WHITE PAPER

Automated Validation

The Next Generation Approach to Accelerating MES Implementations in Regulated Environments

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Critical manufacturing
an ASM PT company

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Executive Summary

Medical Device and Diagnostics manufacturers, along with other manufacturers in regulated industries, face overwhelming challenges to bring the right products to market, at the right time, and most importantly, at the highest quality. Unlike other complex industries, they have to also comply with increasingly stringent worldwide regulations, with massive documentation requirements to ensure patient safety above all else. For many of these manufacturers, using a Manufacturing Execution System to ensure compliance, standardize operations and reduce risk is a standard practice.

MES is considered a GAMP Category 4 (Configurable Software Package) application and its specific configuration is subject to a formal Computer Software Validation process as defined by the medical regulatory agencies, such as FDA in USA and EMA in Europe. This process requires the definition of several artifacts: User Requirement Specifications, Functional Specification, Design Specification and System Build. These are subject to testing and validation: Installation Qualification, Operational Qualification and Performance Qualification.

The greatest challenges in maintaining and performing a Computer Software Validation (CSV) process are 1) the maintainability of the end-to-end traceability between requirement and end-testing; and 2) the execution of the tests themselves. Both of these tasks can be extremely effort and time consuming as well as prone to errors if carried out manually.

The Next Generation Computer Software Validation package for MES includes both templates that adhere to the GAMP 4 as well as the newer GAMP 5 model and tooling support. This ensures a smooth and automated validation process that maintains end-to-end traceability and that can be executed automatically at any time. This Computer Software Validation Package offers a fully integrated validation solution that allows an easy and fast implementation of the MES, where the validation phase takes days instead of months.

Introduction

Validation of products and manufacturing processes/systems/documentation is a requirement for every Life Sciences company. Validation proves adherence to Good Manufacturing Practices (GMP) as well as to industry-relevant requirements, standards, certifications and regulations. For Manufacturing Execution Systems, this validation process comes with its own guidance and oversight.

For regulated industries, software validation has two threads: the specific risk-based approach through Computer System Validation (CSV), now Computer Software Assurance (CSA) and the more process-specific, holistic approach driven by 21 CFR.

In 2011, the FDA released 'Guidance for Industry Process Validation: General Principles and Practices.' Process Validation was founded on the acknowledgment that a single measure or test is not enough to ensure public and product safety. The Guidance emphasizes that the 'validation of manufacturing and commercialization are critical to quality assurance of the product itself.'

A definition of Process Validation

The FDA defines process validation as 'the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.' Process validation involves a series of activities taking place over the lifecycle of the product and process. The FDA sets out three stages of activities for process validation:

- Stage 1: Process Design: the commercial manufacturing process is defined during this stage, based on knowledge gained through development and scale up activities.
- Stage 2: Process Qualification: the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- Stage 3: Continued Process Verification: ongoing assurance during routine production that the process remains in a state of control.

The assurance for the repeatability of the process is gained from objective information and data from laboratory, pilot and/or commercial-scale studies.

A successful validation program depends upon information and knowledge from both process and product development. It is the foundation for establishing an approach for control of the manufacturing process that results in products with the desired quality.

During validation, manufacturers need to:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process, and ultimately on product attributes
- Control the variation in a manner equal with the risk it represents to the process and product

The FDA Guidelines specify process validation guidelines for premarket, retrospective, concurrent and re-validation scenarios. The scenarios cover first time to market, as well as updates or upgrades that are done to the process infrastructure, such as new equipment, new formulations, or new manufacturing software.

Software guidance & validation for Medical Device

The FDA acknowledges that medical device manufacturing fundamentally differs from pharmaceutical, and created a separate set of Guidelines for Medical Device, Quality Management Systems, Process Validation Guidance in 1999. These fall within ISO standards.

Building on the Guidelines for pharmaceutical, the FDA created a specific set of Code of Regulations, Title 21. It is the portion of the regulations that governs food and drug production within the US.

There are three sections of 21 CFR that oversee regulated products manufacturing:

- Section 11: electronic records and electronic signature
- Sections 200 and 300: pharmaceutical manufacturing
- Section 800: medical device manufacturing

Section 800 contains several parts which cover validation:

- 803: medical device reporting
- 814: premarket approval of medical devices
- 820: quality system regulations (similar to cGMP—current good manufacturing practices)

21 CFR Part 820

For the purposes of this paper, we will focus on the validation requirements set forth by 21 CFR Part 820.70, Quality System Regulations.

Part 820 is meant to provide definition, insight and oversight to medical device manufacturing. It has Subparts A (General Provisions) through O (Statistical Techniques) to give manufacturers guidance on how to conduct operations in a compliant manner.

Part 820 provides its own definition of process validation: 'Establish by objective evidence that a process consistently produces a result or product meeting its intended and predetermined specifications. 21 CFR 820.3 (z)(1).'

Part 820.70 is guidance for production and process controls, and specifies 'each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications.' This is in line with the process validation guidelines — ensuring the end product conforms to performance, material and quality specifications for repeatability.

CSV and CSA

CSV, or Computer Systems Validation, is the FDA's equivalent First Principles of Software Validation. CSV proves that the software and systems are performing correctly. Alongside the more complex 21 CFR Part 11 oversight, it became a tool for getting companies into validation by providing scores of backup documentation for audit purposes.

