

Part 11 Is Not Going Away

The New Electronic Records Draft Guidance

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On 20 February, FDA published a new 21 CFR Part 11 draft guidance. Rumors that the new guidance means Part 11 will no longer be enforced are wrong. That new guidance is primarily directed at computerized systems that have a low risk of affecting product quality; systems with a high risk that can affect product quality, such as chromatography data systems (CDS) or laboratory information management systems (LIMS) used for making product quality decisions, remain unaffected.

The Withdrawn Guidance

FDA's 21 CFR Part 11 rule on electronic records and electronic signatures was introduced in 1997 (1). Its subsequent enforcement by regulatory agencies — CDER and CBER, the Center for Devices and Radiological Health (CDRH), the Center for Food Safety and Applied Nutrition (CFSAN), the Center for Veterinary Medicine (CVM), and the Office of Regulatory Affairs (ORA) — has led to a concerted effort within the pharmaceutical industry to:

- interpret the rule
- perform Part 11 compliance assessments of current systems
- perform gap analyses
- develop and execute validation and implementation plans for new systems (along with migration and retirement plans for old systems)
- develop new systems to implement the procedural and technical controls mandated by Part 11.

Many people were, therefore, surprised when FDA announced its intention to reexamine Part 11 and withdraw its previous draft guidance documents and compliance policy guide (CPG) 7153.17 (2). This was announced in the *Federal Register* on 4 February (3) and was followed by the issuance of a new draft guidance *Part 11, Electronic Records; Electronic Signatures — Scope and Application* on 20 February (4).

As we have discussed in a previous article (5), FDA is reexamining Part 11 in light of its current good manufacturing practices (CGMP) initiative that was announced in August 2002 (6).

Finding the Balance

After the original Part 11 rule became effective, FDA published CPG 7153.17 regarding its enforcement policy (2) as well as a number of draft guidance documents, including a glossary of terms (7), and others related to validation (8), time stamps (9), maintenance (10), and copies (11) of electronic records. These guidance documents were studied by industry, which then raised concerns about their compliance costs. Two draft guidances — the *Maintenance of Electronic Records* (10) and the *Electronic Copies of Electronic Records* (11) — were heavily criticized because both suggested that electronic records needed to be able to be processed during the entire retention time required by the predicate rule. That could be 10 years or more, and the industry's concern was that the task could be very expensive and the technology not always available.

The rules for electronic records and signatures still remain in effect. The change means that companies must now justify their decisions on whether or not to implement specific electronic controls with documented risk assessments and considerations of the record requirements detailed in the corresponding predicate rule.

Part 11, however, defines a framework, and many practical system and process issues were identified when industry and its suppliers began working on implementation plans for compliance.

For example, the Parenteral Drug Association (PDA) formed a Part 11 task force to develop guidelines for Good Electronic Records Management (GERM), and the Good Automated Manufacturing Practice (GAMP) Forum formed a special interest group (SIG) to develop a document on how to best implement Part 11. Both papers have been published by the International Society for Pharmaceutical Engineering (ISPE) (12,13).

As stated in many publications, it has been difficult to find the correct balance between doing enough and doing too much: “If there is any doubt about whether a specific validation effort should be done, the final answer can be obtained only by asking if the validation effort adds any scientific value” (14).

New Requirements

Part 11 is not going away. The new draft guidance does not define any new electronic record and signature requirements: It simply redirects the focus to aspects critical to product quality and public health, which are mostly governed by the predicate rules. The final guidance (expected sometime after the discussion period ends in April) is likely to result in less emphasis on the technically complex and validation-intensive areas of audit trails, time stamps, record retention, and record copying. This is particularly so for legacy systems — those electronic systems that were in place before Part 11 became effective 20 August 1997.

FDA reemphasizes, in the new draft guidance, that records mandated by predicate rules are still required, but states that fewer records will be considered subject to Part 11. We expect that the most stringent requirements for data processing during the entire retention period will be replaced by a time frame that is based on a company’s documented risk assessment and business practices.

Until February 2003, Part 11 was loosely interpreted and did not distinguish between systems with a potentially high-risk effect on product quality and safety (such as CDS used for quality control analysis of final drugs) and low-risk systems (such as word processors used to generate standard operating procedures). Companies were required to develop, document, and implement credible action plans for becoming compliant with Part 11 for all electronic records created in a “Good Practice” (GxP) environment — a controversial and confusing mandate.

