White Paper

MasterControl™

How Necessity Led to a New Validation Methodology and Innovative Tool

By Erin Wright[1]

Just as necessity is the mother of invention, it was out of necessity that the U.S. Food and Drug Administration (FDA) required software validation for life science companies. The agency's analysis of over 3,000 device recalls between 1992 and 1998 showed that a staggering 79 percent of those cases were caused by software defects. It was the tipping point that led to the issuance of "General Principles of Software Validation; Final Guidance for Industry and FDA Staff" in 2002.[2]

In this guidance, the FDA stated that software validation must be "commensurate with the risk posed by the automated operation,"3 but the agency didn't specify the methods for successful validation. Although the guidance addressed the medical device industry, other life science companies follow the same principles.

In 2003, the FDA issued a guidance pertaining to the application of 21 CFR Part 11. The guidance reinforced the importance of risk-based validation, stating: "We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety."[4]

Outside of the FDA, there are two notable guidances pertaining to software validation. One of them is the European Union's "Annex 11: Computerised Systems," which was updated in 2011 to specify that risk management should be applied.[5]

The pharmaceutical industry's "GAMP 5: A Risk-based Approach to Compliant GxP Systems," published in 2008, likewise offered a framework of good practice to ensure that computer systems are "fit for use," but it did not prescribe a method.6 Although this document focuses on automated manufacturing processes, life science companies use it as a guide for validation efforts outside of manufacturing.

The abovementioned guidances are not regulations and they don't mandate software validation, but they are key to compliance because they provide best-practice principles and explain why validation matters.

The Meaning of Computerized System

What does a "computerized system" mean within the context of regulated companies? Definitions vary. On the one hand, GAMP refers to it as hardware and software. On the other hand, the FDA defines the term as hardware, software, people, and procedures/processes.

This can cause confusion when purchasing off-the-shelf software and deciding whether it needs validation, according to Janis Olson, vice president of regulatory and quality services at EduQuest.7 "GAMP's category is based on the standalone product, while the FDA's concept of validation assessment is based on intended use of the product," said Olson, whose 22-year career at the FDA includes supervising the NDA/ANDA Program for the FDA's Atlanta District. She gave the

example of Microsoft Word, which regulated companies can use off-the-shelf for SOPs. “While you wouldn’t need to validate Microsoft Word on its own for word processing, you would want to validate the document management software system you are using to make sure it’s compatible with MS Word,” she explained.

Risk Assessment in Validation

Although there’s no single definition of “computerized system,” there is a consensus among regulatory bodies when it comes to the importance of risk assessment as the basis of software validation.

The FDA’s 2002 guidance stated: “Validation coverage should be based on the software’s complexity and risk—not on firm size or resource. The selection of validation activities, tasks, and work items should be commensurate with the complexity of the software design and the risk associated with the use of the software for the specified intended use.”[8]

In the FDA’s Part 11 guidance, the agency emphasized risk assessment in three areas: validation, audit trail, and record retention. It stressed the need to comply with predicate rules and to base validation on justified and documented risk assessment.

As for the European Union’s Annex 11, it stated: “As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.”[9]

No Prescribed Validation Method

Now more than ever, regulated companies rely on software in design, testing, manufacturing, complaint handling, and other processes that impact product safety and efficacy. And yet, none of the guidances prescribe specific validation methods for them to use. “Historically, regulatory bodies do not give specific guidance on how a company should define or calculate risk,” said Olson. “Regulatory agencies recommend using the risk management techniques appropriate to the task and to the company. They do not want to restrict risk assessment or risk management to a few risk assessment tools.”

However, Olson said regulators recommend reviewing certain standards and guidelines, such as ISO 14971:2007 10 (considered by the FDA as a recognized consensus standard) and ICH Q9 11 (adopted by the FDA).

