

21 CFR part 11

Electronic Records; Electronic Signatures

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Introduction

21 CFR part 11 defines criteria under which the United States Food and Drug Administration (FDA, a/k/a Agency) considers electronic records and signatures trustworthy, reliable and equivalent to paper records and handwritten signatures, respectively. It applies to records electronically created, modified, maintained, archived, retrieved, or transmitted under any records requirements per FDA regulations. “CFR” refers to the *Code of Federal Regulations*, which represent the rules and regulations contained in the *Federal Register* by the executive departments and agencies of the Federal Government of the United States. Title 21 of the CFR governs food and drugs, and section (part) 11 within Title 21 specifically addresses use of electronic records and signatures.

This regulatory standard, effective since August 1997, was intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health in the United States. The “use of technology,” in this context, refers specifically to additional regulatory requirements applicable to the use of computerized systems to support processes already within FDA's scope of responsibility (e.g., pharmaceutical and medical device-related activities pertaining to, but not necessarily limited to, research and development, manufacturing, laboratory operations, conduct of clinical trials). The requirements already within FDA's scope of responsibility are referred to as “predicate rules” and are set forth in the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and FDA regulations other than 21 CFR part 11.

As a result of an incomplete understanding of the implementation and applicability of, and enforcement considerations related to, 21 CFR part 11, concerns were raised within the pharmaceutical, biotechnology and medical device industries that the 21 CFR part 11 regulation in fact 1) unnecessarily restricted the use of electronic technology, 2) significantly increased the cost of compliance and 3) discouraged innovation and

technological advances. The FDA responded with enforcement policy guidelines and other draft guidance documents designed to provide additional insight into the Agency's thinking regarding the regulation. Ultimately, in August 2003, the FDA withdrew the enforcement policy guidelines and draft guidance documents and issued a "scope and application" guidance document which introduced the Agency's policy of "enforcement discretion" to address the industry concerns described above. The Agency also issued, in 2007, guidance related to computerized systems used in clinical investigations to supplement both this "scope and application" guidance and the Agency's international harmonization efforts when applying existing guidance to electronic source data generated at clinical study sites.

As the latest development, the FDA announced in July 2010 that it will be conducting a series of inspections to assess the life science industry's compliance and understanding of 21 CFR part 11 in light of the enforcement discretion described in the "scope and application" guidance document. These 21 CFR part 11-focused inspections are currently being performed and, where necessary, compliance issues brought to the attention of company management in the form of FDA-483 observations and, when applicable, warning letters.

Overview

21 CFR part 11 provides control objectives for establishing trustworthiness and reliability of electronic records and electronic signatures. These control objectives can be classified as "technical" controls and "procedural" controls:

- "Technical controls" relate to the status of, and specific functionality built into, computerized systems used to support regulated activities; each applicable computerized system must evidence compliance to these controls. Technical controls include, but are not limited to, the following: 1) the computerized system performs as intended; 2) only authorized access to and use of the computerized system is permitted; 3) all regulated data is maintained, can be reconstructed and can be readily retrieved; 4) the uniqueness of authentications (e.g., User ID and Password combinations) regarding using the computerized system and applying electronic signatures can be guaranteed; and, 5) electronic signatures cannot be removed, copied/pasted to other electronic records or otherwise tampered with. The proper operations to achieve compliance to these technical controls must be supported by appropriate testing (e.g., confirmation of functionality, challenge/stress testing as applicable) and objective evidence (e.g., test scripts and screen prints/reports that provide confirmation of test results, traceability from tests to requirements to confirm that all functionality has been tested). Regarding those instances where the computerized system design provides compliance to a given technical control objective, the pertinent design feature/function (e.g., system functionality) should be documented in adequate detail - in a functional specification and/or technical design document - to permit one to understand how the feature/function works.
- "Procedural controls" are those policies and procedures, preferably global in scope, which define processes that support compliance to 21 CFR part 11. These policies and procedures will be designed to promote outcomes such as, but not necessarily limited to, the following: 1) computerized systems are developed, deployed and maintained in a formal and appropriate manner, 2) all documentation for computerized systems is current and reflective of the operation of the respective system, 3) all electronic records are backed up and recoverable, 4) all electronic records are protected against unauthorized logical and physical access, and 5) all staff who develop, maintain and use the respective computerized system is appropriately trained. All policies and procedures should be developed, approved and maintained as "controlled documents" which are versioned documents, populated with specific information, and are generated and maintained to support a regulated activity.

21 CFR part 11 does not mandate how the above control objectives are to be met. The FDA leaves it to the company to develop appropriate systems, policies and procedures. The Agency will review the system functionality and the existence of, and compliance to, policies and procedures as part of an inspection of the company.

