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White Paper:

21 CFR Part 11:
Risks of Noncompliance

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Introduction

When 21 CFR Part 11 took effect in August 1997, it was considered one of the most important regulations affecting pharmaceuticals, biotechnology, medical device, and other industries regulated by the FDA. The goal of Part 11 is to allow the use of modern technology in submissions and record keeping while ensuring reliability, authenticity, and validity of electronic records. With this rule, electronic records and signatures became as valid as paper records and handwritten signatures.

Numerous discussions between the FDA and regulated industries ensued, primarily focusing on the scope of interpretation of Part 11. According to the FDA, “Concerns have been raised that some interpretations... would (1) unnecessarily restrict the use of electronic technology in a manner that is inconsistent with FDA’s stated intent in issuing the rule, (2) significantly increase the costs of compliance to an extent that was not contemplated at the time the rule was drafted, and (3) discourage innovation and technological advances without providing a significant public health benefit. These concerns have been raised particularly in the areas of Part 11 requirements for validation, audit trails, record retention, record copying, and legacy systems.”

Due to these concerns, the FDA has embarked on a re-examination of Part 11. In the meantime, the agency issued “Guidance for Industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application” to describe how it intends to exercise enforcement discretion during the re-examination period.

Narrow Approach

Issued in August 2003, the guidance clarifies two important points. First, it stated unequivocally that Part 11 will be interpreted narrowly. With respect to records required to be maintained or submitted to FDA under predicate rules, Part 11 would apply only when persons choose to use records in electronic format instead of paper format. People who use computers to generate paper printouts of electronic records, but still rely on paper records to conform to FDA regulations, will not be compelled to follow Part 11.

“We recommend that, for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision (e.g., in a Standard Operating Procedure or specification document),” the FDA stated in the 2003 guidance.

Risk-Based Approach

Second, the FDA is taking a risk-based approach in enforcing compliance to some of the technical controls for Part 11 such as validation, audit trails, record retention and record copying. It will exercise enforcement discretion with regard to so-called legacy systems (systems in operation before Part 11 took effect on Aug. 20, 1997) that otherwise met predicate rule requirements. The agency will only take regulatory action against legacy systems if changes implemented since Aug. 20, 1997, prevent such systems from meeting predicate rule requirements.

Being Compliant

Throughout the guidance, the message is clear: compliance to the underlying predicate rules remains critical; the FDA will enforce predicate requirements for records subject to Part 11.

Although technology is advancing rapidly, FDA regulations remain the same. Regulated industries still need to demonstrate compliance to predicate rules. They must continue to be vigilant in fulfilling Part 11 obligations and in producing safe and high-quality products.

FDA Compliance Policy Guide – Section 160.850

This section represents the agency’s stance as to what is required of companies wanting to be fully compliant with 21 CFR Part 11.

- **Part 11 applies to all FDA program areas.** Part 11 describes the technical and procedural requirements that must be met if a person chooses to maintain records electronically and use electronic signatures. Part 11 applies to those records and signatures required by an FDA predicate rule. As explained in the preamble to the final rule, Part 11 does not grandfather legacy systems and FDA expects that firms using legacy systems will begin taking steps to achieve full compliance.
- **FDA regulatory action.** The agency will consider regulatory action with respect to Part 11 when the electronic records or electronic signatures are unacceptable substitutes for paper records or handwritten signatures, and therefore, requirements of the applicable predicate regulations (e.g., CGMP and Medical Device QSR regulations) are not met.
- **Nature and extent of Part 11 deviation(s).** FDA will consider Part 11 deviations to be more significant if those deviations are numerous, if the deviations make it difficult for the agency to audit or interpret data, or if the deviations undermine the integrity of the data or the electronic system. For example, FDA expects that firms will use file formats that permit the agency to make accurate and complete copies in both human readable and electronic form of audited electronic records. Similarly, FDA would have little confidence in data from firms that do not hold their employees accountable and responsible for actions taken under their electronic signatures.
- **Effect on product quality and data integrity.** For example, FDA would consider the absence of an audit trail to be highly significant when there are data discrepancies and when individuals deny responsibility for record entries. Similarly, lack of operational system checks to enforce event sequencing would be significant if an operator's ability to deviate from the prescribed order of manufacturing steps results in an adulterated or misbranded product.
- **Adequacy and timeliness of planned corrective measures.** Firms should have a reasonable timetable for promptly modifying any systems not in compliance (including legacy systems) to make them Part 11 compliant, and should be able to demonstrate progress in implementing their timetable. FDA recognizes that technology based controls may take longer to install in older systems.
- **Compliance history of the establishment,** especially with respect to data integrity. FDA will consider Part 11 deviations to be more significant if a firm has a history of Part 11 violations or of inadequate or unreliable record keeping. Until firms attain full compliance with Part 11, FDA investigators will exercise greater vigilance to detect inconsistencies, unauthorized modifications, poor attributability, and any other problems associated with failure to comply with Part 11.

Warning Letters

The following are sample FDA warning letters to companies cited for Part 11 nonconformance:

Rosenthal Eye and Plastic Surgery, Great Neck, N.Y. (April 11, 2005)

“...Our review of the inspection results also noted that you use an electronic medical record (EMR) system to maintain medical and other clinical data for your patients, including study subjects...”