Following the launch of their 'Case for Quality' initiative in 2011, which set out to study best practices in medical device manufacturing, FDA discovered that that the burden of CSV deterred companies from investing in automated systems. The lack of technology investments, in turn, inhibited quality best practices. This led to Computer Software Assurance (CSA), which is a framework designed to help manufacturers achieve CSV using a risk based approach which eases documentation requirements.

The FDA's guidance document, titled Computer Software Assurance for Manufacturing and Quality System Software, eases the requirements of CSV and focuses on risks and critical quality attributes (CQA). It aligns itself with quality standards such as ISO and, most importantly, allows an agile implementation environment for faster deployment and recovery of ROI from key software projects.

A key aspect of CSA, especially for Medical Devices, is the recognition of supporting software such as quality management, MES or PLM for validation, versus the software used in the device itself. CSA's intent is to minimize the CSV effort by focusing on COTS (Commercial Off the Shelf) platforms to improve efficiency and validation, data visibility and accountability.

CSA and its predecessor CSV focus on the software within a regulated environment, and establish validation procedures based on a risk-based approach. 21 CFR Part 11/820 focus on the process, ensuring that the entire solution works in harmony to establish standard operating procedures that are controlled, and can be validated, with associated documentation, practices and procedures. For MES software, it's important that both sets of oversight are met when using MES in a regulated environment.

Realities of Validation

It is well known that the traditional validation process is not efficient nor cost effective. According to IVT Network, the lack of efficiency is driven by a number of issues, both organizational and process in nature:

- Inconsistent practices
- Inconsistent objectives and expectations
- Duplicate roles and responsibilities
- Duplication of efforts
- Excessive repetition and rework
- Excessive resource commitments
- Silo organizations and activities
- Excessive reviews and approvals of protocols and other documentation
- Unnecessary handoffs

Traditional software validation can take 4 to 8 months, or more for a single system. A rule of thumb is that validation takes about 1/3 of the total project timeline. So, if an implementation takes 12 months, then the traditional validation of that implementation will take 4 months to complete.
Traditional software validation is also costly; identified costs with standard software validation testing include:

Activity	Current Approach	Modified Approach	Impact
Streamlined Analytics Reporting	Consumes 43 hours per report	Reduced to 10.5 hours per report	• $90 per hour average cost • $3,870 per report reduced to $945 • Drives reduced use of analytics and operational research
Risk-based Software Vendor Qualification	-2000 hours of labor	80% reduction in labor	• $100 per hour average cost • $200,000 reduced to $40,000
Ad-hoc/unscripted testing (AGILE)	14 hours per test script	2 hours	• A $10 billion firm with 100 systems could save $1,62 million annually, which can be reinvested in innovation & quality improvements • More robust software (safer product)

Source: FDA, a collaborative FDA and Industry Perspective Automation · Non-Product CS, Cisco Vicenty, Program Manager, case for quality, FDA CDRH OC Siemens PLM-Medtronic Excellence Event, May 15, 2018, Minneapolis, MN

Fig. 1 Non-product CSV Modification Impact

Automating Validation: A Next Generation Approach

Next generation automated validation for MES can reduce the execution from months to days. It is applicable for both the initial validation phase, as well as for updates and re-validation; for example, in conformance with Part 820.70, taking advantage of new features in your MES.

It can also be used to expand the MES to other lines. Of course, any change to a system will trigger an impact analysis to understand which parts of the system should be considered for re-validation. The new automation tools within this next-gen approach will make the validation faster.

Not all MES software can claim days to validation. Using a 'next gen' approach is designed to help you in your path to validate your Manufacturing Execution System for its intended use, according to an established protocols as required by 21CFR Part 820.70 and CSA.

