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White Paper:

Validating Software Systems to Comply
with CGMP and 21 CFR Part 11
Regulations

Computer Systems Validation Overview

FDA-regulated companies are very familiar with a variety of validation processes ranging from full process and facilities validation to that of qualifying individual utilities, equipment, instruments and everything in between. When it comes to 21 CFR Part 11 and computer systems validation, however, regulated companies are purchasing configurable electronic quality management systems from software manufacturers that may have little or no experience with validation. This is especially important since the vendor is responsible for managing the ongoing development and maintenance of the system.

The use of vendor-supplied “off-the-shelf” configurable software offers many challenges to validation, including supplier audits. A knowledgeable and “validation-ready” supplier can make the process much easier and faster. To this extent, regulated companies must continually educate themselves about validation of computer systems for electronic documentation management as applied in 21 CFR Part 11. FDA expectations for Part 11-compliance and validation of computer systems were seen initially in the FDA 483s and Warning Letters issued during inspections.

Now we are operating within the new FDA enforcement discretion under the September 2003 Guidance for Industry; Part 11, Electronic Records; Electronic Signatures – Scope and Application.

This white paper will provide an overview of computer systems validation and what FDA is requiring companies to do to become or stay compliant.

Validation Realities

- FDA’s interpretation of 21 CFR Part 11 for inspections of computer systems and computer validation has been refocused through the Scope and Application Guidance to emphasize predicate regulation record requirements and shift the emphasis to documented risk assessment of each company’s particular circumstances. Compliance will remain a part of routine FDA inspections based on predicate regulations, including validation.
- Software development methodologies, standards, and guidelines have been available for 30 to 40 years. There is no excuse for developers of configurable “off-the-shelf” software not to be capable of validation and 21 CFR Part 11 compliance. FDA has emphasized that software/engineering principles can be applied to, and are an integral part of, the system development life cycle. Software and system development and testing are part of the System Development Life Cycle (SDLC).
- Software and Computer System Life Cycle principles in a GxP setting should be supported by a Corporate Computer Systems Validation (CSV) Policy with supporting global SOPs for the System Development Life Cycle, Validation, Supplier Assessment and Audits, Change Control, and Revalidation along with local SOPs for specific systems.
- Corporate CSV Policy should be in-place and empower a Computer Systems Validation Committee and a Systems QA Planning process.
- Verification answers the question: “Was the product built right?” and Validation answers the question: “Was the right product built right?”

Current FDA Expectations – 21 CFR Part 11 and Validation

21 CFR Part 11 was developed to set standards for systems containing electronic records and electronic signatures. Inherent in 21 CFR Part 11 compliance is validation of the system used within its current operating environment.

Under the 2003 Guidance for Industry; Part 11, Electronic Records; Electronic Signatures – Scope and Application, “Persons must still comply with all applicable predicate rule requirements for validation (e.g., 21 CFR 820.70(i)).”

Also, “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 and record integrity.”

Finally, “For further guidance on validation of computerized systems, see FDA’s Guidance for Industry and FDA Staff CDRH “General Principles of Software Validation” and industry guidance such as the “GAMP4 Guide for Validation of Automated Systems”.

For additional information, contact MasterControl at 800-825-9117, if interested in receiving the following three companion 21 CFR Part 11 white papers:

- Risks of Non-Compliance: Are You Ready for an FDA Inspection
- What Evidence Do I Show the FDA Inspector?
- MasterControl Feature Compliance

FDA In-house Training and Industry Education

Training for Investigators has expanded since the promulgation of 21 CFR Part 11, focused on evaluation of computer systems validation. Martin Browning provided input into the design of the training program prior to his retirement from FDA and conducted the training through his company, EduQuest, Inc., including Janis Halverson, a former FDA expert on computer systems validation. The primary purpose of the course was to provide FDA personnel (across all program areas) with a greater knowledge of computer system development and validation so as to provide a more consistent and thorough approach to investigation of these systems.

FDA insists that computer systems must be validated through a development life cycle containing strict guidelines with concept, user and functional requirements and design phases, followed by the implementation and testing with qualification protocols.

Since the promulgation of 21 CFR Part 11, extensive education and training programs on software/system development and validation have been promoted in the FDA industry. Initially, Martin Browning provided the FDA compliance training to industry audiences. Now on-line training through FDA’s Virtual University is available. ISPE GAMP offers education and training (see ispe.org). In addition, professional organizations such as PDA and IVT offer courses along with other organizations and consultants in the field.