Is 21 CFR part 11 relevant to your organization?

A US-based or international life science company must comply with 21 CFR part 11 under the following circumstances: 1) the company markets or is planning to market its product(s) in the United States, or supports any domestic or international life science company(ies) that markets or is planning to market its product(s) in the United States and 2) any of the following scenarios apply:

- Records that are required to be maintained under predicate rule requirements will be maintained in electronic format in place of paper format;
- Records that are required to be maintained under predicate rules will be maintained in electronic format in addition to paper format, and the electronic records are relied on to perform regulated activities;
- Records that are submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations), in electronic format (assuming the records have been identified as the types of submissions the Agency accepts in electronic format);
- Electronic signatures are intended to be the equivalent of handwritten signatures, initials, and/or other general signings required by predicate rules. 21 CFR part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with applicable predicate rules (e.g. approval, review, and verification).

Global Adoption

21 CFR part 11 applies only to the United States, so the concept of “global adoption” of the regulation is not applicable. However, similar standards exist. For example, the European Commission has adopted Annex 11 (Computerized Systems) to Volume 4 (Good Manufacturing Practice (GMP) - Medicinal Products for Human and Veterinary Use) of the Rules Governing Medicinal Products in the European Union (EudraLex). Annex 11 is patterned after 21 CFR part 11 and applies to all forms of computerized systems used as part of GMP-regulated activities. The basic premise of Annex 11 is as follows: where a computerized system replaces a manual operation, 1) there should be no resultant decrease in product quality, process control or quality assurance and 2) there should be no overall process-related risks.

Benefits

If implemented correctly, 21 CFR part 11 can help to:

- Ensure the protection and ready retrieval of electronic records
- Ensure operational consistency across all departments
- Improve productivity and efficiency of existing staff through automation
- Minimize and possibly eliminate the maintenance and retention of paper documentation
- Meet study timelines
- Perform faster study-related searches and establish trends
- Provide study-related submission information in formats acceptable to the FDA

Auditing

Ensuring compliance to 21 CFR part 11 (i.e., adequacy of established controls and compliance to established controls) is accomplished primarily through formal and regular internal audits performed by qualified Quality Unit (QU) representatives. These representatives may either be company's employees or independent contractors. Such a choice is usually dependent on 1) internal staff size vs. number of audits to perform and/or 2) internal staff expertise with 21 CFR part 11 requirements and industry-standard compliance practices. In addition, third-party contractors may be used to perform the internal audits in those cases where a company is looking to gain completely independent feedback regarding its compliance to the subject regulation. The frequency of the internal audit of the company's compliance to 21 CFR part 11 can be "as-needed," based on business needs, and/or set forth in a formal audit schedule (e.g., every two years).

Where the company utilizes outsource partners for support, FDA expects the company to audit the vendor/supplier for compliance to the 21 CFR part 11 regulation to the extent that the nature of the support of the outsource partner is related to company's regulated activities. The most common areas of regulated support include, but are not necessarily limited to, manufacturing, laboratory, packaging, data management, distribution, data processing and data hosting operations. These outsource partner audits are referred to as "external audits." The reason for these audits is simple: the company is responsible for the product/service provided by the outsource partner, so it is a requirement to ensure that appropriate regulatory controls are in place. The logistics, activities and timing for conducting audits of outsource partners are, for all intents and purposes, the same as for conducting internal audits (as described above).

The company's compliance to 21 CFR part 11 among other regulations will also be assessed by outside parties, either client companies to whom the subject company is an outsource partner or the FDA itself. Client companies will seek to perform pre-qualification audits as part of the contracting process and periodic follow-up audits to assess the company's continuing regulatory compliance.

The FDA will look to perform, as it considers necessary, a pre-approval inspection to support their review of a submission, a facility inspection as part of their normal oversight of life science companies and/or "for cause" inspections to investigate potential problems. In addition to the company's compliance to 21 CFR part 11, one of the areas that will be included in such an audit is the effectiveness of the QU's operations in general.

In all cases, all auditors are assessing the trustworthiness and reliability of 1) electronic records with respect to safety and efficacy of the product, 2) electronic signatures if applicable, 3) processes that generate, maintain and/or process the electronic data and 4) documentation that should confirm that the respective computerized systems were designed as intended and that the computerized systems do what they are supposed to do throughout their life.

Choosing a Registrar

No registrar is required for 21 CFR part 11. Therefore, this section is not applicable.

Route to registration

No registration is required for 21 CFR part 11. Therefore, this section is not applicable.