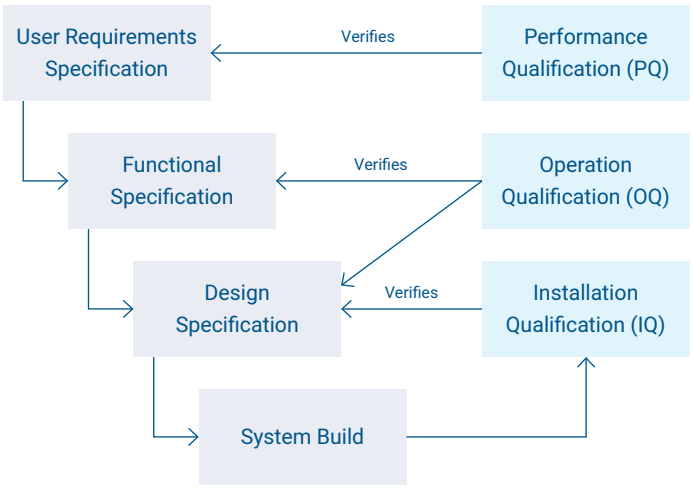
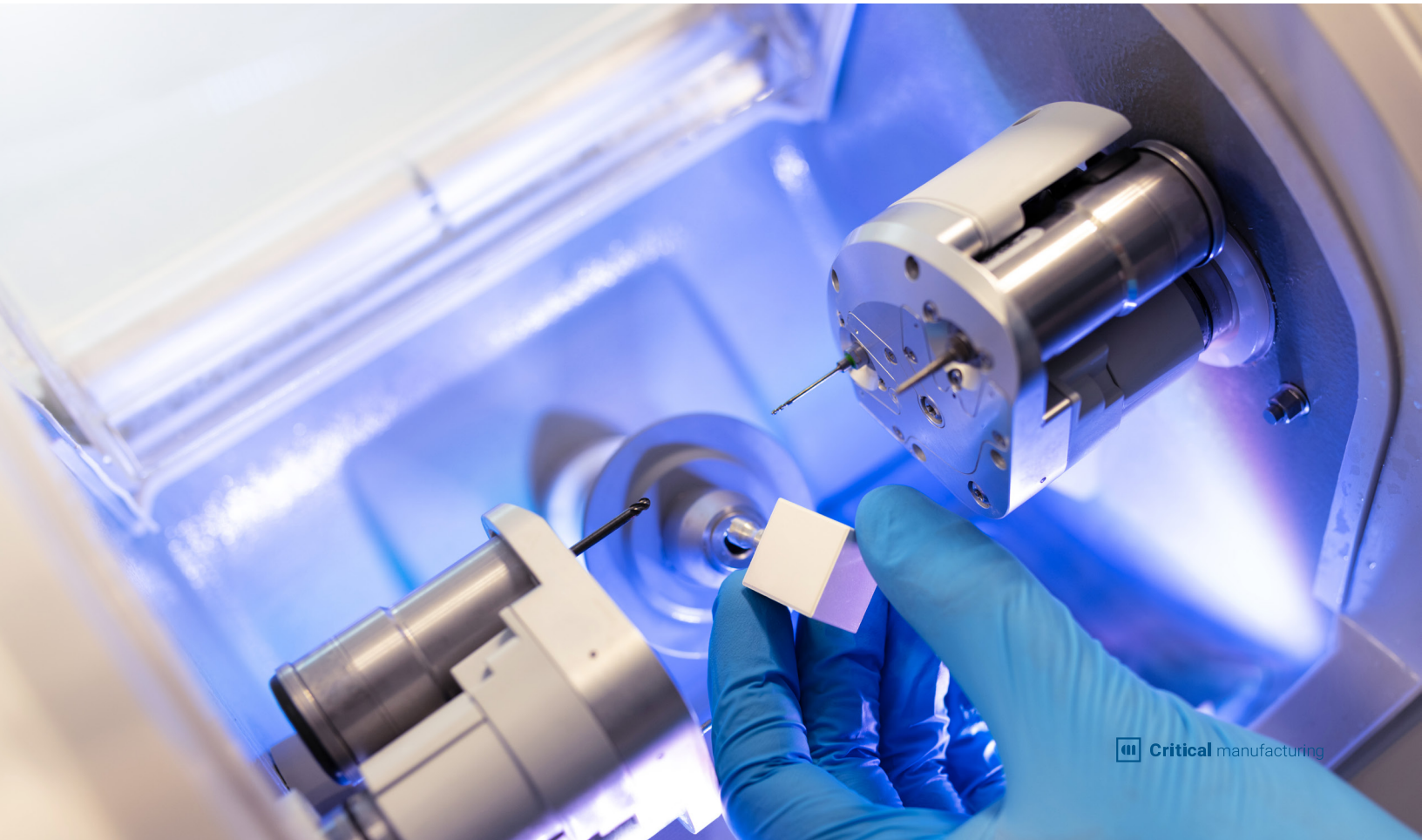


Fig. 2 GAMP 5 Framework for Specification and Qualification



GAMP-5

Most Life Sciences companies are familiar with GAMP-5, a Risk-Based Approach to Compliant GxP Computerized Systems. Critical Manufacturing's MES has long offered tools to assist companies in complying with GAMP-5.

The next generation validation templates cover URS (User Requirements Specifications) through FRS (Functional Specifications) and DDS (Design Specifications), all the way through IQ OQ and PQ (Installation, Operation and Performance Qualification). They include the associated Traceability Matrix, Master Plan and Summary.

Validation Enablement

Validation Enablement starts with Validation Templates. They adhere to the GAMP 5 model with a full set of templates. Many customers have successfully used these templates in order to complete their validation requirements.

CSA guidelines shifted the market to an iterative, risk-based approach for validation. It was the inspiration for the 'next gen' automated validation solution.

The **first level of Automated Validation** is the 'Build and Test' Server. It provides the ability to build and execute automated validation scripts against the resident software solutions.

Automated validation tests are executed using a Test Runner, which will execute a given test suite and record the results for reference and traceability.

The second level of Automated Validation, and the highest level in the Next Generation Automated Validation, is a fully-integrated, fully automated validation solution featuring Azure DevOps. It builds on the validation templates, leveraging the Build & Test Server, Test Runner and a full set of tools to enable a complete and full project-oriented collaboration. It also uses Microsoft's Teams and SharePoint collaboration portal for enhanced exchanges.