GAMP: The “V” Model Framework for Specification, Design and Testing, using IQ/OQ/PQ Qualifications

Basic FDA requirements for computer systems validation include Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). The “V-Model” diagram shown in Figure 1 is one of the most commonly used methods for representing the “basic” framework for specification, design and build qualification. This methodology particularly lays emphasis on creating and maintaining a Master Validation Plan, documenting the entire process, while generating system requirements, design specifications, executing IQ/OQ/PQ qualifications and maintaining the software after it has been validated.

The “V-Model” was taken from the International Society for Pharmaceutical Engineering’s (ISPE) Good Automated Manufacturing Practice (GAMP4) Guide for Validation of Automated Systems, used widely in Pharmaceutical and Medical Device Manufacturing.

GAMP4 is the most widely used, internationally accepted, guideline for validation of computer systems. The GAMP4 Guide is now produced by ISPE and its GAMP Forum, a Technical Subcommittee of ISPE. Sion Wyn, GAMP founder, was part of the FDA Part 11 Workgroup that developed the 2003 Guidance for Industry; Part 11, Electronic Records; Electronic Signatures – Scope and Application. It referenced industry guidance such as the “GAMP4 Guide for Validation of Automated Systems”.

Paul D’Eramo, Executive Director for Worldwide Quality Policy and Compliance Management at Johnson & Johnson, and former FDA investigator, presented the “V-Model” at the ISPE Annual meeting in November 2000 in his Part 11 Implementation Strategies presentation. Johnson & Johnson is utilizing the GAMP methodology as an integral part of their computer validation guidelines in their Part 11 compliance program.

For more detailed information and how to obtain a copy of the GAMP4 Guide, visit: <http://www.gamp.org>.

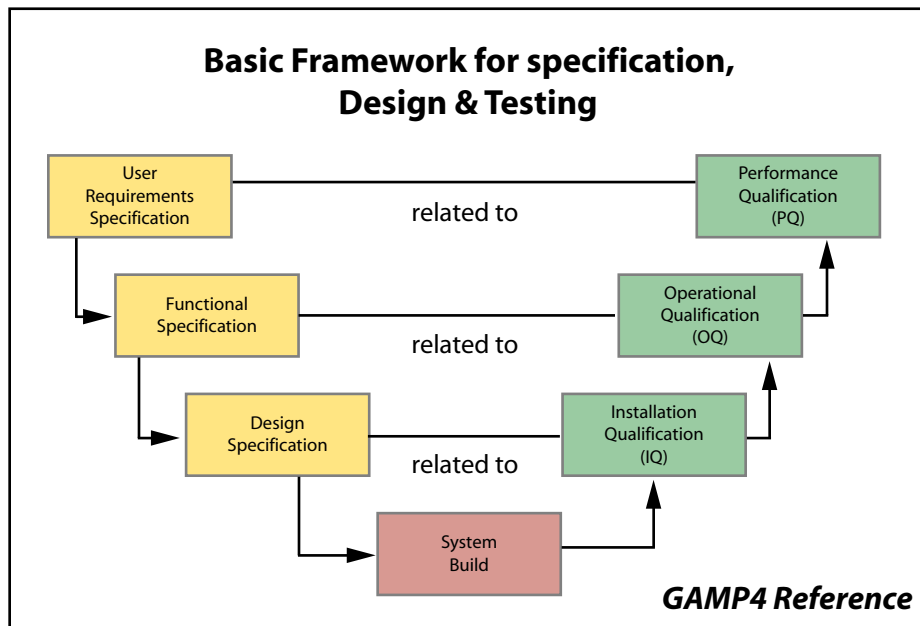


Figure 1 - GAMP4 V-Model for Validation of Automated Systems

GAMP4 defines categories of software and the guidance for the computer systems validation approach, as show in Figure 2. “Off-the-shelf” document control systems, such as MasterControl, fall in category 4 – Configurable Software Packages. GAMP4 Guide for validation includes a supplier audit and validation of the application and any custom code. The validation of the application is focused on specifications tied to IQ/OQ/PQ qualifications.

In order for FDA to consider configurable software systems, such as MasterControl, to be validated, the following steps in the system life cycle must be followed and documented. All these important elements of validation are presented in the GAMP4 Guide and used by MasterControl in performing “full-cycle” validation services:

- Validation Master Plan
- Risk Management Plan *
- User Requirements Specifications
- Vendor Assessment/Audit, Qualification and Acceptance
- Functional Description and Specification
- Design Specifications
- System Installation Qualification
- System Operational Qualification

- System Performance Qualification
- Validation Summary Report
- System SOPs and Training
- Maintenance, Continuous Monitoring, Change Control, and CAPA
- Security Measures

Category	Type of Software	Validation Approach
1	Operating Systems	Record Version
2	Standard Instruments	Record Configuration
3	Standard Software Packages	Validate Application
4	Configurable Software Packages	Audit Supplier, Validate Application and any Customer Code
5	Customer Systems	Audit Supplier and Validate Complete System

Figure 2 - Validation Approach for Software Systems

* The Risk Management Process has been defined through the GAMP4 Appendix M3 and through the FDA-referenced ISO 14971:2000 (Application of Risk Management to Medical Devices) standard.

