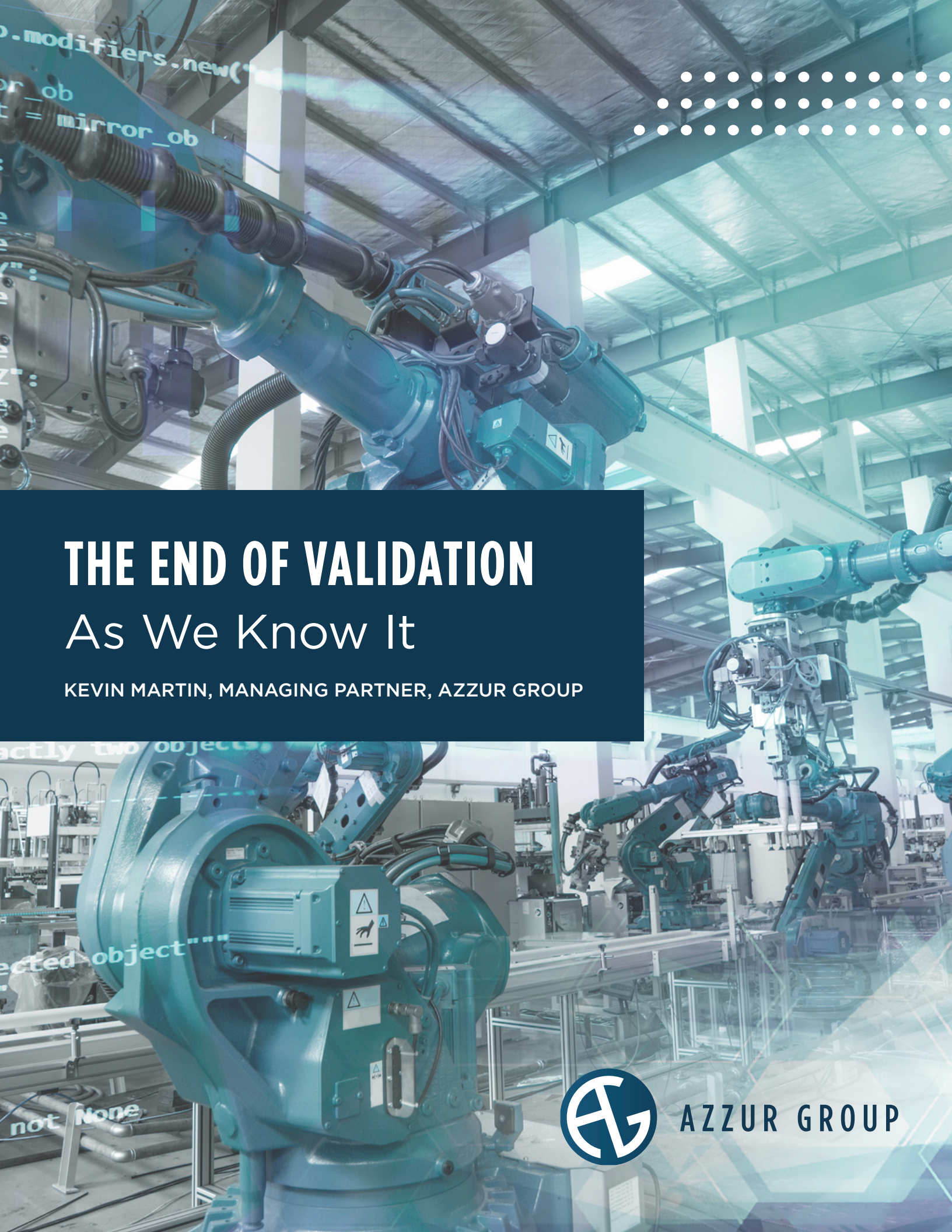

THE END OF VALIDATION
As We Know It

KEVIN MARTIN, MANAGING PARTNER, AZZUR GROUP

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INTRODUCTION

Since its inception, the Center for Devices and Radiologic Health (CDRH) has operated with the vision of providing patients with "access to high-quality, safe, and effective medical devices of public health importance first in the world."[1]