Validation Templates	• Complete set of Validation Templates that follow the GAMP-5 model
Automated Validation	Two critical quality components: • Adds "Build & Test" Server • Adds Test Runner
Fully Integrated Automated Validation	Fully integrated with its MES: • Adds Azure DevOps with relevant plugins • Adds Modern Requirements • Adds Teams/SharePoint for enhanced exchange

Fig. 3 Automated Validation includes templates, test architecture & development infrastructure

Fully Integrated Validation

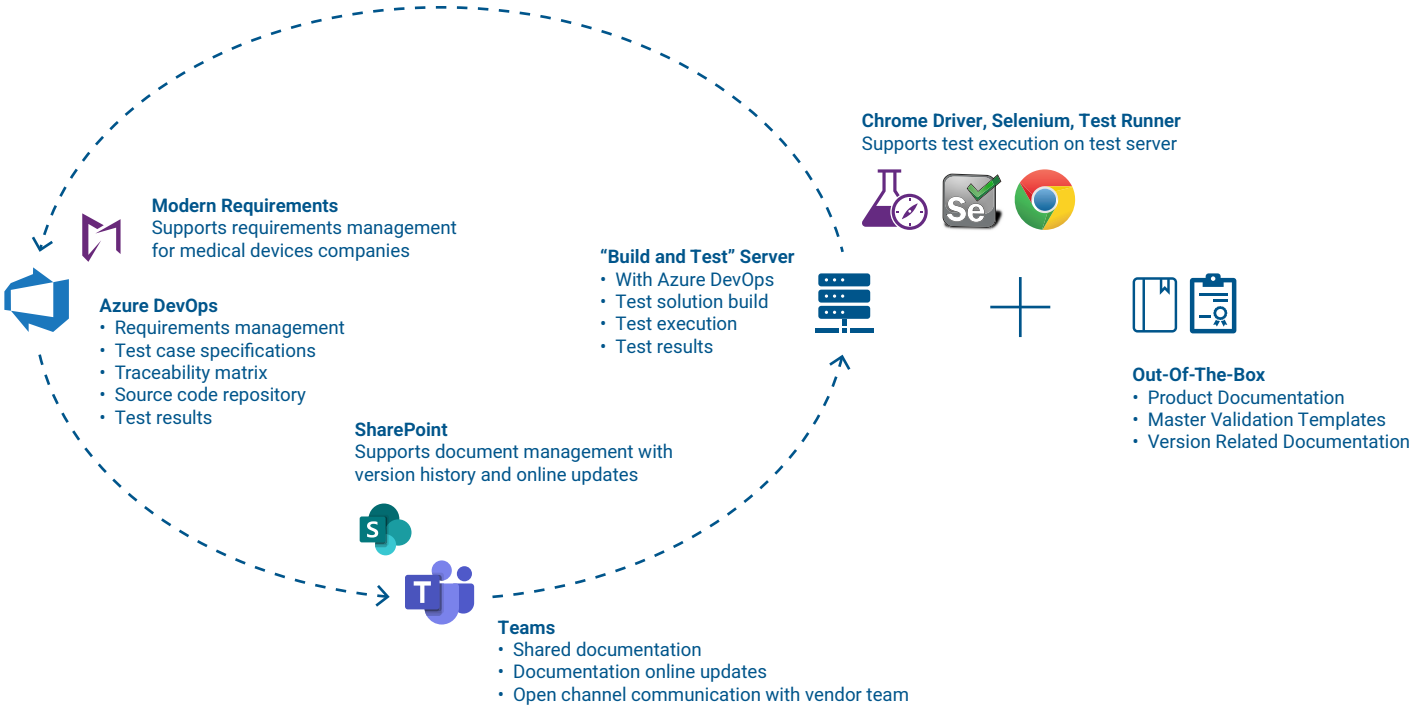


Fig. 4 Fully Integrated Validation is based on the Microsoft Azure DevOps platform.

The fully integrated validation solution features an end-to-end engineering workflow that uses the strength of the Azure DevOps platform for functions such as Requirements Management, Test Case Specifications, Traceability, Source Code Repository and Test Results Repository.

