WHITE PAPER:

Computer System Assurance – The Digital Era of FDA Compliance

Compliance for Digital Transformation

Nearly a quarter of a century has passed since the U.S. Food and Drug Administration (FDA) established regulations on electronic records and electronic signatures, commonly known as 21 CFR Part 11, under which they are considered trustworthy, reliable and equivalent to the traditional paper records. The regulations provide guidance for organizations that maintain records or submit designated information electronically to the FDA, requiring computer system validation, audit trails, and record retention guidelines necessary for regulatory compliance.[1]

While these regulations remain in effect, the informatics landscape has progressed and evolved significantly beyond the scope and intentions of the current code. The emergence of cloud based computing, artificial intelligence (AI), machine learning (ML) applications and SMART technology necessitate a paradigm shift in the current approach to computer system validation.

With digital transformation initiatives progressing in nearly every scientific based organization, digitization and automation of entire laboratory processes create additional challenges within the scope of computer system validation. While these efforts surrounding digitization have impacted nearly every aspect of the modern laboratory, computer system validation has remained at a steady state since the early 2000's. This creates a substantial barrier to fully realizing the digital lab of the future.

The Case for Quality

The current approach to computer system validation in FDA regulated environments focuses heavily on testing and documentation to demonstrate the systems are performing as intended to meet a set of pre-defined requirements. The time, cost, and resources required to achieve and maintain regulatory compliance can be burdensome and impractical for many organizations. These measures are critical to satisfying compliance regulations, however, they seldom converge with the equally important aspects of quality manufacturing practices.

One of the top priorities for FDA's Center for Devices and Radiological Health (CDRH) is a focus on high quality products which will better protect and promote public health. To facilitate this effort, the FDA launched the "Case for Quality" program in 2011. Following an in-depth review of medical device quality data and feedback from industry stakeholders, the FDA identified certain widespread and common

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manufacturing risks impacting product quality. The analysis concluded that manufacturers who identified and proactively managed those risks required less preventive and corrective actions, fewer investigations, and demonstrated less quality related product issues.[2]

The FDA's Case for Quality program is therefore designed to drive innovation in regulated environments by focusing on measures to manufacture high quality products and devices rather than creating validation documentation to satisfy traditional computer system validation requirements for regulatory compliance. Increased product quality can also lead to a more effective FDA submission review process, and therefore faster time to market.

The Future of FDA Compliance

In the new era of digitization, the approach to regulatory compliance must also evolve to keep pace with current advances in technology. In response to this growing need for change, the FDA has embarked on two additional initiatives that recognize the importance and impact of the digital revolution.

In September 2020, the FDA launched their new Digital Health Center of Excellence (DHCoE). With the tagline of "Empowering digital health stakeholders to advance healthcare", their goal is to accelerate digital health advancements by fostering responsible, high-quality digital health innovation while providing efficient and less burdensome oversight while meeting FDA standards for product safety and efficacy.

In a January 2021 white paper, the FDA describes AI and ML technologies as "having the potential to transform health care by deriving new and important insights from the vast amount of data generated during the delivery of health care every day. Medical device manufacturers are using these technologies to innovate their products to better assist health care providers and improve patient care. One of the greatest benefits of AI/ML in software resides in its ability to learn from real-world use and experience, and its capability to improve its performance. FDA's vision is that, with appropriately tailored total product lifecycle-based regulatory oversight, AI/ML-based Software as a Medical Device (SaMD) will deliver safe and effective software functionality that improves the quality of care that patients receive."[3]

To further align their efforts with the changing digital landscape and revised ISO 13485 standards, the FDA's Center for Devices and Radiological Health (CDRH) is preparing new draft guidance, "Computer Software Assurance for Manufacturing, Operations, and Quality System Software" that shifts the paradigm away from compliance towards a quality based approach that embraces automation and new innovative technologies such as AI and ML.

"All ISO standards are reviewed every five years to establish if a revision is required in order to keep it current and relevant for the marketplace.

ISO 13485:2016 is designed to respond to the latest quality management system practices, including changes in technology and regulatory requirements and expectations.