For additional information, contact MasterControl at 800-825-9117, if interested in seeing a sample of IQ/OQ Protocols and the “best practices” Validation Toolkit.

Risk-Based Assessment and Risk Management Plans

As both FDA and industry have discovered over the past few years, “a one size fits all” interpretation of regulations, such as 21 CFR Part 11, is not feasible. The Agency has decided to put the onus of regulatory interpretation on the organizations that it regulates. This will allow and obligate companies to use a professional “science-based” approach with documented justification through Risk Management Plans.

FDA-regulated organizations must now justify their course of action based on their interpretation of the regulations as well as any risk associated with those actions. This has been discussed in the previous GAMP section and in the guidance document itself (2003 Guidance for Industry; Part 11, Electronic Records; Electronic Signatures – Scope and Application). There are various recommendations for using a documented justification to determine the need and/or extent of implementing certain Part 11 controls or performing certain regulatory activities. At the core of such justification would typically be some form of risk-based assessment with the purpose of targeting potential risks that may adversely affect operations and to document the strategies used to manage or avoid those risks. Documentation may include a formal Risk Management Plan that would detail the risk assessment and the risk mitigation activities during system implementation and IQ/OQ/PQ testing.

In regard to Part 11, where predicate rule requirements do not exist, a risk-based assessment may be used to determine the following:

- The critical risk factors
- The need for validation and the extent of testing required
- The need to implement audit trails (or an equivalent control) in the system and the form the audit will take
- The strategy for maintaining records integrity and reliability throughout their record retention period

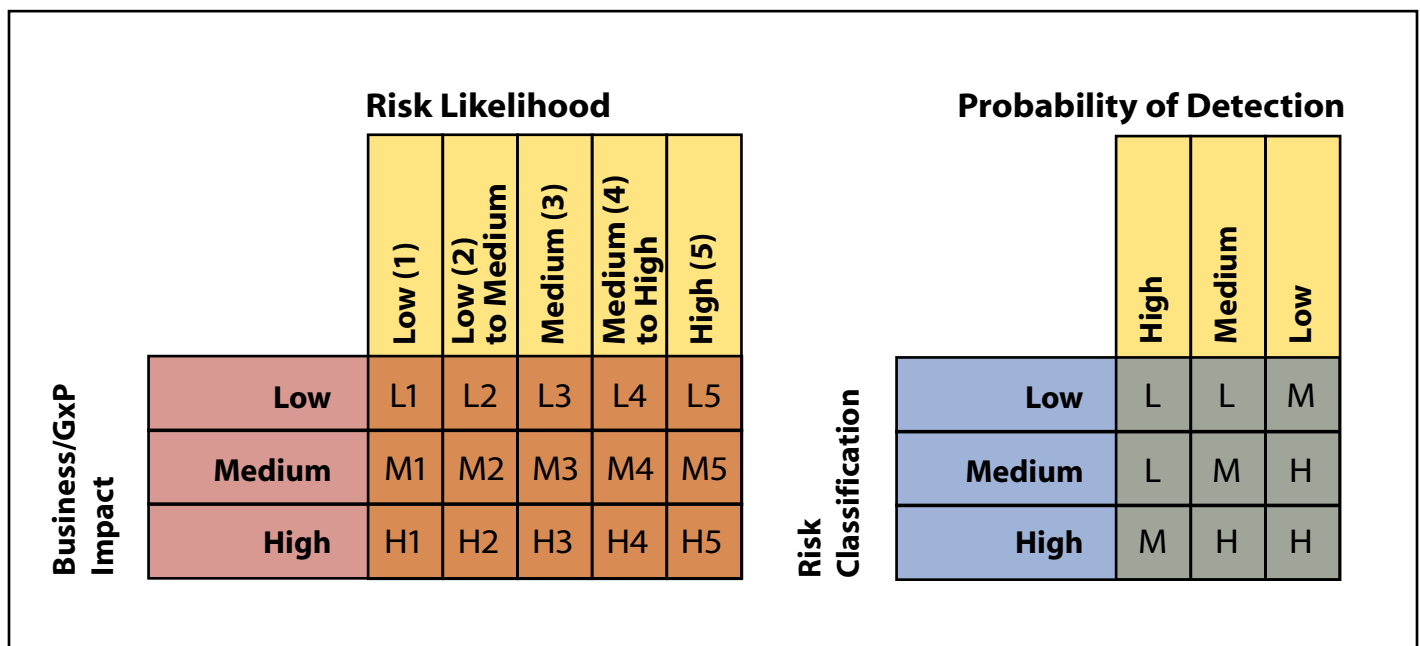
Risk assessment methodologies are well defined and typically involve identifying hazards and risk scenarios and the consequences of those adverse events. The next step is to classify and prioritize those risks using a number of risk factors. Business and GXP “Impact” is the most critical factor. The factors often used to assess are:

- **Impact** – The severity of the negative impact that will accompany an adverse event. This can be expressed on any scale deemed appropriate (High – Low).
- **Likelihood/Probability** – The likelihood of an adverse event occurring. This can be measured on a relative scale such as across a time period or number of operations. (High – Low, 1 – 5)
- **Detection** – The likelihood that a negative condition will be detected before the negative impact occurs.

The purpose of the GAMP4 Guide Appendix M3 is to describe a simple risk assessment process that may be applied to systems to enable targeting of the validation efforts to those areas and functions that most require it.

The following Figures 3 and 4 represent simple, graphical methods for assessing risk, which have been adapted from that found in the GAMP4 Guide. There are many other acceptable methods for performing such assessments including FMEA, FMECA, FTA, HAZOP and HACCP analysis.

Risk factors are generally rated on a scale of low, medium or high, although a wider scale can be used to achieve a finer granularity in classifying and prioritizing the likelihood of risks. There we use a scale of 1 to 5. Once the risk factors are determined, the impact and likelihood factors can be cross-referenced as in Figure 3 to achieve a risk classification. A final risk priority can then be determined by cross-referencing the results from Figure 3 with the detection factor in Figure 4.



Figures 3&4 - Risk Assessment Chart

The 2003 Part 11 Guidance – Scope and Application, references ISO 14971:2000, Medical Devices – Application of Risk Management to Medical Devices as a standard for risk methodology. The schematic representation of the risk management process is shown in Figure 5. This process scheme was used to develop a Risk Management Plan template for MasterControl EDMS validation.

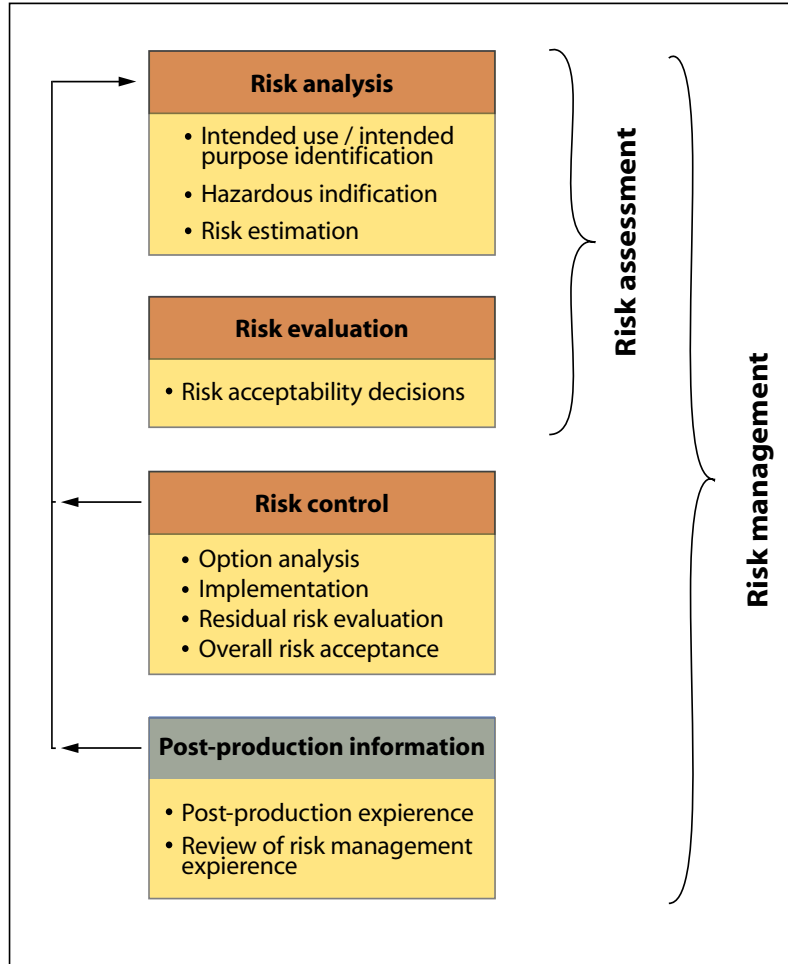


Figure 5 - Risk Management Process

For additional information, contact MasterControl at 800-825-9117, if interested in seeing samples of a Risk Management Plan, utilizing GAMP4 and ISO 14971 principles.