Costs

For most companies - whether computer-related activities are performed internally, are outsourced, or are a combination of internally-performed and outsourced - the "cost of doing business" already includes expenses associated with 1) computerized systems development, deployment, maintenance (change controls), etc., and 2) Information Technology infrastructure to ensure electronic records' protection. In general, the control objectives provided in 21 CFR part 11 (see Overview section) represent goals that companies should be striving to comply with as part of daily operations anyway to ensure quality products and data. Therefore, to the extent

that a company is successful in doing this, any additional costs, specific to compliance with 21 CFR part 11, should not be significant because “best practices” associated with computerized systems and Information Technology operations would already be in place.

Additional cost, specifically related to achieving compliance to 21 CFR part 11, would result from activities such as, but not necessarily limited to, 1) formalizing existing procedures to acceptable industry standards , 2) documenting computerized system development, testing, implementation and maintenance to acceptable industry standards, 3) developing 21 CFR part 11-specific computerized system features and functions, 4) generating and maintaining records to allow auditors to confirm the company’s compliance with policies and procedures, 5) documenting and retaining training documentation in a formal manner, and 6) implementing a formal audit program and a rigid audit schedule. Development of testing documentation for a computerized system is usually commensurate with the nature and complexity of the computerized system and may become the most time-consuming and costly part of the effort.

For companies that are first automating its processes and/or are not employing “best practices” regarding computerized systems and associated operations, the infrastructure described above needs to be created. The associated costs, therefore, will add to the “cost of doing business.” In this circumstance, the documentation for a control-oriented infrastructure and the computerized systems should be implemented correctly from the start, thus encompassing any further additional costs specific to compliance to 21 CFR part 11.

When implementing any of the activities to achieve and maintain compliance to 21 CFR part 11, third-party assistance may be advisable for those companies that have little experience with 21 CFR part 11-related computerized systems or have limited resources. Third-party assistance may be considered for activities like 1) developing documentation in support of 21 CFR part 11 compliance, 2) creating and/or executing testing documentation for a computerized system, 3) performing an internal or vendor audit, 4) developing requisite policies and/or procedures, etc. The following should be taken into account when considering third-party assistance:

- Define functional requirements of the computerized system in enough detail
- Establish realistic timelines for the project completion
- Select third-party vendors based on their experience and industry reputation
- Receive quotations from several third-party vendors
- Do not select the cheapest third-party vendor without a thorough due diligence as either there may be hidden costs or their service may be sub-standard
- Develop a robust service level agreement and tie payments to established and agreed-upon milestones
- Upon project completion, ensure that appropriate knowledge transfer takes place, if applicable

The following additional points regarding costs associated with computerized systems should be noted:

- If a computerized system is purchased/leased rather than developed in-house, 1) “per seat” and/or annual licence fees may apply and 2) the vendor may mandate periodic upgrades to the computerized system, which may require additional staff time and costs to implement and document
- All computerized systems need to be modified from time-to-time due to bug fixes and/or enhancements. Such changes will require additional staff time and will result in additional development-, testing- and documentation-related costs. However, these “maintenance” costs normally are less than the initial costs associated with the implementation of a computerized system that meets 21 CFR part 11 requirements.

Certification Costs

No certifications are required or applicable and, therefore, “certification costs” are not applicable.

Contributing Editor

The Practical Solutions Group, LLC is a Princeton, NJ consultancy focusing on the following support areas:

- ***Developing/simplifying the quality infrastructure and business processes:*** demonstrated success in helping clients to achieve and maintain regulatory compliance without increasing costs, expanding timelines and/or adding resources
- ***Performing high-quality audits and assessments:*** demonstrated added value through performing mock FDA inspections, and auditing/assessing operations for compliance to GxPs, 21 CFR part 11, etc.
- ***Selecting and managing outsource partners:*** demonstrated success with predicting potential operational/regulatory compliance issues and remedying existing ones at prospective outsource partners

The value of our strategic and tactical advice, assessments and deliverables rises to the level of the big name consulting firms but at a much more affordable rate. Our view is that all regulatory compliance issues are symptoms of operational problems. We help companies to avoid and/or remedy both through integrating the principles of regulatory compliance and business operations by 1) assessing efficiency of operations, 2) proposing ways to simplify processes through eliminating redundancies and minimizing documentation and 3) identifying underlying business problems and risk factors that may eventually stifle growth and negatively affect profits.

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Related Standards

- Annex 11 (Computerized Systems) to Volume 4 (Good Manufacturing Practice (GMP) - Medicinal Products for Human and Veterinary Use) of the Rules Governing Medicinal Products in the European Union (EudraLex)
- FDA Guidance for Industry: Computerized Systems used in Clinical Investigations
- FDA General Principles of Software Validation; Final Guidance for Industry and FDA Staff
- FDA Glossary of Computerized System and Software Development Terminology
- FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures - Scope and Application
- ICH E6 – Good Clinical Practice: Consolidated Guidance (issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use)