Type of Records	Category ^a	Predicate Rule Reference
Production, control, and laboratory records to ensure that drug products adhere to established specifications; records for components, drug product containers, and labeling	GMP	21 CFR 211.180
Equipment cleaning and use logs	GMP	21 CFR 211.182
Master production and control records	GMP	21 CFR 211.186
Batch production and control records	GMP	21 CFR 211.188
Production record reviews	GMP	21 CFR 211.192
Laboratory records	GMP	21 CFR 211.194
Protocols for a nonclinical laboratory study	GLP	21 CFR 58.120
Reporting of nonclinical laboratory results	GLP	21 CFR 58.185
Raw data, documentation, protocols, final reports, QA inspection records and samples, job descriptions, training records, and instrument maintenance, calibration, and inspection records	GLP	21 CFR 58.195
Supporting records for INDAs ^b and records described in ICH ^c GCP guidelines	GCP	21 CFR 312.57
	GCP	21 CFR 312.62
Records that ensure that the systems are designed to permit data changes in such a way that they are documented and deletion of entered data is prevented	GCP	ICH GCP 5.5.3 (c)
	GMP	EU GMP Guide Annex 11 §10 ^d
List of individuals authorized to make data changes	GCP	ICH GCP 5.5.3 (e)

^aGMPs are Good Manufacturing Practices; GLPs are Good Laboratory Practices; and GCPs are Good Clinical Practices.
^bINDAs are investigational new drug applications.
^cICH is the International Conference on Harmonisation.
^dSee reference 18.

Table 1. Examples of the types of records that are required by predicate rules, which will still be enforced under the new Part 11

A Risk-Based Approach

In August 2002, FDA announced an initiative that would merge science-based risk management with an integrated quality systems approach: “To provide the most effective public health protection, FDA must match its level of effort against the magnitude of risk. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed” (6).

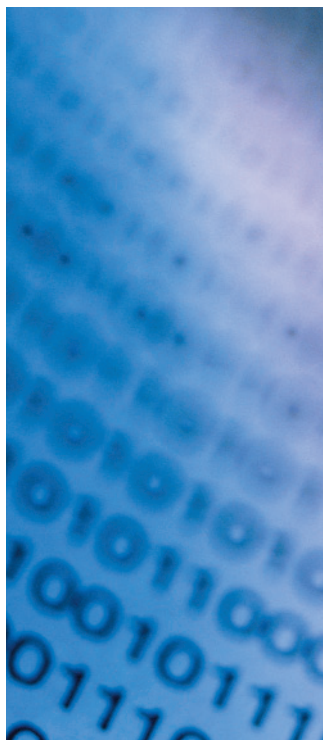
The GAMP guide. Before 20 February 2003, in the absence of precise guidance from regulatory agencies on how to conduct assessments, industry forums published guidelines. Appendix M3 — “Guideline for Risk Assessment” — of the GAMP 4 guide establishes the missing link between validation processes and risk management (13). It proposes a formalized and documented risk assessment process, which:

- identifies and rates business and GxP risks through risk scenarios
- assesses the likelihood and severity of potential failures or deviations

Type of Records	Subject to Part 11	Examples
Records required to be maintained by predicate rules and maintained in laboratory electronic format in lieu of paper records	Yes	<ul style="list-style-type: none"> • Original observations • Instrument raw data worksheets • Instrument calibration records • Metadata to prove that the specified sampling, testing, and inspections were actually done • Test results of materials and bulk and finished products
Records that are maintained in electronic format but are not required by any predicate rule	No	Instrument diagnostics files, presentations or business reports
Records required to be maintained by predicate rules and maintained in leading electronic and paper format and are relied on to perform regulated activities	Yes	Quantification results from a chromatography sequence to the release of a production batch
Records electronically submitted to FDA under the predicate rules	Yes	<ul style="list-style-type: none"> • Clinical study protocols • INDAs^a
Electronic records that are not submitted and are not required to be maintained by predicate rules but are used in generating a submission	No	Batch file (script) to collate the submission package for an NDA ^b from the individual source documents
Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signatures required by predicate rules	Yes	Electronic signatures used to sign-off on data entry changes for samples, sequence information, methods, and calculations in a chromatography data system

^aINDAs are investigational new drug applications.
^bNDA is new drug application.

