21 CFR Part 11: The Role of Predicate Regulations and Associated Internal Policies

Are the records maintained in a computerized system subject to 21 CFR 11? Does 21 CFR 11 apply to a computerized system that is only used for “administrative/tracking” functions? Is an e-mail of an electronic record subject to 21 CFR 11?

We often lose sight of the fact that answers to these types of questions depend on underlying predicate regulations and internal policies. 21 CFR 11 does not stand alone; record and signature requirements flow from current Good Clinical Practice (GCP), Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and the Quality System Regulation (collectively referred to as GxP). A company’s internal policies, as well as the behaviors of system end users, also influence, and potentially expand, the scope and applicability of 21 CFR 11. This article provides an overview of: key record and signature provisions in GxP; the role of internal policies in defining identification and maintenance of regulated records and signature requirements; and the potential impact of computerized system end user behavior when utilizing general purpose applications such as e-mail.

INTRODUCTION

One of the most common questions a compliance professional encounters about 21 CFR 11 (hereinafter Part 11) is “Does Part 11 apply to System X?” The person asking the question usually expects a quick and ready answer (and more often than not, hopes the answer is “no”). The answer, however, usually requires more analysis because Part 11 is not a standalone regulation. Part 11 mandates a number of technical and procedural controls that must be in place for the Food and Drug Administration (FDA) to consider electronic records and signatures equivalent to their paper counterparts. Part 11 does not, however, enumerate what records must be kept or signed, or how long to keep them. These requirements come from predicate regulations and internal policy.

The term predicate regulation, however, does not appear anywhere in the preamble or body of Part 11. The term has evolved to generically refer to the host of other regulations that work in conjunction with Part 11. These regulations were written prior to Part 11 and took, understandably, a paper-based perspective. The FDA made it clear, however, that these underlying regulations would not need to be rewritten to accommodate industry’s use of electronic records and signatures. These earlier regulations do indeed make reference to things such as “paper,” “handwritten,” “initials,” and so forth. However, as long as industry complies with Part 11, electronic records and signatures can be used in lieu of their paper counterparts unless specifically exempted by regulation.

Part 11 mentions three types of predicate regulations:

• FDA regulations,
• Federal Food, Drug and Cosmetic Act (hereinafter FD&C Act), and
• Public Health Service Act (hereinafter PHS Act).

FDA made an important distinction between the role of the FD&C and PHS acts versus agency regulations under Part 11. Electronic records submitted to the agency under the FD&C and PHS acts are subject to Part 11 even if those records are not specifically identified in agency regulations.

The scope of Part 11 appears to be much broader for electronic records and signatures subject to agency regulations (In February 2005, FDA announced withdrawal of all 21 CFR
Part 11 draft guidance documents as well as the 21 CFR Part 11 Enforcement Compliance Policy Guide 715.17. The agency’s decision is based on a reexamination it is undertaking with respect to Part 11 under its new initiative: “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach.” Through this initiative, the agency lead on implementation of Part 11 has now shifted to the Center for Drug Evaluation and Research, with continued involvement from other FDA centers and the Office of Regulatory Affairs, FDA’s enforcement arm [1,2].

However, in February 2003, FDA released a draft guidance document on the scope and application of Part 11 (3). In that guidance, the agency announced its intent to reexamine Part 11 as an outgrowth of its risk-based current GMP initiative. While this examination is underway, the agency states it “will narrowly interpret the scope of Part 11.”

Under this narrower interpretation of scope, FDA acknowledges, “fewer records will be considered subject to Part 11.” In particular, there appears to be broader acceptance of paper print-outs of electronic records.

Instead of focusing on whether or not an electronic record has been created in the first place, the agency will now focus on whether:

1. The paper print-outs meet all of the requirements of the applicable predicate rules, and
2. Persons rely on the print-outs to perform their regulated activities.

If these requirements are met, FDA would not consider persons to “be using electronic records in lieu of paper records” under sections 11.2(a) and 11.2(b) of the regulation. Moreover, in keeping with the original language contained in comment 22 of the Part 11 Preamble, this would qualify as merely incidental use of computers and would not trigger Part 11.

FDA has also stated that it may take a company’s business practices into account in determining whether Part 11 applies. The agency now recommends that companies determine in advance whether they plan to rely on the electronic record or paper record to perform regulated activities. These decisions should be documented in standard operating procedures.

The agency has also narrowed the scope of Part 11 with respect to records that are not submitted to FDA. Under the regulation, Part 11 applies to electronic records that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. The agency specifically acknowledges, however, that nonsubmitted electronic records used to generate a submission are not subject to Part 11 so long as a predicate rule does not require their maintenance.

Long-term electronic record preservation under Part 11 has also presented considerable implementation hurdles for industry. FDA has attempted to address this in the draft guidance by stating: “FDA normally does not intend to object if you decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format, such as PDF.”

Bear in mind, however, that the agency still expects that any archived copies will preserve record content and meaning. Copying records to nonelectronic media will not be a viable archival option for “media-rich” electronic records (eg, sound and video).

