

Based on research by:

Karl Mousley

Written by:

Karl Mousley

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EDC Management

P.O. Box 384
Conshohocken, PA 19428
484-530-0300 (voice)
610-567-0357 (fax)
info@edcmanagement.com
www.edcmanagement.com

FDA Withdraws Guidance for Industry 21 CFR Part 11

EDC Today is an independent publication on current information and issues in Electronic Clinical Systems (ECS) strategies and technologies for the Biotechnology and Pharmaceutical (biopharma) industry. Each month we examine topics related to ECS theory, technology, practice, or implementation.

To assist organizations making the transition from paper-based clinical trials to Electronic Data Capture (EDC) facilitated trials, our seventeenth issue takes a look at the ramifications and implications of the Food and Drug Administration's (FDA) withdrawal of its Guidance for Industry Part 11, Electronic Records; Electronic Signatures on February 4, 2003.

Introduction

In the Federal Register: February 4, 2003 (Volume 68, Number 23) the FDA published a notice stating:

The Food and Drug Administration (FDA) is announcing the withdrawal of a draft guidance entitled "Guidance for Industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records."¹

It should be clearly noted that the FDA did not withdraw 21 CFR Part 11. The regulation is still in place. The guidance, however, which has the force of "strongly recommended", was withdrawn.

What happened? What does this mean?

A Little Background

When a biopharma embraces an EDC system, they are faced with compliance issues in converting from the requirements of the paper-based process to the new electronic environment.

In response to requests from the biopharma industry, the United States Food and Drug Administration (FDA) issued a regulation that provides criteria for the FDA's acceptance of electronic records. With this regulation, entitled Rule 21 CFR Part 11, a biopharma could effectively adopt electronic record keeping systems.

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Currently the use and submission of electronic records is voluntary. Nonetheless, biopharma companies are trying to implement the rule as quickly as possible for two distinct reasons. First, companies want to maintain their competitive advantage by streamlining data management processes with electronic records. Second, companies predict that the FDA will ultimately migrate entirely to electronic record systems from the more labor-intensive and error-prone practice of paper record keeping. In fact, the FDA had an internal mandate to be able to accept fully electronic filings by June 2003. While this does not require industry sponsors to submit electronic filings, it certainly foreshadows an evolving preference for electronic data over paper records.

Still, some biopharma companies are slow to embrace emerging technologies, in part from an uncertainty of how to achieve and maintain compliance. Whether companies are already equipped with the latest technologies or are new to electronic record keeping, 21 CFR Part 11 compliance has become a fundamental business priority. As the FDA has begun enforcement activities around 21 CFR Part 11, all existing electronic record systems must come into compliance within a reasonable time frame.

Scope of 21 CFR Part 11

When 21 CFR Part 11 was signed into law in 1997, its scope was poorly understood. In essence, it was a response to advances in the tools and equipment being used in conducting clinical trials. The regulation’s premise was to maintain proper identifiers for electronic data relevant to product safety, purity and efficacy.

In theory, the regulations found in 21 CFR Part 11 are only extensions to existing regulations. Part 11 essentially takes rules pertinent to paper documents (i.e., “predicate rules”) and applies them to electronic records. Part 11 is built on these predicate rules – the specific regulations that require “documentation” on the part of the sponsor.

With 21 CFR Part 11, biopharma companies must take the familiar predicate rules – for example, the Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (cGMP) regulations – and apply them to electronic records. Just as the predicate rules established requirements for paper-based record content, signing, and retention, 21 CFR Part 11 establishes the requirements for electronic record keeping.

Quick Definition:

A Predicate Rule – Any requirement set forth in the Federal Food, Drug, and Cosmetic Act, the public Health Service Act, or any FDA regulation is referred to as a predicate rule. Most predicate rules are contained in Title 21 of the Code of Federal Regulations (21 CFR.)

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Though the spirit of 21 CFR Part 11 can easily get lost in the blur of technical terms and requirements, it is important to remember the two main goals of the regulation. First, the FDA wants to be able to verify data from the moment of collection through the final statistical analysis. This requires tracking who handled the data, when, and why. Second, the FDA wants to know that software and hardware systems supporting 21 CFR Part 11 are working correctly. This requires validation. Both of these goals are carried over from the world of paper-based data collection, management, and analysis.²

For more information about the nature and scope of 21 CFR Part 11, refer to EDC Today™ Issue 3, “Regulations and EDC: Assuring Compliance”.