“...Please note that Title 21, Code of Federal Regulations, Part 11, ‘Electronic Records; Electronic Signatures,’ outlines specific requirements that must be met for any system that is being used to maintain required records. In addition to the information requested above, please submit the following:

- documentation of the validation of your EMR system to ensure accuracy, reliability, and the ability to detect altered or invalid records.
- documentation of the ability to generate accurate and complete copies of records suitable for inspection, review, and copying by the agency.

- documentation of a secure, computer-generated, time-stamped audit trail that can independently record the date and time of the operator entries and actions that create, modify, or delete electronic records, and to verify that record changes do not obscure previously recorded information....”

Earlham College Analytical Laboratory, Richmond, Indiana (July 29, 2002)

“...The inspection reported the laboratory is performing analytical testing for a drug manufacturing firm in serious violation of the Federal Food, Drug, and Cosmetic Act...Our investigator documented numerous significant deviations from the Good Manufacturing Practice Regulations, Title 21, Code of Federal Regulations (CFR), Part 211....”

“...In addition to the above listed violations, our investigator noted that the laboratory is using an electronic record system for processing and storage of data from the atomic absorption and HPLC instruments that is not set up to control the security and data integrity in that the system is not password controlled, there is no systematic back-up provisions, and there is no audit trail of the system capabilities. The system does not appear to be designed and controlled in compliance with the requirements of 21 CFR Part 11, Electronic Records....”

Baxter Healthcare Corp., Deerfield, Illinois (Aug. 11, 2000)

“...We further request details regarding steps your firm is taking to bring your electronic cGMP records into conformance with the requirements of 21 CFR Part 11; Electronic Records; Electronic Signatures. Part 11 establishes requirements to ensure that electronic records and signatures are trustworthy, reliable, and generally equivalent substitutes for paper records and traditional handwritten signatures. Electronic records and signatures may be used to meet record and signature requirements of 21 CFR Parts 210 and 211, when Part 11 requirements are met....”

“Please outline your firm’s global corrective action plan, including timeframes for correction, to address this Part 11 issue....”

MasterControl Solution

The MasterControl[™] quality management solution offers an integrated approach to meeting FDA and ISO regulations. It provides time-stamped audit trail, document control, routing, and electronic signature capabilities that fully satisfy 21 CFR Part 11 requirements. MasterControl also offers comprehensive software training and validation services to ensure quality implementation.

The MasterControl quality suite consists of the following configurable, easy-to-use, off-the-shelf products that interconnect data, processes, and people to maintain compliance and promote efficiency throughout an organization:

- **MasterControl Portal[™]** – a 100 percent Web-based delivery platform for the entire MasterControl quality suite. It’s especially critical for companies with FDA 21 CFR Part 11 requirements for electronic records and signatures.
- **MasterControl Documents[™]** – The essential building block within the MasterControl suite, this software manages and controls documents in a secure environment. It can handle all types of documents regardless of the software used to create them. Document types, vaults, lifecycles, routes, and users’ roles are all configurable.
- **MasterControl Submissions[™]** – This application provides complete document lifecycle management from document creation and control to submission and beyond. It streamlines the dossier-creation process with ready-to-use templates authorized for FDA submissions, such as new drug application (NDA), biologic licensing application (BLA), common technical document (CTD), and investigational new drug (IND).

- **MasterControl Forms™** – This module automates forms-based processes, such as audits, nonconformances, deviations, and customer complaints. It makes the transition from a manual/hybrid system to an automated solution easier because it allows users to create electronic forms identical to their existing hard-copy forms. Companies can also design new forms to suit their needs.
- **MasterControl CAPA™** – Closely related to the Forms module, this application is designed to make implementation of corrective/preventive actions (CAPA) efficiently and effectively. It collects data from multiple sources, manages trends, connects and automatically triggers sub-system processes to solve production issues.
- **MasterControl Training™** – This software allows the creation and deployment of simple or extensive training courses that require trainees to learn their tasks and demonstrate competency. It seamlessly integrates with MasterControl Documents to automatically task trainees when required SOPs or other documents change and a new training becomes necessary.
- **MasterControl Collaboration™** – Its Internet-based architecture connects employees and departments – regardless of location – to make it easier to share ideas, improve document content, and obtain approval and sign-off. Tasks are automatically sent to all affected users, accompanied by e-mail notification. Everyone in the collaboration group gets to see each other’s input, avoiding duplication.
- **MasterControl PDF Publishing** – With this module, a company can put a stop to unauthorized circulation of printed and electronic “rogue” documents. It preserves record authenticity, enhances security, and improves compliance by restricting users’ rights to copy or revise documents.

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About MasterControl

MasterControl Inc. is a global provider of GxP process, quality audit, and document management software solutions for life science companies. MasterControl™ products are easy to use, easy to deploy, easy to validate, and easy to maintain. They incorporate industry best practices for automating and connecting every stage of the product development cycle, while facilitating regulatory compliance. By combining an integrated platform with a continuum of risk-based software validation products and services, MasterControl drives down the total cost of ownership and enables customers to extend their investment across the enterprise. Hundreds of companies, including 50 percent of the top 20 pharmaceutical enterprises, currently use MasterControl solutions for easier compliance, faster validation, and better process management. For more information about MasterControl, visit www.mastercontrol.com, or call 800-825-9117 (U.S.) or +44 (0) 1256 325 949 (Europe).



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