Table 1 provides a brief summary of the predicate regulations with examples of the types of record and signature requirements contained in each. The predicate regulations play a pivotal role, therefore, in identifying what electronic records and signatures (and by extension the systems in which they are maintained) are subject to the provisions of Part 11.

A thorough analysis of the seemingly simple question “Does Part 11 apply to System X?” cannot stop here, however, because some agency regulations require standard operating procedures (SOPs). Consider the following examples:

- cGCP 21 CFR 56.108—Institutional Review Board (IRB) Functions and Operations,
- cGMP 21 CFR 211.130—Packaging and Labeling Control, and
- GLP 21 CFR 58.81 (c)—Data Handling, Storage and Retrieval.
These SOPs, in turn, may require creation of a record or execution of a signature. If the records and signatures under SOPs mandated by agency regulations are electronic, Part 11 may apply. As a result, the scope of Part 11 depends on record and signature provisions of the predicate regulations as well as these internal policies.

The interplay between predicate regulation and internal policy in determining the scope of Part 11 applicability is further illustrated by a brief examination of record retention periods. In some cases, record retention periods are specified in agency regulations. For example:

- **cGCP** 21 CFR 312.57—Record Retention (for two years after marketing application approval).
- **cGMP** 21 CFR 210.80—General Record Requirements (retention for one year after expiration of the batch).
- **cGMP** 21 CFR 211.180—General Record Requirements (retention for five years after submission of the application or two years after approval, whichever is shortest).

Due to other regulations or business reasons, however, record retention schedules contained in internal policies might prescribe a longer retention period than those listed in the agency regulations. If this is the case, the longer retention period may be applied by the agency, for example, when examining electronic records and signatures subject to Part 11.

In order to fully explore the answer to the question “Does Part 11 apply to System X?,” the following subquestions must be answered:

<table>
<thead>
<tr>
<th>Predicate Regulation Type</th>
<th>Reference</th>
<th>Record Requirement</th>
<th>Signature Requirement</th>
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<tbody>
<tr>
<td>Agency Regulations GCPs</td>
<td>21 CFR 50</td>
<td>Financial records</td>
<td>Informed consent</td>
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<td>21 CFR 54</td>
<td>Case histories</td>
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<td>21 CFR 312</td>
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<td>GLPs</td>
<td>21 CFR 58</td>
<td>Training records</td>
<td>Protocol</td>
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<td>Standard operating procedures</td>
<td>Final report</td>
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<td>GMPs</td>
<td>21 CFR 210</td>
<td>Written procedures</td>
<td>Equipment logs</td>
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<td>21 CFR 211</td>
<td></td>
<td>Batch records</td>
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<td></td>
<td>21 CFR 810</td>
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<tr>
<td>FD&amp;C Act</td>
<td>Section 505</td>
<td>New Drug Application</td>
<td>Drug sample request</td>
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<td>Section 506B</td>
<td>Postmarketing studies</td>
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<td>Section 503</td>
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<td>PHS Act</td>
<td>42 USC Section 263a</td>
<td>Certification of clinical laboratories</td>
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• What electronic records and signatures in System X fall within the scope of the predicate regulations?
• What electronic records and signatures in System X fall within the scope of SOPs that are mandated by the predicate regulations? and
• What is the applicable record retention period (either in the predicate regulation or internal policy)?

There may be situations, moreover, where the scope of Part 11 has been unintentionally broadened based on internal policies. Organizations would be well advised to conduct an internal analysis of this by answering the following questions:

• What company SOPs require signatures on records subject to a predicate regulation where the regulation itself does not require a signature?
• What company SOPs mandate longer record retention periods than those specified in a predicate regulation?

If there are SOPs that fall under either of these categories, it would be prudent to decide whether there is a good business reason to justify internal policies that potentially expand the scope of Part 11.

It is also important to remember that whether or not Part 11 applies may also depend on how System X is used. This is especially true with “general purpose” applications such as spreadsheets, personal databases, and e-mail. System end users need to understand general good electronic record keeping practices to help minimize the potential creation and use of electronic records subject to Part 11 in noncompliant systems.

Publications may be a helpful starting point for developing company-specific internal policies. Some of these include the Parenteral Drug Association and International Society for Pharmaceutical Engineering “Good Practice and Compliance for Electronic Records and Signatures” (4). The Global Electronic Records Association also publishes high-level guidance in this area, including the Electronic Records “System” Lifecycle Specification, Legal Acceptability Guidelines for Electronic Records Systems, and Validation Guidelines for Electronic Records Systems (5).