The new version has a greater emphasis on risk management and risk-based decision making, as well as changes related to the increased regulatory requirements for organizations in the supply chain."[4]

- International Organization for Standardization (ISO)

Computer System Assurance – The New Approach to Validation

The emphasis on quality standards as the governing measure for computer system performance provides the foundation for the new approach to validation – computer system assurance (CSA). This new risk based

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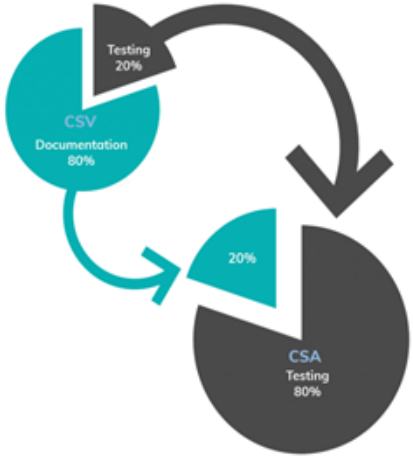
approach focuses testing on areas having a direct impact on product quality and patient safety and less on the compliance-centric approach of CSV. Computer system assurance can be divided into two risk based testing categories:



(Geaney, Kneat, 2020)[5]

- **Unscripted testing:** Used for testing low risk systems or features that do not directly impact product quality or safety. The testing is carried out without the use of detailed scripts and testing procedures with the objective of a Pass/Fail rating outcome of the testing.
- **Scripted testing:** Used for testing high risk systems or features that may have a significant impact on product quality or safety. The testing is based upon well-defined test scripts and procedures with an outcome of expected results and a Pass/ Fail rating.

As with traditional CSV testing, any failure or deviations from expected results require the necessary documentation and corrective action procedures to be employed. Factors that facilitate CSA methodology rely on vendor audits and software documentation in addition to the use of automated validation testing to reduce the in-house testing burden for lower risk systems.

The primary principles of CSV as compared to CSA can be summarized as follows:

Functional Area	Computer System Validation (CSV)	Computer System Assurance (CSA)
DEFINITION	Process of developing assurance that a computerized system does exactly what it is designed to do in a consistent and reproducible manner through documented evidence	Process of applying critical thinking combined with a risk-based approach and developing a new framework to assure quality, patient safety, and data integrity
APPROACH	Risk-based approach applying different validation methodologies, such as Waterfall, Agile, Scrum and/or Hybrid	Risk-based approach with emphasis on critical thinking, applying automated/unscripted testing and digital technologies
BENEFIT	Documented evidence that system is fit to purpose	Refocus on software quality, new technologies, reduced documentation, and increased automated/unscripted testing, with emphasis on quality assurance, patient and product safety, and data integrity
RISK	Lack of documented evidence and extensive system testing	Implementing automated/unscripted testing and new technologies unproven

(Warner, Pharmaceutical Online, 2020)[6]

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By leveraging the vendor's quality systems and unscripted testing for validating low risk systems and components, the paperwork and testing burden can be reduced by nearly 80%, allowing you to focus on the more critical quality based aspects of your processes or manufacturing systems.

Conclusion:

Bridging the gap between science and technology is essential to foster today's digital transformation revolution in FDA regulated environments. The adoption of new technologies drives scientific innovation, bringing new therapies and advancements in medicine to market faster while improving product safety and efficacy. The FDA recognizes that outdated regulatory compliance requirements, such as current computer system validation standards, hinder the forward progress of science and create financial and resource burdens on life science organizations.

To address this disparity, the FDA's plans to release the "Computer Software Assurance for Manufacturing, Operations, and Quality System Software" document in FY2021, providing revised guidance for a risk based, quality approach to regulatory compliance. Computer System Assurance is the new compliance framework for the digitally transformed laboratory of the 21st century. The progressive efforts taken to date by the FDA to establish 'the Case for Quality' and 'the Digital Health Center of Excellence' substantiate their commitment in support of digitization and automation.

With these fundamental changes on the horizon impacting the validation strategy that has been in place for the past quarter century, organizations must incorporate this new 'critical thinking' in their approach to regulatory compliance to emphasize risk management, quality assurance, and data integrity throughout their product development lifecycle. This investment in long term quality measures results in increased product quality, reduces development and manufacturing costs, and streamlines the FDA submission process, thereby accelerating time to market and ultimately the advancement of scientific innovation.

References:

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[5] D. Geaney, "What is Computer Software Assurance (CSA) and why are the FDA transitioning from traditional Computer System Validation", Kneat, Sept.2020, What is Computer Software Assurance (CSA) and why are the FDA transitioning from traditional Computer System Validation? | Kneat, accessed Jun. 8, 2021.

[6] K. Warner, "Are You Ready? FDA's Transition From Computer System Validation To Computer Software Assurance", Jun. 2020, RCM Technologies, Pharmaceutical Online, Are You Ready FDA's Transition From Computer System Validation To Computer Software Assurance (pharmaceuticalonline.com), accessed Jun. 8, 2021.

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