incorporated into relevant training programs to ensure that everyone has the same understanding on how CSA is being implemented. In addition, updated processes need to be audited internally to ensure that they are properly implemented and work as intended, in that potential failures impacting patient safety, product quality, and data integrity are being detected through the testing.

CONCLUSION

As indicated in the CSA guidance, significant benefits can be realized by following the critical thinking process, updating the risk assessment methodology, involving subject matter experts, and leveraging vendor qualification documents for out-of-the box, base level functionality. The benefits include a reduction in documentation and costs, and an overall reduction in the implementation timeline for CSV projects (**FIGURE 4**).

FIGURE 4: CSA benefits.

Although the CSA guidance has not yet been published, the CSA framework is acceptable under the current guidelines and there is encouragement from the FDA to leverage this guidance even prior to its release. As the FDA prepares to release the CSA guidance, life sciences companies need to be proactive and develop a strategy on how to transition from their current CSV methodology to CSA—a methodology that focuses on software assurance but, most importantly, ensuring that life sciences companies are developing products or drugs that are focused on patient safety and are of high quality.