A recent warning letter from the agency illustrates how poor electronic record keeping practices can lead to problems. During the course of an inspection at a clinical site, an FDA inspector found that the principal investigator, as well as his staff, had created a number of “personal” data files containing trial-related information. In the warning letter to the investigator, the agency stated: “You failed to verify the reliability of subject data entered into three different databases for your subjects; your personal database, the database maintained by your study coordinator, and a FHCRC database. In the letter dated 7/9/01, you said that you will enhance your current processes to consolidate data collection and provide for formal crosschecking for the purpose of data verification.” (6)

While not specifically mentioning Part 11 per se, this warning letter emphasizes the importance of data verification—even when the data reside on a computer instead of paper. In order to avoid this type of compliance pitfall, sponsoring companies should educate all potential system end users about general good electronic record keeping practices. Moreover, as this case illustrates, the system end users may well be persons outside the immediate organization.

Consider also the use of e-mail in the clinical setting. In many ways, e-mail can be used as a communication tool in the same way the telephone is used. In fact, it may be viewed as preferable since a “record” is automatically created. It could be quite tempting, for example, to use e-mail to report adverse experiences, request shipment of investigational drug, or transmit monitoring reports.

E-mail, however, differs in important ways from the telephone in terms of the way the information is transmitted. Telephone users can safely assume a basic level of confidentiality of transmission; unfortunately, this is not true with e-mail.

Naïve e-mail users may, for example, assume their message goes directly to the intended recipient. E-mail generally operates on a store and forward mechanism. Therefore, e-mails can be stored on a number of various servers along a delivery route before they are delivered to the
intended recipient. Unless specific measures are taken, such as encryption or a virtual private network, an e-mail message moves across the Internet unprotected. From a Part 11 perspective, e-mail transmitted over the Internet would be treated like an open system.

Moreover, out of the box, most commercial e-mail systems do not provide the necessary technical controls required under Part 11. At the most basic level, most e-mail systems lack basic audit trail capabilities. In addition, there are considerable obstacles to overcome in attempting to validate any type of general use application; they are simply not developed with Part 11 requirements in mind.

FDA has, in fact, cited a clinical investigator for using the Internet to transmit information to a study monitor and failing to implement the necessary controls for an open system: "No security password is used on the computer for entering of data or when sending data to the study monitor over the Internet. Subject medical records are, therefore, easily accessible. 21 CFR 812.100 states that an investigator is responsible for ensuring the rights and welfare of subjects, which includes security of their records." (7) (While outside the scope of this article, one must also consider the potential impact of the privacy provision in the Health Insurance Portability and Accountability Act of 1996 when collecting clinical research data [8]).

Hence, without the proper guidance, people may inadvertently send or receive e-mails that contain electronic records that are subject to Part 11. Moreover, the impact of such behavior goes beyond the potential lack of compliance of the e-mailed records themselves. Electronic records subject to Part 11 in an e-mail system increase the risk that the entire e-mail system will be subjected to regulatory scrutiny.

The business and technical advantages of e-mail may support its use to transmit electronic records subject to Part 11. It is important, however, that the e-mail system has the necessary procedural and technical controls in place as mandated by Part 11.

In particular, e-mail users need guidance on how to identify whether or not their specific use of e-mail is subject to Part 11. The sample policy outline below walks a clinical e-mail user through this decision:

**CONSIDER THE FOLLOWING QUESTIONS:**

1. Does the e-mail constitute a “record” under GCP or a company SOP mandated by GCP (eg, is the e-mail replacing what used to be maintained on paper site/IRB contact logs)?
2. Is the e-mail being used to support study conduct in a manner that could be used to substantiate study events (eg, scheduling monitor visits, ordering study supplies)?
3. Is confidential patient information contained in the e-mail (eg, initials, birth date)?

If the answer to 1, 2 OR 3 is “YES” then the e-mail may be subject to 21 CFR 11 electronic record provisions.

**CONTINUE PART 11 COMPLIANCE EVALUATION AS FOLLOWS:**

1. Is the e-mail sent over the Internet? If “YES,” the e-mail is sent over an OPEN system and must be encrypted.
2. Does the e-mail contain a record that must be signed according to GCP or company SOP? If yes:
   2A. Is the signature recorded electronically? IF “YES,” the e-mail is subject to 21 CFR 11 electronic signature provisions.
   2B. Is the signature recorded on a paper print-out of the e-mail? If “YES,” the e-mail is part of a “HYBRID” system and appropriate technical and procedural controls must be in place to keep the e-mail and its signed paper counterpart synchronized.

This proposed guidance for the unsuspecting e-mail user in the clinical setting hopefully illustrates the point that Part 11 does not exist in a vacuum. Even though Part 11 applicability questions often seem simple on their face, a prudent approach frequently requires further analysis to reach an accurate answer.

Predicate regulations, internal company policies, and system end user behavior all play a pivotal role in determining whether or not Part 11 applies to electronic records and signatures in any given computerized system. The question “Does Part 11 apply to System X?” may not have a quick and easy answer. Analyzing the question

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correctly, however, will pay off in two ways. First, correct identification of impacted systems helps an organization focus its Part II compliance efforts where they are most needed. Second, a broader understanding of system end user behavior will highlight where additional guidance is needed to avoid compliance pitfalls.

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REFERENCES