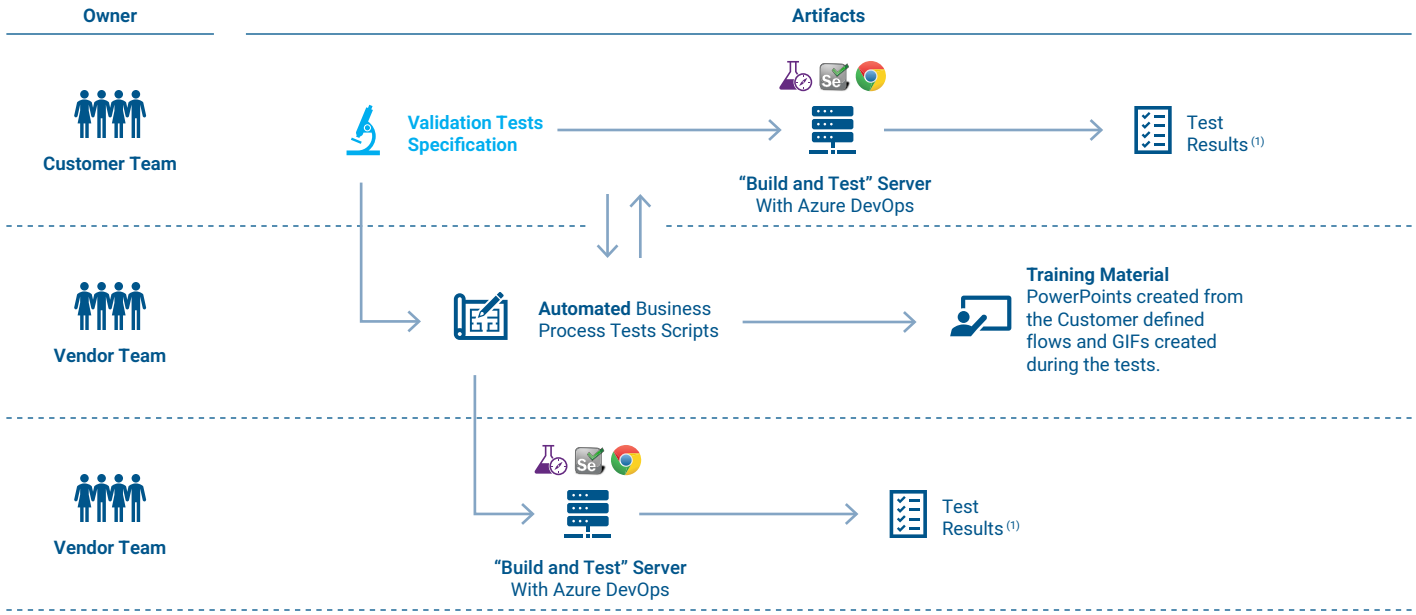
Azure DevOps uses plugins that are fully integrated within its environment. One of these plugins, Modern Requirements4DevOps, can be used for both test case management and Requirements Management. This fits naturally within the development of an implementation project and can close the loop on the validation side.

Other Modern Requirements features include:

- Links of all of the functional requirements to backlog items
- 'Smart' document management system
- Printouts of reports
- Development of a full traceability report in a matter of minutes, not days
- eSignature based approvals for Part 11 compliance

Validation Collaboration is enhanced by using Microsoft Teams and SharePoint to allow customers to fully engage to ensure that collaboration is continuous throughout the project.

Validation Lifecycle



(1) Includes print screens for all steps and/or GIFs.

Fig. 5 Automated Validation Lifecycle Solution.

The Automated Validation lifecycle is built around the Build & Test Server. The test scripts are run through this server, and the vendor will run a second Build & Test Server on their side. The servers are not mirrored; rather, test scripts are pre-run to make sure that everything executes as expected before the test scripts are run on the customer's Build & Test server. This accommodates unexpected issues that could arise prior to deploying to the actual customer site to do the validation efforts. It dramatically smooths out the validation process.

Validation Use Case

The customer is a manufacturer serving regulated, high tech industries. They are using Automated Validation for MES to execute Business Test Cases that cover end to end operator processes and procedures, as well as to create Training Documentation derived from running the test scripts.

The customer is using the automated test scripts feature to save time in capturing as-is training.

They were able to generate a step by step printout of all of the automated test scripts that were created. Printouts can be done for any implementation and any validation. Screen captures are used throughout testing, so that their validation documentation is gathered continuously, and objective evidences registered. They also converted their screen captures to short videos which will be used in training documentation, both for their customers as well as their internal operators.

The customer was able to complete validation in 30% less time during the implementation phases and run validation concurrently with the implementation instead of waiting until the end of the process.

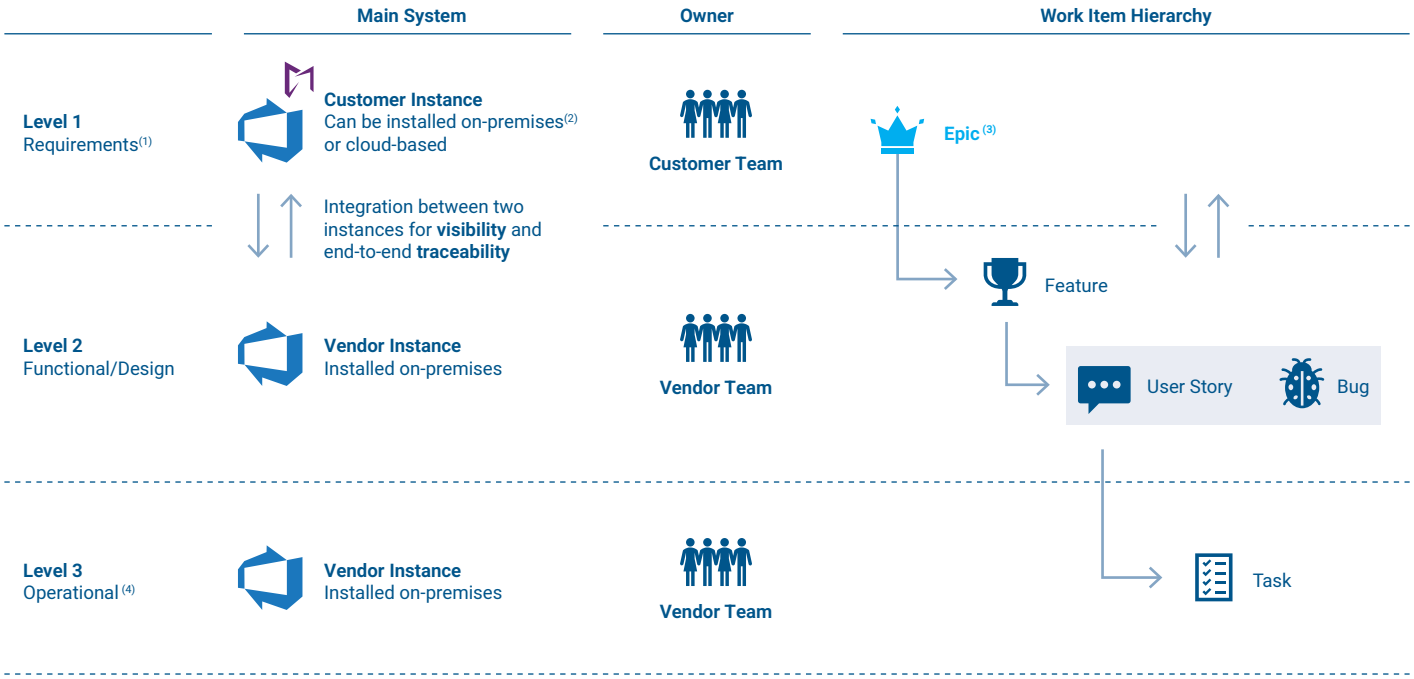
Focus on Backlog Management: Using Epics