Table 2. Examples of the types of records that will (and those that will not) still be enforced under the new 21 CFR Part 11



- judges the probabilities for detecting the failure
- asks for the definition of appropriate risk mitigation strategies.

A key part of appendix M3 is the “determination of whether the system function or subfunction represents a risk when assessed against a series of GxP criteria.” This risk-based approach will help the industry, its suppliers, and regulatory agencies focus resources on the critical issues for public health and consumer safety.

Continued Enforcement

A primary message of the new draft guidance is that FDA now intends to interpret Part 11 with a narrower scope, to “exercise enforcement discretion with respect to certain Part 11 requirements” (4). Enforcement discretion will be exercised in such areas as “validation, audit trails, record retention, and record copying” (4). These are areas in which industry was spending extraordi-

nary amounts of effort trying to manage the technical complexity — and for very little return. However, “enforcement discretion” does not mean that technical controls for audit trails, electronic processes, and procedures for record retention are no longer required: 21 CFR Part 11 still remains in effect. FDA is just saying that a company must now justify its decision on whether or not to implement a specific control with a documented risk assessment and with consideration of the record requirements in the corresponding predicate rule.

Predicate records rule. The new draft guidance emphasizes the importance of the record requirements outlined in the predicate rules. Records required by predicate rules that relate to product quality will continue to be subject to Part 11 regulations and continue to be enforced. Specifically, key technical controls for access security, operational system and device checks, open system controls, and electronic signatures are still required, along with appropriate staff training, documentation, and change control. Some predicate rules, such as Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), explicitly require audit trails for tracking changes, particularly when users are expected, during normal operation, to create, modify, or delete regulated records.

Table 1 lists examples of records required by predicate rules. The list reinforces our statement that the new Part 11 guidance has little applicability to CDS used in analytical laboratories subject to GxP regulations. GMP and CGMP regulations strongly influence business processes and practices in this industry. Different categories of records are summarized in Table 2, which also lists whether such records are still subject to 21 CFR Part 11 and subsequent enforcement as defined by the original GxP regulations.

Established business processes. Records that are relied on to perform regulated activities and that are part of established business processes are still subject to Part 11 requirements. Networked data systems (NDS), CDS, LIMS, and Enterprise Resource Planning (ERP) systems manage critical decision-support data and continue to be a focus of GxP enforcement. The trustworthiness and reliability of data managed by these systems is highly dependent on efficient technical controls that ensure security, data integrity, and traceability.

The new draft guidance stresses that FDA can use business practices to determine whether an electronic record is used instead of a paper record. We recommend, therefore, that you deter-



mine and document whether you will use an electronic or a paper record to document regulated activities.

Enforcement discretion. FDA announced that it will exercise “enforcement discretion” for a number of technical controls mandated by 21 CFR Part 11. That decision acknowledges that the affected industries and their suppliers are now in a transition period during which their approach to GxP and Part 11 compliance may have to be revisited. With the withdrawal of the previous guidance documents, the role of industry “com-

mon good practice,” such as that contained in PDA’s GERM guidelines, will be instrumental in helping companies focus on the right things (12). Similar to the approach taken by this type of industry guideline, the new guidance is aimed at doing the right things, instead of doing things right.

Part 11 Still Applies

Table 3 illustrates the GxP requirements that are “The Most” and “The Least” affected by the new draft guidance. The table shows that the majority of the original Part 11 technical controls on records will continue to be enforced. The primary requirements of Part 11 are correlated in Table 4 to the resulting user requirements. Obviously, several requirements have not changed at all.

System access must be limited to authorized personnel, and the system needs to perform authority checks where appropriate. Technical controls need to ensure that “impersonation” is prevented. In modern systems, these controls are implemented through security mechanisms — consistent with company security policies — by the underlying operating system, which can easily align access control to the CDS with general IT practices.

Device checks continue to be key mechanisms for ensuring that critical records are trustworthy and reliable. Level 4 mechanisms (5,15,16) implement this requirement effectively and efficiently (see the sidebar on the “Importance of Level 4 Controls”).

