Part 11 is Dead – Long Live Part 11

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Introduction

21 CFR 11, the Electronic Records and Electronic Signatures final rule [1], that is applicable to the pharmaceutical and other FDA regulated industries has been effective for over six years and actively enforced by the Agency since 1999. Part 11 is a regulation that was originally requested by the pharmaceutical industry to take advantage of electronic signature technology and reduce the paper burden in manufacturing. The FDA included electronic records in addition to the electronic signatures requested by the industry. As the regulation itself notes, it is "intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to promote and protect public health" and the preamble stated that the implementation of 21 CFR 11 would be "broadly cost-neutral" [1].

Since its publication in 1997, the pharmaceutical industry has concentrated on the high cost of remediation and implementation to meet the requirements of the regulation. To help remediation, the FDA published the Compliance Policy Guide 7153.17 in 1999 [2] that stated the overall approach to assessment and remediation should be to have the administrative and procedural controls in place as soon as possible and work towards technical controls against a documented action plan. Since September 2001, five draft guidances for industry were released for industry comment; these were validation, glossary, time stamps, maintenance of electronic records, and electronic copies of electronic records [3-7]. However, the scope of Part 11, in the absence of definitive guidance from the FDA, could be narrower or wider depending on who was being asked.

In parallel, the FDA itself has been undergoing change in 2002 the Agency announced system not product based inspections, Process Analytical Technology (PAT) and risk based approaches to cGMP. At the request of the FDA, the ISPE wrote a white paper [8] that advocated a risk-based approach to Part 11 compliance. This document is significant, as we shall see later, as many of the concepts and wording were incorporated in the FDA's draft guidance on the scope and applicability of Part 11 [9].

FDA Activities February – September 2003

During February 2003, the FDA started a period of reflection and possible change concerning 21 CFR 11. Before many companies think that Part 11 is dead and start practicing the Clint Eastwood approach to Part 11 compliance (i.e. Do You Feel Lucky?); think again. As the FDA noted in the final guidance [10], the majority of Part 11 remains in force.

Early in the February, the FDA withdrew the draft guidance for industry for electronic copies of electronic records stating that it no longer reflected its current approach to risk based GMP [11]. This draft guidance was issued for industry comment in early November 2002, and comments were still being accepted from the industry. In essence, it was very difficult for any company to comply with the document's requirements, especially the statement in Section 5.6 "We consider it very important that we be able to process the data in electronic records using our own computer hardware and software." Unfortunately, we live in a mainly proprietary data world and lack universal data standards to exchange and transfer data electronically. If some of the more extreme requirements of the November 2002 draft guidance on Electronic Copies of Electronic Records [7] had been implemented, industry would not have been able to comply for a number of years until data standards had been established and implemented.

Furthermore, on February 20, 2003, the FDA published the Draft Guidance for Industry on 21 CFR: Scope and Applicability [9]. This new draft guidance must be viewed within the overall direction of the FDA's risk based approach to current Good Manufacturing Practice (cGMP) as discussed above. The guidance announced that the FDA would review some sections of Part 11, and, during this review period, would "exercise enforcement discretion." Instead of a 90-day review period, this guidance had only a 60-day review period and there were indications from the FDA that a final version would be produced rapidly after the close of the comment period that finished at the end of April 2003. However, we are talking about a Government Agency here – and the final version of the guidance was published in September 2003 [10].

Key Highlights of Part 11 Scope and Applicability

The main features of the Guidance for Industry on the Scope and Applicability of Part 11 are:

- The 21 CFR 11 rule remains in force; however, the FDA is re-examining Part 11 as it applies to all FDA regulated products. As a result, the original rule may be revised in the future, although no timeframe is quoted. However, as any new regulation needs to go through due process, this is likely to take years (evidence the timescale of Advance Notice of Proposed Rulemaking (ANPR) published in 1992 to the final version of Part 11 issued in 1997).
- The new intention is that 21 CFR 11 will be interpreted more narrowly with fewer records being included within the scope. The document makes it clear that Part 11 must be interpreted under the existing predicate rule or rules that are applicable to the organization. As a result, organizations must determine and document, based on the predicate rule(s), those records they regard as Part 11 records.
- During the period of re-examination, the FDA is to exercise discretion in enforcing the ruling, but note that this enforcement discretion applies only as identified in the guidance. In effect, this means that the agency does not intend to take enforcement action against several key areas of the rule, in particular the validation, audit trail, record retention and record copying requirements.