Agile software development includes Epics as an iterative deliverable. An Epic is a defined body of work that is segmented into specific features based on the needs/requests of customers or end users.

The implementation team drills down Epics and Features into User Stories, which allows for the work to be broken down into buildable tasks and shippable pieces, so that projects can be completed faster. In contrast, a Feature typically represents a shippable component of software, while an Epic represents a business initiative to be accomplished. User Stories are the primary unit of work for the implementation team.

In order to ensure successful validation, traceability between the User Stories and the initial requirements (captured as Epics) is essential. The highest level of automated validation is the fully-integrated solution based on Azure DevOps, which enables the customer and the implementation team to collaborate on an integrated platform, ensuring full traceability and integration throughout the development and validation workflow.

The same process of collaboration is used for validation purposes. Validation test scripts are associated to the Epics, representing the requirements to be validated during IQ/OQ/PQ, and can be executed first or on the Vendor's side, and later on the Customer's side. As with the backlog items, both teams have visibility over the tests to be executed and their traceability down to the individual User Story delivered by the implementation team.



(1) Requirements baselines and versioning supported by Modern Requirements. (2) Integration with on-premises Azure DevOps Server requires access to remote network from Vendor servers.
(3) Custom work items for requirements management can also be used. (4) Not synchronized.

- Full traceability between Requirements – Acceptance Tests – Test Scripts – Test Results

Fig. 6 Focus on Backlog Management.

Fully Integrated Validation Solution

The fully integrated validation solution uses the Microsoft Azure DevOps platform. It provides:

- Full traceability between Requirements, Business Test Specifications and Automated Test Scripts
- The ability to create Business Test Specifications based on the Automated Tests
- The ability to use the Customer's team to update the automated tests.