A department of the U.S. Food and Drug Administration (FDA), CDRH promotes quality medical devices and radiation-emitting products through facilitating innovation throughout the United States by advancing regulatory science, providing industry with consistent and transparent pathways for treatment and use, and assuring consumer confidence in marketing devices.[2] Basically, CDRH authors the pathways to approval that manufacturers must follow during Step 3 of the five-step medical device development process, prior to FDA review.[3]

To help steady the device industry's regulatory plod when it comes to manufacturing software, later this year the FDA is issuing Draft Guidance for Computer Software Assurance for Manufacturing, Operations, and Quality System Software.

When compared to the pharmaceutical and biotech industry, it's oft-noted that medical device manufacturers are behind their counterparts when it comes to software validation. The reason for the lag, it's suspected, lies in the differentiation between the devices' native software as opposed to the software used to manufacture the devices.

Preliminary discussion on the guidance indicate that the new FDA guidance seeks to alleviate confusion around CSV in medical device manufacturing and, instead, put forth an outline for creating a culture of appropriate risk-based quality, grounded in scientific data, that will allow medical device manufacturers to innovate effectively and efficiently while still ensuring patient safety.

Section 1

NEW GUIDANCE AND CURRENT PROCESSES

Despite some of the initial "all-or-nothing" concerns about the forthcoming draft guidance, the FDA Guide is said to promote a shift away from inspection and control and, instead, drive connections within the quality systems and the organization, ideally instilling a culture of rapid learning and continuous improvement.

Now coined by the FDA as Computer System Assurance (CSA), swapping out "Validation" for a more value-driven approach, the new model aims to flip the paradigm of Computer System Validation (CSV) on its head, adjusting the focus from documentation and validation to critical thinking and identification of assurance needs. According to the FDA, the new approach is aimed at delineating the degree of confidence that a system will deliver what is needed for intended use not for the FDA, but for the manufacturer itself.[4]

In December 2017, the Voluntary Medical Device Manufacturing and Product Quality Pilot Program was announced. This pilot leveraged the Capability Maturity Model Integration (CMMI) framework to assess a medical device company's capability to promote high-quality devices and increase patient safety. Commencing in January 2019, the 12-month program gathered "active industry input" from 21 industry leaders, according to Francisco Vicenty, FDA Case for Quality Program Manager.

The intent was to streamline non-product computer validations. In the same way GAMP® has promoted the risk-based approach to GxP computer systems validation, users are to apply value-derived and patient-focused approaches using critical thinking and applying a risk-based approach.

All in all, the FDA believes that automation is king. And, it's time to move away from the 22-year-old guidance set forth in 21 CFR Part 11.[5]

Section 2

The Challenge:

THINKING OUTSIDE THE VALIDATION BOX

Moving into 2020, it's imperative that current processes are streamlined and employees are educated on novel approaches and encouraged to think outside the box. Simply put, the "same old, same old" will no longer fly in these facilities.

Real-life example: One of my customers was still promoting three identical production runs as part of their PQ, which is a throwback to the old process validation mentality. This was never appropriate or needed for computer validation.

According to the initial discussions of the proposed draft guide, for any validation (or assurance) effort, the user must understand their own process.

1. The process must be documented, ideally with a flow diagram (process or data), and illustrate the intended use.
2. A risk assessment should be conducted to identify features, operations, or functions that directly impact the device's safety and/or quality.
    - Direct impact areas should generate the most effort and focus.
    - Indirect areas should require minimal effort and focus.[6]

FIVE-STEP QUALITY RISK MANAGEMENT

STEP 1
Perform Initial risk assessment & determine system impact.

STEP 2
Identify functions impacting patient safety, quality, & data integrity.

STEP 3
Perform functional risk assessments & identify controls.

STEP 4
Implement & verify appropriate controls.

STEP 5
Review Risks & monitor controls.

At this point in the process, any test approach should provide assurance that the system or function is operating as expected and is performing in accordance with its intended use. Although traditional IQ/OQ/PQ is still "acceptable" and well understood, it is not the only approach.