The lack of a specific method for either calculating risks or performing validation has always been a source of uncertainty in the industry. Olson cited a viable formula proposed by Ludwig Huber in Pharmaceutical Technology.12 Huber proposed calculating risk this way:

(Business Impact + Safety + Compliance Impact) × Probability of Occurrence = Risk Factor.

Validation Burden

At MasterControl, we have seen up close the struggle of life science companies in complying with software validation requirements. For most of them, validation is a major burden in terms of time, cost, and manpower. Most of our clients have a firm understanding of the predicate rules, but due to the varying philosophies and comfort levels with computer system validation (CSV), we still see a wide variation in approaches to system validation across our client base.

The biggest problems we see when implementing MasterControl with our clients is understanding the true risk of software usage. I have had clients want to test every single configured item of the software. This doesn't always add value to the validation of the system. Once we've proven a configured route functions as expected, we can do a visual inspection of the rest of the route configurations to ensure they will work. We don't have to test the functionality of each route.

Another common issue is making a distinction between functional and usage testing. MasterControl performs a full internal functional validation of our software and provides it to our clients as part of their validation package. Some clients want to add the same functional testing to their usage testing, which duplicates validation efforts. In our client usage testing, we ensure the configuration of the software works for their intended production usage. By duplicating the functional testing, we are adding to the physical weight of the validation, but not necessarily adding value.

MasterControl Validation Excellence

Our search for ways to streamline and improve the validation process for our clients led us to the development of an innovative approach and tool for software validation in 2017. Our methodology, MasterControl Validation Excellence (Vx), accelerates the validation process from months to days, if not hours, by combining a best-practice testing and software lifecycle approach with the use of a risk-evaluation tool that focuses on critical business processes (CBPs).

Vx makes use of both the FDA and GAMP definitions of a computerized system. It reviews the standalone product risk as the “software risk” and risks to the client based on their intended usage as the “client risk.”

MasterControl Validation Excellence Tool (VxT), a cloud-based application, streamlines the risk-evaluation process by providing prepopulated assessment of software feature risks and mitigations. This means regulated companies can focus more on their CBPs and specific usage testing.

The VxT evaluates multiple risks, such as software usage, impact of failure, regulatory requirements, variation from best practices, and testing mitigations. The risks are provided through scores.

MasterControl uses the following variables to assess risk:

Initial Risk = Software Risk + Client Risk
where
Software Risk = (Conformance to Standard Configuration + Impact of Failure) – OQ Testing
and
Client Risk = (Variation from Best Practice + Regulatory Impact + Client Assessment) – Usage (TPQ) Testing.
Change Risk = Software Risk + Client Risk
where
Software Risk = (Complexity of code change+ size of code change + Touch points of code + Frequency of occurrence) – OQ Testing
and
Client Risk = (Variation from Best Practice + Regulatory Impact + Client Assessment) – Usage (TPQ) Testing.

The above risk-assessment method is close to Huber's proposed formula, except for these key differences:

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- Huber multiplies the probability of occurrence to show the importance of frequency of occurrence of an issue, while MasterControl's assessment focuses on configuration and usage. We discovered that using multiplication inflates the numbers of the outcome but doesn't necessarily explain the value of those numbers. For example, a company with a high risk in software usage may get a rating of 1-10 according to one scale, while another scale may show it as 25-75. Although the two scales use different numbers, the evaluation shows the same high risk, making their difference irrelevant. In our tool, we chose to use high/medium/low as the end result, which is easier to grasp and leaves no room for doubt.[13]

Our tool combines the scores for software risk and client risk to give an overall risk for the system and offers recommendations. If the system's risks are low, the VxT may recommend leveraging MasterControl's documentation of its internal testing. If the risks are high, it may recommend additional client specific usage testing.

The Value of VxT

Olson said MasterControl's risk calculation is another way to assess risk, similar to failure modes effects analysis (FMEA), or failure modes, effects, and criticality analysis (FMECA).[14]

"The difference is that FMEA and FMECA use detectability (for MasterControl that is testing) on a reverse scale and multiplies it with severity and frequency of occurrence," said Olson. "The most significant advantage of the MasterControl Validation Excellence Tool beyond standard risk assessment of modules is that it is specific to the MasterControl application and its use." Olson was among the consultants who lent their expertise to MasterControl during the development of the VxT.