What is Presently Happening

On February 4, 2003, the FDA withdrew its draft guidance “Guidance for Industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records.” In outlining its reasons for the withdrawal, the FDA states:

“Concerns have been raised that some interpretations of the Part 11 requirements 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.”³

The FDA says the guidance was withdrawn “because we wanted to avoid loss of time spent by industry in an effort to review and comment on the draft guidance when that draft guidance may no longer be representative of FDA's approach under the new CGMP initiative.” Furthermore the FDA says,

“As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics³, FDA is embarking on a re-examination of Part 11 as it applies to all FDA regulated products. We may revise provisions of Part 11 as a result of that re-examination. This guidance explains that, while this re-examination of Part 11 is under way, we will narrowly interpret the scope of Part 11. It also explains that we intend to exercise enforcement discretion with respect to certain Part 11 requirements. We will not normally take regulatory action to enforce compliance with the validation, audit trail, record retention, and record copying requirements of Part 11 as explained in this guidance.

In addition, we intend to exercise enforcement discretion and will not normally take regulatory action to enforce Part 11 with regard to systems that were operational before August 20, 1997, the effective date of Part 11, (commonly known as existing or legacy systems) while we are re-examining Part 11.”⁴

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The FDA will be re-examining 21 CFR Part 11 and will potentially revise the regulation. In the meantime, they will be restricting their actions in regards to enforcing compliance. The FDA will narrowly interpret 21 CFR Part 11 and they will not concern themselves with existing or legacy systems implemented prior to August 20, 1997. Biopharmas should still be concerned with legacy systems since the FDA will likely revisit them, but for the time being they are of lesser importance in the eyes of the FDA.⁵

Section III.B.2 of the draft guidance defines Part 11 Records, specifically identifying those records that it will continue to expect to comply with regulation 21 CFR Part 11.

In short, the following will fall under 21 CFR Part 11 regulations:

- Records required by predicate rules that are maintained in electronic format in place of paper.
- Records required by predicate rules that are maintained in electronic format in addition to paper if the electronic record is relied on to perform regulated activities. The FDA recommends the sponsor determine in advance and document in SOP, which records (electronic or paper) will be used for regulatory activity.
- Records submitted to the FDA, under predicate rules, in electronic format.
- Electronic signatures that are intended to be the equivalent of handwritten signatures or initials required by predicate rules.

Section III.C describes the FDA's Approach to Specific Part 11 Requirements and its enforcement intentions.

- Validation – The FDA intends to exercise enforcement discretion regarding specific Part 11 requirements for validation.
- Audit Trail – The FDA intends to exercise enforcement discretion regarding specific Part 11 requirements for computer-generated, time-stamped, audit trail. The FDA further states that even when there are no predicate rule requirements to document changes, it suggests an audit trail be maintained.
- Legacy Systems – The FDA intends to not enforce Part 11 compliance with these systems, stating only that they must comply with predicate rules and “be fit for their intended use.”
- Copies of Records – The FDA intends to exercise enforcement discretion regarding specific Part 11 requirements for generating copies of records. They recommend copies of records be produced in common portable formats and use established automated conversion or export methods to make copies in a more common format (including PDF.)
- Record Retention – The FDA intends to exercise enforcement discretion regarding specific Part 11 requirements for the protection of records throughout the records retention period.

We recommend that those who work within the FDA predicate rule regulated environment read the new draft guidance (<http://www.fda.gov/cber/gdlns/prt11elect.pdf>).⁴ It is fairly concise and understandable.

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Conclusion

While it was somewhat surprising that the FDA withdrew its draft guidance on 21 CFR Part 11, it should be noted that they did not withdraw 21 CFR Part 11. The regulation is still in force and compliance will be expected.

Many EDC products support electronic signatures and have extensive audit trailing capabilities so that implementing EDC should not be problematic in regards to 21 CFR Part 11 in any event.

Biopharmas should use this “grace period” to revisit their 21 CFR Part 11 initiatives and continue to be diligently implementing their plans to become compliant. They should not expect the FDA to “drop” the matter completely or even indefinitely.

References

¹ Food and Drug Administration, <http://www.fda.gov/cber/gdlns/esigcopieswdr1.htm>

² *EDC Today*TM, Issue 3, “Regulations and EDC: Assuring Compliance”

³ Food and Drug Administration, <http://www.fda.gov/cber/guidelines.htm>

⁴ Food and Drug Administration, <http://www.fda.gov/cber/gdlns/prt11elect.pdf>

⁵ Food and Drug Administration, <http://www.fda.gov/cber/>



Who's behind the research?

Our lead researcher, Kirk Mousley, PhD received BS and MS degrees in Electrical Engineering from MIT and a PhD in Computer Science from Lehigh University. He has been the President of Mousley Consulting, Inc. since its founding in 1993 and has directed the company's efforts in the areas of clinical database design, data editing/cleaning, document management, and submissions.

Karl Mousley received his BS in Mechanical Engineering from Rose-Hulman Institute of Technology and a MS in Computer Science from Villanova University. He has been a senior member of the technical staff at Mousley Consulting, Inc. since 1993. Among his significant accomplishments are the investigation, evaluation, and implementation of new computer technologies for clinical data management systems and developing strategic plans for integrating these technologies into current systems. He has extensive experience preparing Standard Operating Procedures (SOPs).



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