Operational checks are still required to enforce the permitted sequence of steps, such as the steps for review and approval of results.

Electronic signature requirements have not changed. If a company is using electronic records with electronic signatures, then the technical controls mandated by Part 11 for such signatures in closed or open systems still apply, just as they did before 20 February 2003.

A useful discussion covering these topics can be found in “Appendix 4: Key Areas for Guidance, Part 2” of the PDA and ISPE guide *Complying with 21 CFR Part 11* for implementing these requirements (17).

Trustworthy, Reliable Records

Even with FDA’s announced reexamination of Part 11, the enforcement focus continues to be on predicate rule requirements for records subject to Part 11. Records that fall into this category need to be trustworthy and reliable. Therefore, key

Type of Records Still Required and Enforced by the New Guidance (for Records Subject to Part 11)	Records Affected by the New Guidance and Over Which FDA Will Exercise “Enforcement Discretion”
<ul style="list-style-type: none"> System validation Limiting system access to authorized individuals Use of operational system checks Use of authority checks Use of device checks Determination that people who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks Accountability for signatures Requirements related to electronic signatures 	<ul style="list-style-type: none"> Part 11 specific requirements, for example e-audit trails, validation, record maintenance, electronic copies if there is no or a low effect on product quality according to a documented risk assessment Part 11 enforcement for legacy systems (those installed before 2 August 1997)

Table 3. Part 11 regulations that will still be enforced under the new draft guidance and those record requirements over which FDA will exercise “enforcement discretion” as outlined in the new draft guidance

Technical Controls Required	Resulting User Requirements
<ul style="list-style-type: none"> Limiting system access to authorized individuals 	<ul style="list-style-type: none"> Enforce logins Security policies Password policies Inactivity time outs
<ul style="list-style-type: none"> Use of authority checks Use of device checks 	<ul style="list-style-type: none"> Configurable user capabilities Level 4 instrument controls^a Instrument log books Network monitoring Early maintenance feedback
<ul style="list-style-type: none"> Use of operational system checks 	<ul style="list-style-type: none"> Execution of calculations and customized calculations as part of the data system method (without manually transcribing results to another program) Enforce result review process (analyst review, peer review, and QA approval)
<ul style="list-style-type: none"> Requirements related to electronic signatures 	<ul style="list-style-type: none"> Electronic sign-off for critical system tasks Electronic review and rejection or approval of results

^aSee reference (6).

Table 4. Examples of required technical controls that should be available in compliant systems and the resulting user requirements

The Importance of Level 4 Controls

Would a regulatory agency ask, for example, a pharmaceutical quality control laboratory that tests finished drug products for documented evidence on the instrument parameters for the analytical equipment used to acquire raw data?

From our point of view, the answer is “yes” because the lab relies on the electronic raw data to perform “regulated activities,” such as QA/QC testing of the finished drug products against the specifications before a product is released for shipments. It would be very difficult to prove that a given result was generated according to the defined procedures or monographs without proper documentation of the instrument control parameters used during the analysis.

Managing metadata electronically (including the instrument’s control parameters) is important for ensuring trustworthy and reliable results in the original spirit of 21 CFR Part 11. It also reduces the risk of artifacts that adversely affect a product’s quality.

Level 4 instrument controls use advanced mechanisms for automatic tracking of an instrument’s identification or configuration information, and these controls are a prerequisite for the implementation of additional failure warning mechanisms, such as early maintenance feedback (EMF). We have previously discussed the details of the levels of instrument control and EMF (2,15). Electronic records generated by an analytical instrument are only reliable and trustworthy if the communication between the instrument and the system controller is reliable and trustworthy. We are convinced that reliable and traceable Level 4 instrument control continues to be a relevant and important measure of the accuracy of electronic raw data, metadata, and results that are still subject to the new CGMP initiative and the new Part 11 draft guidance.

technical controls are required for access security, operational systems and device checks, open system controls, and electronic signatures, along with appropriate staff training, documentation, and change control. Records managed in NDS, CDS, LIMS, or ERP systems continue to be subject to Part 11 and predicate rules, especially if their risk potential on product quality is high.