The final risk classifications and priorities can be used to make decisions on the need for/extent of validation, the need for/extent of audit trail implementation, and the strategy for record retention. For EDMS applications, the risk classification is sufficient.

In determining the need for validation, the risk assessment should generally involve reviewing, at a high level, the major functionalities and usage of the system and the potential health & business risks posed by adverse events based on those functions.

For justifying the extent of validation to be performed, the risk assessment will be similar to the one for identifying the need for validation. The key difference is that this assessment will be much more detailed and includes “digging down” into the sub-functions and user requirements and identifying the potential health and business risks posed by adverse events associated with those functions. The MasterControl Validation and Risk Management Plan address these in Section 3 - Risk Assessment Worksheet, and Section 4 - Risk Mitigation Activities and Project Monitoring.

To establish the need for and extent of audit trail functionality required by a system, the risk assessment should generally involve reviewing the potential health and business risks posed by both accidental and intentional adverse events associated with the traceability of and data integrity of the records. To determine the strategy for record retention, the risk assessment should generally involve reviewing the potential health and business risks posed by a loss in value of the records over time.

Consider an automated electronic document management system (EDMS) as a risk assessment example. It is used to store and revise documents; it maintains a database of all documents. Persons in different job descriptions can generate and automatically reference documents. In quality and production systems, the quality management documents include numerous predicate rule documents, such as Master Batch Records, Product Specifications, Test Methods, SOPs, Training Records and CAPA forms.

In an FDA-regulated industry, the system is subject to validation requirements. Validation is pertinent under the 21 CFR 820.70(i) reference.

One company that deploys this system is a small biotech pharmaceutical company. Performing risk assessment early and quickly identified that the failure of this system could lead to serious implications, for regulatory risk (inability to demonstrate the necessary control of documents required by 21 CFR 210/211/820), and more pertinently, that insufficient control could possibly result in compromise of regulatory documentation and/or the adulteration of the drug. Thus, the “full cycle” of validation with IQ/OQ/PQ was undertaken, as delineated in the GAMP section.

MasterControl Software Validation

The MasterControl family of quality management suite of software products is currently being used in over one hundred FDA-regulated companies. MasterControl meets and exceeds the functional requirements needed to help you comply with 21 CFR Part 11. MasterControl has been the subject of numerous pharmaceutical and medical device manufacturer supplier audits. Supplier auditors at Teva Pharmaceutical USA had this to say about MasterControl. “We have never reviewed a more complete and impressive validation plan offered for its software, than we have seen at MasterControl.”

MasterControl FDA Edition is “validation ready.” IQ/OQ Protocols can be purchased from MasterControl in the form of detailed validation test scripts for companies to do their own initial functional requirements qualification. The MasterControl Validation Services Staff can also perform the IQ/OQ Protocols, and can assist on-site with developing the “full cycle” of validation documentation, including the live, on-site PQ testing execution, if desired.

PQ is a process that insures the system meets specified user requirements and can do so repeatedly. PQ testing involves the documentation prep and execution of the PQ Protocols by trained users in a live, production environment. The testing is performed in accordance with SOPs developed for the application.

About MasterControl Inc.

MasterControl Inc. has been at the forefront of providing quality management software solutions since 1993. Hundreds of companies worldwide use MasterControl to help ensure compliance with FDA regulations such as 21 CFR Parts 11, 210-211, 820, 606; ISO quality standards such as ISO 9000, ISO 13485, ISO 14000; and Sarbanes-Oxley Act requirements. In addition to providing off-the-shelf products, MasterControl also offers comprehensive technical and customer support, including product training, implementation, and validation services.

For additional industry white papers about automating quality and regulatory processes, visit www.mastercontrol.com, or call, 800-825-9117.



MasterControl's integrated quality management system helps connect quality processes enterprise-wide. The solution provides automatic triggers to ensure tasks for handling quality-related incidents don't fall through the cracks. MasterControl's integrated architecture ensures that the completion of one system process automatically launches the next quality sub-system until the process loop is closed. Managers have analytical and reporting capabilities at their fingertips to track and manage each quality process through completion.

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