The FDA will focus on ensuring compliance with predicate rules, and the associated validation requirements.

Table 1

Part 11 Requirements Still Enforced	Part 11 Requirements with Enforcement Discretion
11.10(d) Limiting system access to authorized individuals	11.10(a) Validation
11.10(f) Use of operational system checks	11.10(e) Audit trail
11.10(g) Use of authority checks	11.10(k)(2) Audit trail of system documentation
11.10(h) Use of device checks	11.10(b) Copies of records
11.10(i) Persons.. have the education, training, and experience to perform their assigned tasks	11.10(c) Record Retention
11.10(j) Written policies that hold individuals accountable for actions	Legacy Systems operating before 20th August 1997
11.10(k) Appropriate controls over systems documentation	
11.30 Controls for open systems	
11.50 Signature manifestations	
11.70 Signature / record linking	
11.100 General requirements	
11.200 Electronic signature components and controls	
11.300 Controls for identification codes/ passwords	

- Throughout the document there is reference to documented risk assessment for many of these activities.
- The Guidance provides some clarification of the requirements for validation, audit trail, legacy systems, copies of records, and record retention where again enforcement discretion will be allowed.
- Enforcement discretion will also be exercised for legacy systems, i.e. defined as systems that were operational before August 20, 1997, the date that Part 11 became effective. However, for enforcement discretion to be given, the legacy systems must meet four key requirements that will be discussed later in this article.
- The draft Guidances for Industry and the Compliance Policy Guide 7153.17 that were withdrawn in February 2003 will not be re-issued. However, the FDA did provide succinct guidance that time stamps should be implemented with a clear understanding of the time zone reference used, and this should be specified within the system documentation.

Just to make life interesting, splashed across the top of each page is the phrase "contains nonbinding recommendations." Make of this what you will.

What is the Current Status of 21 CFR 11?

After the issue of this final Guidance for Industry – where does Part 11 stand? We will discuss this in the remainder of this article.

Majority of 21 CFR 11 Requirements Still Enforced

So, before cheering the demise of Part 11, think again; quoting from the new guidance document [10]: "Note that part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance." The FDA uses bold text in the final guidance [10].

It is important to stress that Part 11 is still in effect, and the regulation remains unchanged at this time and all other areas will continue to be enforced by the Agency. The guidance only describes the FDA's current thinking about the scope and application of Part 11 with regard to four specific requirements and legacy systems. Table 1 summarizes the status of the main requirements of the regulation, including the areas where the FDA intends to exercise enforcement discretion during the Part 11 review period.

Narrow Interpretation of Part 11 During FDA Review

The FDA is re-examining Part 11 as it applies to all FDA regulated industries, and, during this time, the agency has decided to narrow the interpretation of the scope of Part 11. Note this is temporary with no time limit specified. At the end of this period, the FDA may revise provisions in 21 CFR 11. The new guidance for industry outlines the areas where the FDA proposes to temporarily modify its approach to enforcement of the regulation during the review period; however, the length of time of this proposed review period has not been defined.

Where Does Part 11 Now Apply?

During the review period, the FDA will now consider that Part 11 applies to the following records or signatures:

- Records required by predicate rules that are kept electronically instead of paper.
- Records required by predicate rules, which are maintained in electronic format in addition to paper format and are relied on to perform regulated activities. Business use of a system may determine if this applies. Therefore, "for information only" systems and electronic records may be implicated under this section as being under Part 11 as these generally are a front for a multitude of evils, e.g. Excel spreadsheets used for collating data for annual product reviews.
- Records submitted to FDA, under the predicate rules (even if such records are not specifically identified in Agency regulations), in electronic format (assuming the records have been identified in the docket 92S-0251 as the types of submissions the Agency accepts in electronic format).
- Electronic signatures that are the equivalent to handwritten signatures and other general signings required under the predicate rule (note that the latter can appear in the predicate rules as reviewed, approved, verified etc).