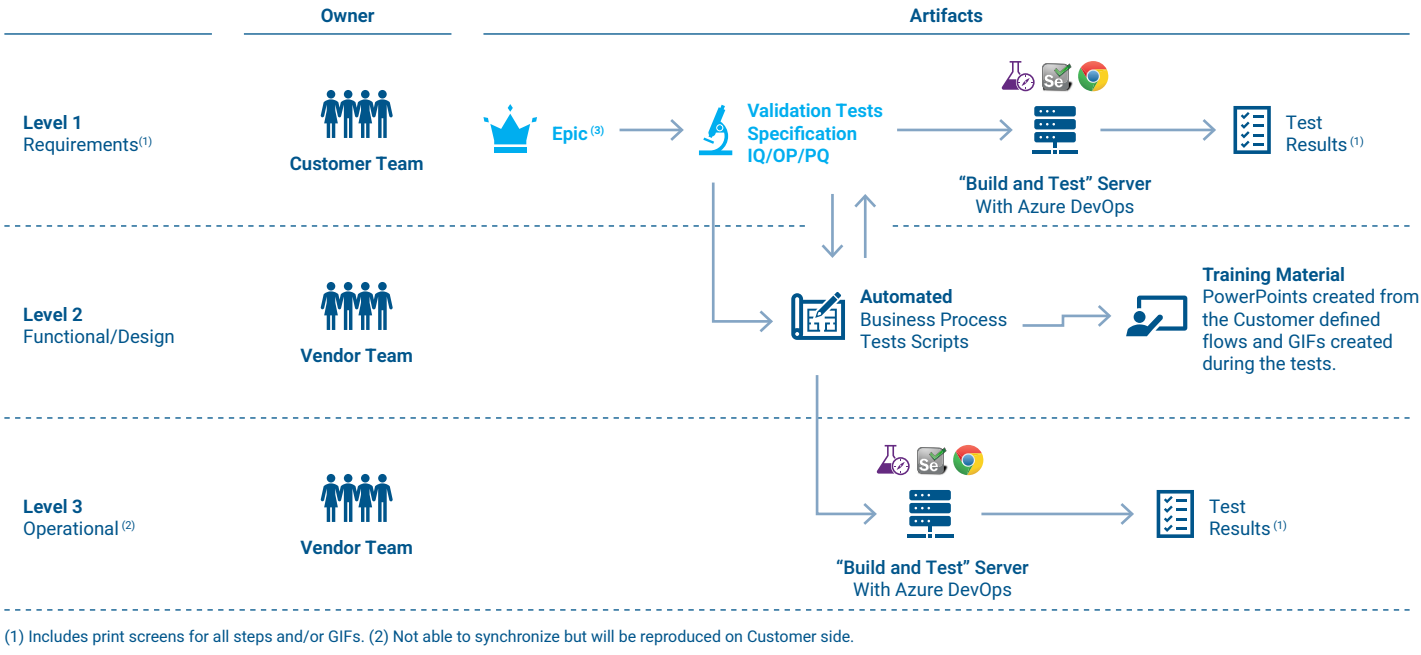


Fig. 7 Fully Integrated Validation is based on the Microsoft Azure DevOps platform.

Test Library Repository & Tying Everything Together

On the vendor side, there is a NuGets repository for customers and partners usage, with all the resources needed for creating the automated tests.

Test scripts, written in C# allow the MES provider, customer or partner to contribute to test script development.

The strategy will be to continue to grow the repository and expand the available toolkit, so that any type of validation effort in the future would be optimized. There will also be full test scripts already available, ready to support out-of-the-box implementations, which can further ease the validation process.

The end result? Everything comes together in an automated way, working through qualification, with a Validation Master Plan laid out before everything begins. Once qualified and a validation summary report is created, the validation can be completed and signed off.

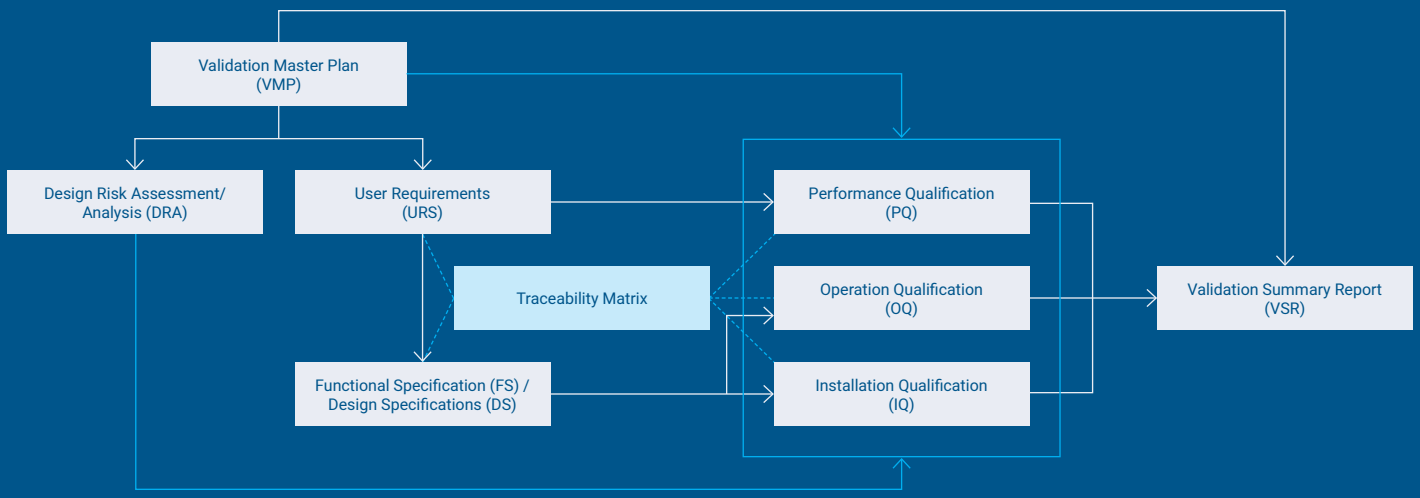


Fig. 8 Everything connected

Benefits of the New Automated Validation Approach

Initial customer feedback on the new Next Generation Automated Validation for MES confirms less effort and faster completions. Customers utilizing these two new levels of validation support—Automated Validation using the Test & Build Server/Test Runner, and Fully Integrated Validation using Azure DevOps, report that it is that it is taking less effort on their part to actually perform the validations, and the validations are completing much faster than ever before.

The reductions in both time and effort have been the program goal—simplifying the process for customers, and subsequently leading to a faster ROI and time to market. The next generation automated validation for MES also allows customers the flexibility to make changes more elegantly, utilizing the infrastructure of the product for cleaner, more efficient updates. Lastly, it allows customers to validate their system in parallel to implementation to save time and cost in validation efforts.