Olson said the adoption of a standards configuration for the system used and recommended by MasterControl lowers the amount of client work in validation. "Since all changes made to the system, including bug fixes, must be assessed for impact and MasterControl's standard configuration allows them to do more of the testing that is needed, this allows the client to leverage the supplier documentation," she added.

Amber Bawden of the consulting and training firm Axeon15 said MasterControl's Vx methodology balances best-practice software testing with customer configuration and deviations to calculate usage risk. "This allows for more focused validation where needed, and at times, no validation at all," said Bawden, one of the consultants who worked with MasterControl during the development of the VxT.

Olson cautioned that some clients may not fully understand and claim ownership of the risk assessment process and results. "Regulators expect that the regulated client can explain the risk analysis and the values for each of the variables," she said.

To mitigate such possibility and help our clients fully grasp software risks, MasterControl provides all the data for risk calculation as part of the VxT. Indeed FDA guidances place the validation burden squarely on the regulated companies, so we made sure that our tool helps carry that weight by providing all the necessary data.

Validation & Cloud

Some regulated companies are wary of cloud-based systems because they are accustomed to controlling their data, its storage, and the software validation and upgrade process, whereas cloud systems necessitate relinquishing part of that control. This is unfortunate because the cloud offers the most viable solution to their validation burden.

MasterControl began offering cloud-based solutions in 2006, recognizing that cloud technology is fast, scalable, and flexible. As a cloud provider, we host and manage the cloud-based infrastructure for our customers, but each company's data is secluded to avoid commingling. This seclusion means when one company is down, not everyone is affected.

We deploy the latest software version to our cloud clients at once, which dramatically speeds up the process of upgrading. The monthly cost of a cloud system is also significantly lower than the upfront investment required when a company buys an on-premise solution.

In our search for a sustainable approach to validation, we leveraged the cloud's power when we developed the VxT, a cloud-based application. The cloud enables us to implement upgrades more often, so each upgrade consists of fewer enhancements. This means fewer new features to validate with each upgrade. MasterControl executes all the installation and functionality testing for its cloud customers and provides the executed protocols to them. We have even started executing our best-practice usage testing internally for clients to leverage as well. Using VxT, clients will review their usage of the software and determine what usage is outside the best practice for additional testing.

"There is no reason to distrust cloud environments if they are properly managed and controlled," said Olson. "Frequent and fully validated upgrades can minimize risk of production bugs that could compromise the safety or efficacy of products."

Olson said the cloud offers many advantages, including staying on the latest software. "These [cloud solutions] will have new features that the company may want to take advantage of and up-to-date bug fixes that make the software and system safer to use," she said.

Bawden agreed, saying, "Modern cloud servers allow for fast updates and reduce onsite storage needs for IT infrastructure."

8 Things to Evaluate

Olson advised regulated companies thinking of switching to the cloud to conduct a thorough evaluation of the software provider. "The cloud platform must meet the most stringent internationally recognized compliance standards, internal safety, and security standards," she said. "It matters who has assessed the software provider and for what level of compliance."

Olson suggested evaluating a cloud provider for the following things:

- Cloud up time and performance must be evaluated based on the client's needs
- Cloud security and segregation of instances on the cloud
- Notification processes for issues and downtimes
- Data backup and recovery systems and systems for redundancy
- Business continuity systems and the testing of it
- Controls to secure data between client and the provider
- Network management
- Upgrade frequency, including patches and their evaluation for impact to validation

Conclusion

Regulated companies are beginning to embrace risk-based validation. "The primary reason for the transition is the update to ISO 9001: 2015," said Bawden. "As always ISO standards are based on best business practices, so industry drives the change to the regulations, and in turn the regulations reflect best practices." Among life science companies, the adoption of risk-based validation is relatively slow even as automation in their processes has increased considerably. Over a decade after the publication of the first FDA validation guidance, the need for an effective validation method is as great as ever.