Specifically the guidance document removes word processing systems from the scope of Part 11. However, still protect the file produced, as you will not retype the document from scratch; you will go back to the original file and modify it. Yet, if a company had automated their word processing by incorporating it within an Electronic Document Management System (EDMS), then this would be under Part 11 especially if electronic signatures were used.

Apart from word processing, no specific examples are discussed. However, in the laboratory, clinical and production areas not many systems would be excluded based on this approach. Therefore, document in an SOP or system requirements specification the records required by predicate rules and if electronic or paper records are used to perform regulated activities. The best approach is to justify each system on a case-by-case basis to see if Part 11 applies and if so what records are contained within the system. In many instances, this will mean revisiting many systems in the organization's Part 11 assessment and remediation program and reassessesing how the system is being used and if the records produced still fall under Part 11or paper.

Where Part 11 is not Applicable

However, the FDA has suggested where 21 CFR 11 does not apply as follows:

- Records (and any associated signatures) that are not required to be retained by predicate rules, but that are nonetheless maintained in electronic format, are not Part 11 records.
- However, a record that is not itself submitted, but is used in generating a submission, is not a Part 11 record unless it is otherwise required to be maintained by a predicate rule and it is maintained in electronic format.

Without further information in the guidance, the key requirement here is to know and understand the applicable predicate rules that pertain to the operations being carried out and how they impact the computerized systems being used to support them. This can be difficult as there are explicit record requirements and many implicit requirements for records plus the impact of the "current" in cGMP. Regardless, documented assessment of computerized systems to show that they are either within or outside of the remit of Part 11 is essential. Therefore, as in the above section, documented assessments are the only way to approach this.

Part 11 Interpretation via Predicate Rules

21 CFR 11 has always been interpreted using the predicate rules applicable to the area where work is carried out. Throughout the guidance document, there is a high emphasis placed on the existing GXP predicate rules (21 CFR 58, 21 CFR 211, 21 CFR 820 etc). Therefore, it is imperative that personnel working with computerized systems have a good understanding of the actual regulations they work against as they impact the computerized systems they use. This is not always the case, in the author's experience, and training is essential in this area to ensure that interpretation balances the regulatory interpretation versus compliance work equation.

However, have we simply replaced one evil with another? What happens when we reach the nirvana of the predicate rule? Let us look at 21 CFR 211 for Good Manufacturing Practice under equipment design:

§ 211.63 Equipment Design, Size, and Location

Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

How are you going to interpret the following for computerized systems, including any legacy ones:

- Adequate design?
- Adequate size?
- Suitably located?

As we look though the existing predicate rules, there are sections where there are no stated or explicit requirements for records, for example for GMP:

§ 211.25 Personnel Qualifications

(a) Each person engaged in the manufacturing, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.

This is in contrast to another predicate rule (GLP) for the same requirement:

§ 58.29 Personnel

(a) Each individual engaged in the conduct of or responsible for the supervision of a non-clinical laboratory study shall have education, training, and experience, or a combination thereof, to enable that individual to perform the assigned functions.

(b) Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a non-clinical laboratory study.

Therefore for computerized systems holding GMP training records, it appears that Part 11 would not apply in contrast to GLP systems holding similar records where it would. Welcome to the world of the new Part 11!

Are the Predicate Rules Up to Snuff?

Several times in the document there is the statement "even if there is not a predicate rule requirement, it many still be important to ….. validate a system or have an audit trail et.c" A way of looking at this and the other similar statements is that the predicate rules are not adequate and also need to be revised.

FDA "Exercises Enforcement Discretion"

In five areas of the regulation only, the FDA states that they intend to exercise enforcement discretion during the period of review. Note that "exercise enforcement discretion" does not mean that firms should simply do nothing; validation of computerized systems must still be done and include fitness for purpose and audit trails where the latter exist, especially on critical or high risk systems. I suggest that the FDA will walk softly but carry a big stick for organizations that do nothing as the predicate rules will allow an inspector to cite an organization without invoking 21 CFR 11.

§11.10(a) Validation

The specific Part 11 requirements for validation (accuracy, consistent intended performance, altered and invalid records) will have enforcement discretion. However, be careful with your reading of this section - systems must still be validated to predicate rule requirements, such as adequate size and fitness for purpose under GMP §211.63 has highlighted above.

