

White Paper:

21 CFR Part 11

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What's The Status of Part 11?

Organizations regulated by the U.S. Food and Drug Administration (FDA) like pharmaceutical, biotechnology, medical device, and others continue to experience the peaks and valleys of complying with 21 CFR Part 11. While the regulation itself has not changed, industry and the technological environment certainly have. As a result, FDA has announced its intention to provide additional guidance regarding Part 11 compliance and enforcement in 2005.

Adhering to the Part 11 requirements is a significant undertaking for most companies. However, the effort expended in doing so has proven beneficial because it allows an organization to capitalize on current technologies to automate existing paper-based processes. In order to do this, companies not only must filter through all the technologies available to automate current paper-based processes, but must understand how to comply with Part 11 and execute their plan.

This paper provides an overview of 21 CFR Part 11 and how it came about, how it is affecting the industry, and how companies can ready themselves for compliance. At the conclusion, a description is provided detailing the MasterControl suite of quality management solutions and how it has been designed with all the features necessary to go beyond 21 CFR Part 11 requirements and regulations for “best practices” (CGxP).

Background

The FDA published the 21 CFR Part 11 final ruling on March 20, 1997, to provide a standard of acceptance for electronic documents, electronic signatures, and handwritten signatures being used to execute electronic documents.

Because of the scare of “Y2K”, FDA withheld strict observance of Part 11 until after 2000 to allow IS professionals to focus their efforts on ensuring a flawless system transition. After Y2K settled, FDA started more vigorously enforcing Part 11. As a result, form 483 citations for Part 11 compliance started to build and became the focus of scrutiny by the industry because of varied enforcement interpretations given by FDA inspectors. In February 2003, FDA withdrew its Part 11 draft guidance communications pertaining to electronic copies of electronic records, validation, glossary of terms, maintenance of electronic records, and time stamps. In the withdrawal, FDA explained that its efforts to publicize and educate industry on Part 11 caused many aspects of the ruling to be misunderstood and that the guidance may not be representative of FDA’s approach under the new Current Good Manufacturing Practices (CGMP) initiative. According to the FDA, the withdrawal was made because Part 11, “(1) unnecessarily restricts the use of electronic technology in a manner that is inconsistent with FDA’s stated intent in issuing the rule, (2) significantly increases the costs of compliance to an extent that was not contemplated at the time the rule was drafted...” These two factors alone proved to hinder the use of new technology to advance automation and productivity which was contrary to what the regulation was intended.

Current State

In response to the February 2003 withdrawal, FDA issued the new 21 CFR Part 11 Scope and Applicability Final Guidance document in August 2003.

<http://www.fda.gov/cder/guidance/5667fnl.htm>

This guidance stated that electronic records must still be maintained in compliance to the underlying predicate rules, but that FDA will take a “risk-based” approach to enforcing compliance to some of the technical controls for Part 11 such as validation, audit trails, record retention and record copying. FDA stated it would be exercising enforcement discretion with regard to legacy systems that otherwise met predicate rule requirements prior to August 20, 1997, and would not take regulatory action to enforce compliance with any Part 11 requirements.

Recently, FDA has included 21 CFR Part 11 in its formal review of CGMP regulations and followed a more subjective course in taking regulatory action for compliance. The intent is to get back to regulations for “best practices” (together referred to as CGxP), or predicate rule fundamentals for the interpretation and enforcement of Part 11. These fundamentals involve systems for generating electronic records required in support of the CGxPs that encompass current good clinical practice (CGCP), current good laboratory practice (CGLP) and CGMP as mentioned earlier.

Re-examination of Part 11 is underway. FDA has stated that its next step is to issue a proposed amendment for public comment during 2005 as mentioned in the following report, “Pharmaceutical CGMPs for the 21st Century - A Risk-Based Approach Final Report,” that was released in the Fall of 2004. http://www.fda.gov/cder/gmp/gmp2004/GMP_finalreport2004.htm#_Toc84065746

Becoming Compliant

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. In the August 2003 Part 11 Guidance, FDA decided to put the onus of regulatory interpretation on the organizations that it regulates. This will allow and obligate companies to use a proven, “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. 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. 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 Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (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 CGxP “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

Risk assessment processes that may be applied to systems to enable targeting of the validation efforts to those areas and functions that most require it can be found in the Good Automated Manufacturing Practices 4 (GAMP4) Guide.