For instance, combining qualification documents, or having a hybrid (i.e., automation protocol) may be sufficient and satisfactory. Just remember, whichever approach the team chooses to implement, it is ideal to leverage any documentation that supports the effort.

There is no need to recreate anything.

For instance, if you're looking at a legacy system that has been in place for years, it makes no sense to reverse engineer the process and create a requirements document. Instead, one satisfactory approach is to prepare an As-Built Document that describes the system, its functions, and its specific characteristics. From there, the document testing can be conducted to verify that the system is operating as expected and as documented.

CASES IN USER RISK TOLERANCE

Whenever a risk-based approach is put into place, there will always be some risk involved. The question then becomes, “What is the user’s risk tolerance?” There are ways to minimize risk through technology or human factors, and the question then becomes, “To what extent do we incorporate and apply these mitigating measures?”

For a medium risk function such as confirming an SOP or a downstream verification, it would only require a specific test of that function. A more complex series of tests may be warranted depending on your risk tolerance. High-risk functions, such as product release or distribution-related information require several tests applying a rigorous documentation method.

When applying the risk-based approach to testing, typically a low-risk function, such as confirming a setup or configuration parameter, or something that does not have direct impact to the product or patient, requires only basic testing (one test of the function). Often, a low-risk function can be tested inherently when testing other functions within the system and does not need to be tested independently. In fact, testing multiple low-risk functions simultaneously is perfectly acceptable.

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Section 3

TESTING REGIMENS AND VALIDATION EFFORTS

The FDA/CDHR Draft Guidance likely will address what may be acceptable as a record of results. Unscripted testing, Ad-Hoc, Error Guessing, and Exploratory are acceptable methods.[7] However, these typically are conducted in conjunction with a larger test regimen, such as decision-condition testing or boundary testing, and should not be relied upon as the sole testing regimen.

Whenever a risk-based approach is put into place, there will always be some risk involved. The question then becomes, "What is the user's risk tolerance?" There are ways to minimize risk through technology or human factors, and the question then becomes, "To what extent do we incorporate and apply these mitigating measures?"

Formalized Script Testing may be the ideal option. Either Limited or Robust, the Script Testing will require the following elements:

- Step-by-step instructions
- Acceptance criteria
- Pass/fail determination
- Conclusion statement
- Evidentiary documentation to prove that the test was satisfactorily conducted with sufficient detail to illustrate the outcome

As stated above, the script and evidence should be sufficient enough to illustrate that the test could be verified and repeated, as required.

In an early presentation given by the FDA* the Paradigm Shift was illustrated. It's agreed that validation efforts in the past were not conducted efficiently, resulting in waste in terms of resources, time, and cost.

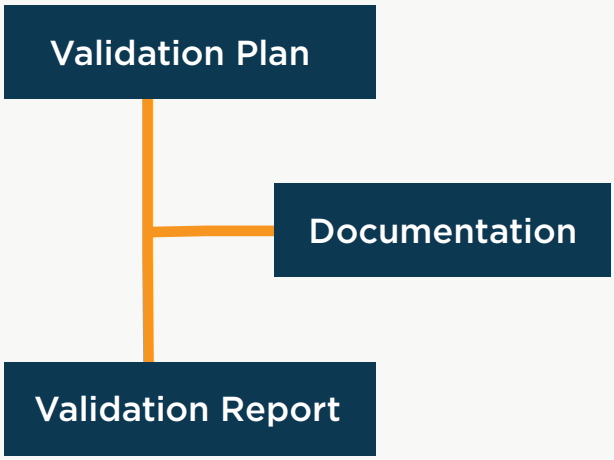
In the past, too much time was wasted on large PQs or in staging multiple runs of different configurations. Instead, using science, a risk-based approach, and—quite frankly—common sense (with an educated understanding of the process and compliance), such time-wasting practices are a thing of the past.

Right now, incorporating an Agile[8] approach is a hot and current industry method, which allows a phased system implementation utilizing sprints to put small segments into production quickly.