Care needs to be exercised here as the FDA also states that, even if no predicate rules exist, it may be important to validate for Part 11 records stored in a system. "Even if there is no predicate rule requirement to validate a system in a particular instance, in some instances it may still be important to validate the system." Giving with the one hand and taking away with the other ….

However, as the FDA note, the validation and its extent should be based on a documented and justified risk assessment of the system.

In their only specific example in the whole of the guidance document, the FDA notes that validation would not be important for a word processor used to generate SOPs. Please do not extrapolate this to include document management systems that will be covered by Part 11 and the new guidance via electronic signatures and business process considerations. However, it is important to protect the electronic files produced by the word processing system, as users do not retype the whole document when it is due for update but refer back to the original held on disk.

§11.10(b) Copies of Records

The FDA guidance on electronic copies of electronic records was too extensive and resulted in an excessive compliance burden [11], as a result it was withdrawn; in its place is a far more achievable and pragmatic approach via enforcement discretion for providing elec-

tronic copies of records.
- Provide the inspector with copies of records held in common portable format when records are maintained in these formats e.g. PDF
- Use established (i.e. documented and validated) automated conversion or export methods to make copies in a more common format e.g. XML, SGML, ASCII, CSV. The conversion or export process must ensure that content and meaning of the records are preserved.
- If your electronic records can be searched or trended, then the copies supplied to the FDA should also be capable of this where reasonable and technically feasible.
- Inspection, review and copying of human readable records are made on site using your system and your procedures for accessing the records only.

This is a more achievable system and follows the ISPE paper on risk-based approach to Part 11 compliance [8]:
- Using industry standard portable formats where possible, if the use of such formats brings more benefits than disadvantages.
- Utilizing established automated conversion or export methods where available, to make copies in a more common format (e.g. PDF or paper copies).
- Allowing inspection and review of records on the firm's site, using the firm's hardware and software, following the firm's established procedures and techniques for accessing those records.

My advice is that you write an SOP that covers how you will handle copies of records for inspectors and ensure that you retain an exact copy of the records you provide to an inspector.

§11.10(c) Records Retention

Gone is the poorly worded draft guidance phrase of "FDA does not normally intend to object," which was vague and subject to interpretation itself, and in the final version this is much improved.

Now, a firm must still comply with all predicate rule requirements for record retention and availability to gain enforcement discretion under the guidance. Maintenance strategies of the records and their stored form must be based on a document risk assessment, but options can include archiving in standard electronic file format (the most common is PDF) as well as on non-electronic media such as microfilm, microfiche and even paper.

The requirements of 11.10(c) were always the most difficult part of 21 CFR 11 to comply with. This has been substantially relaxed. However, it is often important to retain records for longer than the predicate rule requirements. For example, product liability is 11 years in Europe and 20 years in the U.S.; furthermore, the ICH requirement for the electronic Common Technical Document (eCTD) states that data have to be kept for the lifetime of the product which could be as long as 50 years. For the pessimists amongst readers, aspirin has been on the market for over 100 years….

This section has its greatest impact when systems are being changed, and the electronic records from the original system are not compatible with the new system and where data migration is not a practicable or feasible option. Here, with a documented risk analysis, the migration to paper or other format can be justified. The guidance notes that after conversion the electronic version of the records can be deleted. Do not do this without a procedure, authorization and evidence of destruction, as you will have a problem. As noted in the FDA's Guide to the Inspections of Pharmaceutical Quality Control Laboratories, "Expect to see written justification for the deletion of all files" [12].

Also consider the issues before taking your records out of the electronic domain as they are easy to share and trend when available electronically; in paper or microfiche they are not. In the short term (the active use phase of the GERM records life cycle model), keep records in their original format unless absolutely necessary [13] so that they can be accessed if required and the FDA has completed their Part 11 review.

§11.10(e) Audit Trail

To ensure enforcement discretion, computerized systems must still meet predicate rule requirements for date and time sequence of events; but, the way this can be done is now expanded under the guidance to include procedural approaches with a paper record outside of the system as well as technical controls. Again, a documented risk assessment is recommended to support this approach.