Specifically, we at MasterControl wanted a sustainable and cost-effective validation approach that can be repeated with every software upgrade to help regulated companies keep their systems current. We saw that many companies avoided software upgrades for fear of a lengthy, costly, and disruptive validation process.

All of this led us to the development of the groundbreaking VxT and Vx methodology, a risk-based validation approach based on the principles of FDA guidances. The VxT accelerates validation without sacrificing a thorough risk evaluation by leveraging our internal risk assessments and usage testing and allowing clients to focus on their CBPs.

Just as necessity led to the validation requirement in the life science industry, the need for a viable tool and a sustainable validation process compelled us to innovate. The path toward validation compliance may be long, but we hope to make the journey faster, less expensive, and less cumbersome with the help of the right tool and approach.

References

(1) Erin Wright, MasterControl's validation product manager, spearheads the efforts pertaining to the development of the company's groundbreaking Validation Excellence Tool (VxT), which streamlines the risk-assessment process and greatly reduces validation time. She created and implemented the configuration-based testing that drives the VxT and developed the formalized risk-based approach at the heart of MasterControl's Validation Excellence methodology.

She joined MasterControl in 2013 as a professional services consultant and worked closely with hundreds of regulated companies, including the FDA's Center for Drug Evaluation and Research (CDER), Ancestry.com, Abbott Point of Care, Institute for Transfusion Medicine (ITxM), and the University of Utah, in conducting custom validation implementations. Her extensive experience in quality, validation, and regulatory compliance includes working for an automated-testing software company and several clinical-trial software providers. Wright graduated summa cum laude from West Chester University with a degree in psychology.

(2, 8) General Principles of Software Validation; Final Guidance for Industry and FDA Staff, Section 2.4, Regulatory Requirements for Software Validation.

(3) General Principles of Software Validation; Final Guidance for Industry and FDA Staff, Section 6.1, How Much Validation is Expected.

(4) Guidance for Industry, Part 11 Electronic Records; Electronic Signatures–Scope and Application

(5, 9) Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 11: Computerised Systems

(6) GAMP 5 Guide: Compliant GxP Systems

(7) EduQuest Inc., a global team of FDA compliance experts, provides regulatory consulting, auditing, training, and validation services for FDA-regulated companies.

(10) ISO 14971:2007 (Medical Devices - Application of Risk Management to Medical Devices). From the FDA website: Recognized Consensus Standards.

(11) Guidance for Industry, Q9 Risk Management, published in the U.S. Federal Register in June 2006.

(12) "Risk-Based Validation of Commercial Off-the-Shelf Computer Systems," by Ludwig Huber, Pharmaceutical Technology, Vol. 2005 Supplement, Issue 6, Nov. 1, 2005.

(13) This article makes a similar argument against the use of inflated numbers: "The Problem with Risk Priority Numbers" by Donald J. Wheeler, Quality Digest, June 27, 2011.

(14) Read more about the ASQ's definition of FMEA and FMECA.

(15) Axeon Corp., based in Utah, specializes in ISO 9001:2008, AS9100, and ISO 13485 standards.

About MasterControl

MasterControl Inc. creates software solutions that enable life science and other regulated companies to deliver life-improving products to more people sooner. MasterControl's integrated solutions accelerate ROI and increase efficiencies by automating and securely managing critical business processes throughout the entire product lifecycle. More than 1,000 companies worldwide, ranging in size from five employees to tens of thousands, rely on MasterControl cloud solutions to automate processes for new product development, clinical, regulatory, quality management, supplier management, manufacturing and postmarket surveillance. MasterControl solutions are well-known for being scalable, easy to implement, easy to validate and easy to use. For more information, visit www.mastercontrol.com.

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