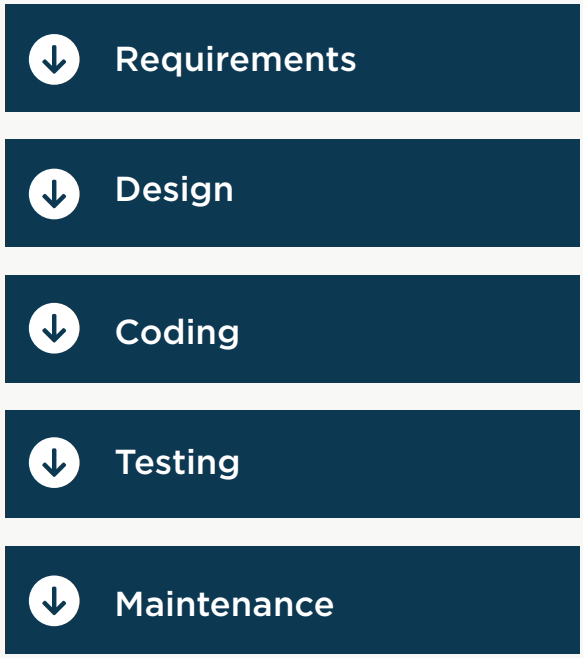
Another observation is that, although the Agile model may enable validated segments of a system to be placed into production quickly, the cost of putting the entire system into production may actually be higher than using a more traditional approach.[9]

Agile may mean quick, but doesn't necessarily mean cheap.

AGILE



WATERFALL



A PERSONAL OPINION

During the initial demonstration of the draft guidance, another observation was that the Unscripted Exploratory testing was used for a spreadsheet that was determined to have high functional risk, but low patient risk. The testing activity in question was to create, update, and delete analyses and observe that all calculated fields were correctly updated. No additional documentation was required.

Although this reader would like more information as to the actual testing performed, I find it curious how one could make a statement that all calculated fields were updated when there is no mention of any documentation that defines what these fields are, or what they are calculating. It has always been required to test to predetermined specifications.

CONCLUSION

Although the Draft Guidance has yet to be released, it's my belief that the encouragement of unscripted (ad-hoc or exploratory) testing as acceptable is misleading if used in the wrong setting. In fact, it reminds me of another Draft Guide on Equipment that came out a few years ago, touted as "The End of Validation".

At that time, customers were asking if they still had to qualify their equipment and validate their processes.

The answer then is the same as the answer now: It is not the end of validation; *it is the end of validation as we know it.*

Today, what we know of the Draft Guidance focuses on the delineation of Assurance vs. Validation. So, we're not doing away with everything we've practiced for the past 22 years. Instead, we must apply a scientific, risk-based approach with educated users, owners, and team members, as we put an end to the wasteful approaches of yesterday and move our companies into a future state of efficiency, compliance, and cost savings.

Kevin Martin
Managing Partner

ABOUT THE AUTHOR

Kevin has more than 40 years of FDA-regulated industry experience that includes management positions at Wyeth and McNeil Pharmaceutical. He is considered a subject matter expert on risk-based systems validation conducted within QA, IT, Manufacturing, Operations, Clinical and R&D in FDA-regulated environments.

He has been a member of the PhRMA Computer Systems Validation Sub-Committee, was the Core Team Secretary for the PDA Part 11 Task Group, former co-chair of GAMP® Global, and was previously a chair on the GAMP® Americas Steering Committee.

He received his Bachelor's degree in Chemistry from Delaware Valley University, and his Master's of Engineering from the Pennsylvania State University.

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AZZUR.COM

BOSTON, MA
781.893.1251

PRINCETON, NJ
609.681.5816

RALEIGH, NC
919.377.9069

SAN FRANCISCO, CA
650.989.0405

PHILADELPHIA, PA
215.322.8322

WASHINGTON, D.C.
202.788.6226

LOS ANGELES, CA
949.682.7003

SAN DIEGO, CA
858.401.7716

AZZUR LABS - HEADQUARTERS
484.550.7709

AZZUR LABS - RALEIGH
919.342.8337