(NOTE: An additional white paper about risk management, risk management planning and validation, is available from MasterControl, entitled, “Good System Implementation and Validation Practices for Implementing and Validating Software.”)

Process & System Evaluation

Organizations should arrange a team consisting of members from Quality Assurance, Operations, Information Technology and Regulatory Affairs and Compliance to evaluate the areas Part 11 can impact. An area in which companies can misunderstand during their internal evaluation process is whether a process/system does or does not fall under Part 11. There are many information resources now available through various professional organizations and on the Internet, including FDA's Web site, to help avoid this common pitfall.

Once all core processes and systems are identified, they must be evaluated and then prioritized. During evaluation, the investment to bring existing or new systems into compliance should be determined. A decision can then be made whether a software solution from a professional software supplier is available that can replace the current system and can easily be validated and be Part 11 compliant, or whether it is more cost-effective to redo the system in-house. In the end, the easiest and most cost-effective method should be chosen.

System Validation

Validation of the software is mandated by FDA CGxP. A company must demonstrate that the software consistently does what the company intends it to do — repeatedly. In other words, it must meet company requirements for each purpose for which the software is used. One of the first items of information that could be asked by FDA Field Investigators is a list of users and functional and design requirements and how the system meets those requirements.

“If it isn't documented, it didn't happen,” is the common thinking within the FDA. Any quality management system must be Part 11/validation-ready. Not only must the software be qualified, but the processes or requirements the software fulfills must also require validation at the location the software is being used. IQ, OQ, and PQ methodologies should be used for each of these system validations, whether it is the initial validation or after software or systems have been upgraded. PQ must be done at the site in which the system is in use as a critical element of validation. Ongoing maintenance and scheduled internal reviews are necessary steps to maintaining the system. Companies must train all people involved with each process. If training has been completed and documented properly, the system is more likely to be repeatable and consistent.

MasterControl – In the Forefront of 21 CFR Part 11

Prior to the first release of 21 CFR Part 11 in 1997, MasterControl Inc. closely followed the creation and advancement of the regulation. In 1998, the company released a version of the MasterControl quality suite that became the first software solution to address 21 CFR Part 11 by providing all the security and electronic signature features necessary for regulated companies to ensure compliance. Although 21 CFR Part 11 requirements have evolved for system-wide compliance to documents and records that are at the highest risk, MasterControl continues to go beyond requirements for implementing a quality management software solution compliant with 21 CFR Part 11 and FDA CGxP requirements.

Since 1998, MasterControl Inc has helped many companies with Part 11 compliance. The MasterControl quality management suite offers off-the-shelf solutions for automating quality systems like corrective and preventive actions (CAPA), change control, training control and other document and forms/data-collection processes that are quality-driven. Each application is designed to provide all the security features to comply with 21 CFR Part 11. Validation test plans have been developed to simplify and speed IQ and OQ validation requirements. MasterControl's Professional Services Team can help support onsite and application-based PQ, consistent with user requirements, to fulfill Part 11 and CGMP requirements for computer systems validation requirements.

MasterControl has helped over 175 FDA-regulated companies implement electronic quality management system solutions. The MasterControl quality suite not only satisfies 21 CFR Part 11 technical requirements and ISO quality standards, but also exceeds the agency's strictest requirements.

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About MasterControl Inc.

MasterControl Inc. produces software solutions that enable regulated companies to get their products to market faster, while reducing overall costs and increasing internal efficiency. MasterControl securely manages a company's critical information throughout the entire product lifecycle. Our software is known for being easy to implement, easy to validate and easy to use. MasterControl solutions include quality management, document management/document control, product lifecycle management, audit management, training management, bill of materials, supplier management, submissions management, and more. Supported by a comprehensive array of services based on industry best practices, MasterControl provides our customers with a complete information management solution across the entire enterprise. For more information about MasterControl, visit www.mastercontrol.com, or call: 800-825-9117 (U.S.); +44 1256 325 949 (Europe); or 03-6801-6147 (Japan).



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