Consequently, 21 CFR Part 11 is not going away, or as we stated in a previous *BioPharm* article, “Electronic records are here to stay” (16). The scope of Part 11 has been narrowed. And the decision about whether Part 11 mandates are needed will now be based on the risk that the record can have on product quality and on a company’s documented business practices. **BPI**

References

- (1) FDA, “Code of Federal Regulations, Title 21 Food and Drugs, Part 11 Electronic Records; Electronic Signatures: Final Rule,” *Federal Register* 62(54), 13429-13466 (20 March 1997).
- (2) Office of Regulatory Affairs, “Enforcement Policy: 21 CFR Part 11; Electronic Records; Electronic Signatures (CPG 7153.17), Section 160.850, *Compliance Policy Guide* (FDA, Rockville, MD, 13 May 1999).
- (3) FDA, “Withdrawal of Draft Guidance for Industry on Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records,” *Federal Register* 68(23), 5645 (4 February 2003).

- (4) FDA, “Draft Guidance for Industry on ‘Part 11, Electronic Records, Electronic Signatures — Scope and Application;’ Availability of Draft Guidance and Withdrawal of Draft Part 11 Guidance Documents and a Compliance Policy Guide,” *Federal Register* 68(37), 8775–8776 (25 February 2003). Available at www.fda.gov/cber/gdlns/prt11elect.htm.
- (5) Winter, W. and Huber, L., “Instrument Control in Pharmaceutical Laboratories — Compliance with 21 CFR Part 11, Part I,” *Pharm. Technol. Eur.* 15(3) suppl., 40–45 (2003).
- (6) Office of the Commissioner, “Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach (FDA, Rockville, MD, August 2002). Available at www.fda.gov/oc/guidance/gmp.html.
- (7) FDA, “Draft Guidance for Industry; Electronic Records; Electronic Signatures, Glossary of Terms; Availability,” *Federal Register* 66(185), 48886–48887 (24 September 2001). Available at www.fda.gov/cber/gdlns/essigglos.htm.
- (8) FDA, “Draft Guidance for Industry; Electronic Records; Electronic Signatures, Validation; Availability,” *Federal Register* 66(185), 48886 (24 September 2001). Available at www.fda.gov/cber/gdlns/esigvalid.htm.
- (9) FDA, “Draft Guidance for Industry; Electronic Records; Electronic Signatures, Time Stamps; Availability,” *Federal Register* 67(54), 12999 (20 March 2002). Available at www.fda.gov/cber/gdlns/esigtime.htm.
- (10) FDA, “Draft Guidance for Industry; Electronic Records; Electronic Signatures, Maintenance of Electronic Records; Availability,” *Federal Register* 67(172), 56848–56849 (5 September 2002). Available at www.fda.gov/cber/gdlns/esigmaint.htm.
- (11) FDA, “Draft Guidance for Industry; Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records; Availability,” *Federal Register* 67(218), 68674–68675 (12 November 2002). Available at www.fda.gov/cber/gdlns/esigcopies.htm.
- (12) PDA, “Good Electronic Records Management (GERM),” *Good Practice and Compliance for Electronic Records and Signatures*, Part 1 (ISPE, Tampa, FL, September 2002).
- (13) GAMP Forum, “Management Appendices, M3: Guideline for Risk Assessment,” *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture* (ISPE, Tampa, FL, October 2001).
- (14) Huber, L., *Validation of Computerized Analytical and Networked Systems* (Interpharm Press, Inc., Buffalo Grove, IL, 2002).
- (15) Huber, L. and Winter, W., “Implementing 21 CFR Part 11 in Analytical Laboratories, Part 5: The Importance of Instrument Control and Data Acquisition,” *BioPharm* 13(9), 52–56 (2000). Agilent publication number 5988-0946EN.
- (16) Winter, W., “Electronic Records Are Here to Stay,” *BioPharm Eur.* Special issue of *Pharm. Technol. Eur.*, 29–31, (September 2002).
- (17) PDA, “Complying with 21 CFR Part 11: Electronic Records and Electronic Signatures,” *Good Practice and Compliance for Electronic Records and Signatures*, Part 2 (ISPE, Tampa, FL, October 2001).
- (18) European Commission, “Annex 13: Manufacture of Investigational Medicinal Products,” *Good Manufacturing Practices*, Vol. 4 (Enterprise Directorate-General, Brussels, Belgium, November 2001).

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