This is a pragmatic approach to dealing with non-compliant systems, as many remedial actions can use a paper audit trail and SOP as a temporary stage before technical compliance of the system.
However, it is important to understand that a paper based audit trail to ensure trustworthiness and reliability of electronic records for legacy system is inefficient and will result in a higher compliance overhead than using an electronic system. Therefore, in the long term this should not be used for large multi-user and critical computerized systems; only low risk single user systems should be considered for this in the long term. For critical and large systems, audit trails will make like easier to monitor the creation, modification and deletion of records by users.

However, there is still a sting in the tail from the Agency, where there is a statement "even if there is no predicate rule to document for example, data time or sequence of events, in a particular instance, it may still be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and reliability of the records."

Legacy Systems

Legacy systems, defined as computerized systems in operation before August 20, 1997, will not normally have FDA regulatory action to make them compliant with Part 11 provided that they comply with all applicable predicate rule requirements and are fit for their intended use. Therefore, legacy systems are exempt from the requirements of 21 CFR 11.

BUT – there are four specific requirements for any legacy system to claim this exemption:
- The system was in operation before the effective date of Part 11
- The system met all applicable predicate rules before the effective date (this probably eliminates 75% of all legacy systems)
- The system currently meets all applicable predicate rule requirements
- There is documented evidence and justification that the system is fit for its intended purpose (including having an acceptable level of record security and integrity, if applicable)

If changes have been made since August 20, 1997 (e.g. Year 2000 remediation, operating system updates/changes, database updates, patches, application updates and service packs), the system needs to be assessed to see if any of these changes would prevent the system from meeting any of the predicate rule requirements. If so, then suitable Part 11 controls would be required.

Again, this must be documented and approved for all systems.

For all other systems implemented since August 20, 1997, there is no exemption under this section and these must meet all predicate rule and Part 11 requirements (except requirements for validation, audit trail, copies of records and records retention outlined in the guidance document).

Impact on Hybrid Systems

Taken as a whole, the contents of the draft guidance document appears to make hybrid systems more acceptable - as long as the electronic records generated by them are trustworthy and reliable as well as meeting the applicable predicate rule requirements.

Although this appears to be good news for many companies; economic pressures, however, will drive companies towards fully electronic systems for greater efficiencies and cost savings [14].

Current Remediation Efforts

From a practical perspective, this means that Part 11 remediation programs underway should begin a careful re-evaluation of the scope and inventory of systems in light of these changes. As noted in Table 1, there are still the majority of Part 11 requirements that have not changed and systems must comply with them.

The draft guidance also supports a move to a risk-based approach toward compliance. This approach will allow companies to analyze their own processes, identify and define critical records and signatures, and implement appropriate controls to mitigate risks. Companies would then be able to implement justified and documented controls commensurate with the criticality of the electronic record and risks identified for that record. This is extremely beneficial as the focus is put on critical electronic records instead of all electronic records managed by companies. More details about the risk-based approach will be available once the FDA publishes the implementation plan for its updated cGMP initiative later on this year.

Space does not permit inclusion of a section on approaches to risk assessment, so this will be the subject of another article.

Current FDA Validation Guidance Still Available

Not all FDA guidance documents on computerized system validation have been withdrawn; the following documents are still available:

- Computerized Systems in Clinical Trials, CDER, 1999 [15]
- Compliance of Off-The-Shelf Software Use in Medical Devices CDRH, 1999 [16]
- General Principles of Software Validation, CDRH and CBER 2002 [17]

Conclusions

The following conclusions can be drawn from the guidance on Part 11 Scope and Applicability [10]:

- 21 CFR 11 has not been withdrawn and the majority of the regulation will still be enforced.
- There is an increased emphasis on the requirements of existing predicate rules and their interpretation. The applicability of these to a system and the records any computerized system contains in either electronic or paper form should be justified and documented.
- An effective, quick and documented risk analysis methodology or methodologies is/are imperative.
- Those sections included under "exercise of enforcement discretion" will be subject to ensuring trustworthiness and reliability of electronic records.
- To do zero is not an option; progress towards an electronic environment on business grounds alone is financially justified.

References

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11. *Withdrawal of Draft Guidance for Industry on Electronic Records; Electronic Signatures, Electronic Copies of Electronic Records [Docket No. 00D–1540], FDA 2003.*
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