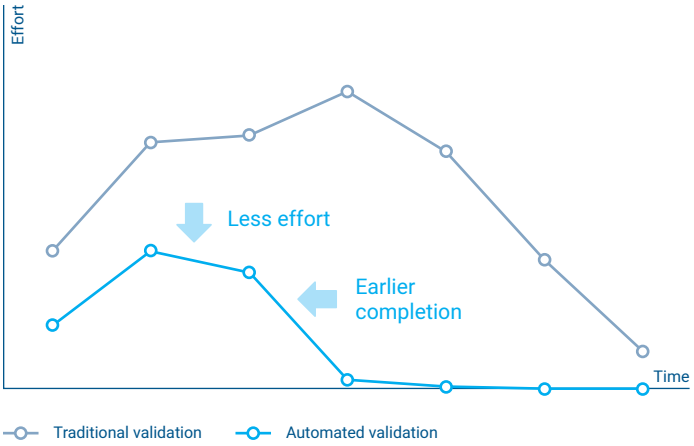


Fig. 9 Results Impact on the Overall Project

Glossary of Terms

Azure DevOps
A Microsoft product that provides version control, reporting, requirements management, project management, automated builds, testing and release management capabilities. It covers the entire application lifecycle, and enables DevOps capabilities.

Backlog Management
A list of tasks required to support a larger strategic plan. In a product development context, it contains a prioritized list of items that the team has agreed to work on next.

Build & Test Server
A Build Server is a centralized, stable and reliable environment for building distributed development projects. It speeds up the development process by freeing up resources on developers' local machines. The Test Server is a place where new updates, features, and mechanics are tested before being released to the main servers. Most of the time these servers are in a closed-testing mode, meaning that only Developers and Testers can access them.

CSA
Computer Software Assurance uses a risk-based approach to validation for non-product software. It is part of the FDA's Case For Quality Program.

CSV
Computer Systems Validation is the FDA's equivalent First Principles of Software Validation. CSV proves that the software and systems are performing correctly.

DDS
The Detailed Design Specification (DDS) describes how the hardware and software functionality identified in the Functional Specification will be developed and implemented.

EPIC
An Epic is a defined body of work that is segmented into specific features based on the needs/requests of customers or end users.

FDA 21 CFR 820
Part 820 is meant to provide definition, insight and oversight to medical device manufacturing. It has Subparts A (General Provisions) through O (Statistical Techniques) to give manufacturers guidance on how to conduct operations in a compliant manner.

Features
Functionality offered by the software program to enable users to conduct activities.

FRS
Functional Requirements Specifications is the document that describes all the functions that software or product has to perform. It is a step-by-step sequence of all operations required to develop a product from start to end.

GAMP-5
The acronym GAMP-5 refers to the "Good Automatic Manufacturing Practices issue 5", document. Although this document has no legal standing and is purely advisory, it does contain information and methodologies that are of interest to anyone engaged in validation activities within the cGMP regulated environment.

IQ, OQ and PQ
Installation, Operation and Performance Qualification protocols are used for demonstrating that equipment or software being used or installed with offer a high degree of quality assurance, such that production processes will consistently manufacture products that meet quality requirements.

MES
Manufacturing Execution Systems are computerized systems used in manufacturing to track and document the transformation of raw materials to finished goods.

Modern Requirements4DevOps
Azure DevOps plugin for documentation, testing and reporting.

NuGet
NuGet is the package manager for .NET. It enables developers to create, share, and consume useful .NET libraries. NuGet client tools provide the ability to produce and consume these libraries as "packages".

Requirements Management
Requirements Management is the process of documenting, analyzing, tracing, prioritizing and agreeing on requirements and then controlling change and communicating to relevant stakeholders. It is a continuous process throughout a project.

Test Runner
A Test Runner is the execution unit of the invocation flow. This is where tests actually run.

URS
User Requirements Specifications describes the business needs for what users require from the system. They are written by the system owner and end users, with input from Quality Assurance.

User Stories
A small, self-contained unit of development work designed to accomplish a specific goal within the product. It describes the intent or desired outcome of a small but complete slice of user functionality. A given product feature may be comprised of several user stories.

Validation
Validation is the process of establishing documentary evidence demonstrating that a procedure, process, or activity carried out in testing and then production maintains the desired level of compliance at all stages.

Validation Master Plan
A VMP is a formal document explaining how the validation program is operated. It is the manufacturer's roadmap for qualification throughout a facility, clearly defining the systems which must be validated and detailing the program the organization will use to conduct validation activities.

Carla Neves holds an Electric and Electronics Engineering Degree from University of Porto. She has been working in the software industry since the beginning of her career as a Design Engineer and later as a Software Engineer.

She has been working at Critical Manufacturing since 2009 and is the Quality Manager since 2017, helping the company to achieve high quality standards. Recently, she embraced a new challenge and now, besides being the company Quality Manager, is also the Product Owner for Medical Devices.

Carla is certified as a Scrum Master and Advanced Software Test Analyst.

Critical Manufacturing provides the most modern, flexible and configurable manufacturing execution system (MES) available. Critical Manufacturing MES helps manufacturers stay ahead of stringent product traceability and compliance requirements; reduce risk with inherent closed-loop quality; integrate seamlessly with enterprise systems and factory automation and provide deep intelligence and visibility of global production operations. As a result, customers are Industry 4.0-ready. They can compete effectively and profitably by easily adapting their operations to changes in demand, opportunity or requirements, anywhere, at any time.

To learn more visit: www.criticalmanufacturing.com