Quo Vadis
21 CFR 11

R.D. McDowall, McDowall Consulting, Bromley, Kent, UK.

Introduction
21 CFR 11, the Electronic Records and Electronic Signatures final rule1 — applicable to pharmaceutical and other US Food and Drug Administration (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 added electronic records to be included in the regulation, which is "intended to permit the widest possible use of electronic technology, compatible with FDA’s responsibility to promote and protect public health." The preamble stated that the implementation of 21 CFR 11 would be "broadly cost-neutral."1

Since the rule’s publication in 1997, industry has concentrated on the high cost of remediation and implementation to meet the requirements of the regulation. To help remediation and clarify their enforcement approach, the FDA published the Compliance Policy Guide 7153.17 in 1999.2 According to the guide, administrative and procedural controls should be put in place as soon as possible and work towards technical controls should be performed against a documented action plan. Since September 2001, five draft guidances have been 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-based (instead of product-based) inspections, Process Analytical Technology (PAT) and risk-based approaches to current Good Manufacturing Practice (cGMP). At the request of the FDA, the International Society for Pharmaceutical Engineers (ISPE) wrote a white paper8 that advocated a risk-based approach to Part 11 compliance. This document is significant, as we shall see later, as its concepts and wording frequently appeared in the FDA’s draft guidance on the scope and applicability of Part 11.9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 you think that Part 11 is dead and start practising the Clint Eastwood approach to compliance (i.e., Do you feel lucky?), think again: the FDA notes in the final guidance that the majority of Part 11 remains in force.10

Early in 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 had been issued for comment in early November 2002 and comments were still being accepted from 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 are 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 Records7 had been implemented, industry would not have been able to comply, possibly for a number of years, until data standards had been established and implemented.

On 20 February 2003, the FDA published the draft guidance for industry on 21 CFR 11: scope and applicability.9 This new draft guidance must be viewed within the overall direction of the FDA’s risk-based approach to 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 in April 2003. However we are talking about a government agency here — the final version of the guidance was published on 3 September 2003 but dated August 2003.10

Highlights of the Part 11 Scope and Applicability Guidance
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 time frame is quoted. As any new regulation needs to go through a specified process this is likely to take years (evidence the timescale between publication of the Advance Notice of Proposed Rulemaking (ANPR) 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
It is important to stress that Part 11 is still in effect; the regulation remains unchanged at this time and all other areas will continue to be enforced by the agency.

- During the period of re-examination, the FDA is to exercise discretion in enforcing the ruling but note that this discretion applies only as identified in the guidance. In effect, this means that the agency is unlikely to take enforcement action against several key areas of the rule, in particular the validation, audit trail, record retention and record copying requirements. FDA will focus instead on ensuring compliance with predicate rules and the associated validation requirements.
- Throughout the document there is reference to documented risk assessment for many of these activities; however, there is no mention of how this is to be accomplished.
- 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 (defined as systems that were operational before 20 August 1997, the date on which Part 11 became effective) and they are exempt from the requirements of 21 CFR 11. To qualify for enforcement discretion, a legacy system must meet four key requirements that will be discussed later in this article.
- The drafts of Guidance for Industry and the Compliance Policy Guide 7153.17 that were withdrawn in February 2003 will not be re-issued. The FDA provided 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: “Note that Part 11 remains in effect and that this exercise of enforcement discretion applies only as identified in this guidance.” The use of bold text is by the FDA in the final guidance.10

It is important to stress that Part 11 is still in effect; 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 in which 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. 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 in which the FDA proposes to temporarily modify its approach to regulation enforcement 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 and are kept electronically instead of in paper format
- Records required by predicate rules and are maintained in electronic format in addition to paper format, and are relied upon to perform regulated activities; business use of a system may determine if this applies: under this section “for information only” systems and electronic records may be subject to Part 11 as these are generally 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 925-0251 as the types of submissions the agency accepts in electronic format)

Table 1: Current main requirements of 21 CFR 11.

<table>
<thead>
<tr>
<th>Part 11 Requirements Still Enforced</th>
<th>Part 11 Requirements with Enforcement Discretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.10(d) Limiting system access to authorized individuals</td>
<td>11.10(a) Validation</td>
</tr>
<tr>
<td>11.10(f) Use of operational system checks</td>
<td>11.10(b) Copies of records</td>
</tr>
<tr>
<td>11.10(g) Use of authority checks</td>
<td>11.10(c) Record retention</td>
</tr>
<tr>
<td>11.10(h) Use of device checks</td>
<td>11.10(e) Audit trail</td>
</tr>
<tr>
<td>11.10(i) Persons have the education, training and experience to perform their assigned tasks</td>
<td>Legacy systems operating before 20 August 1997</td>
</tr>
<tr>
<td>11.10(j) Written policies that hold individuals accountable for actions</td>
<td></td>
</tr>
<tr>
<td>11.10(k) Appropriate controls over systems documentation</td>
<td></td>
</tr>
<tr>
<td>11.30 Controls for open systems</td>
<td></td>
</tr>
<tr>
<td>11.50 Signature manifestations</td>
<td></td>
</tr>
<tr>
<td>11.70 Signature/record linking</td>
<td></td>
</tr>
<tr>
<td>11.100 General requirements</td>
<td></td>
</tr>
<tr>
<td>11.200 Electronic signature components and controls</td>
<td></td>
</tr>
<tr>
<td>11.300 Controls for identification codes/passwords</td>
<td></td>
</tr>
</tbody>
</table>
• Electronic signatures that are the equivalent of 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.).
• What does this mean in practice? What does this mean for chromatographers? Specifically the guidance document removes word processing systems from the scope of Part 11, which is good as many inspectors have indicated that this is within its remit. However, my advice is to protect the final version of a file produced; you won’t have to retype the document from scratch as you can go back to the original file to modify it. There is no Part 11 implication and validation is not required. However, if your company has automated its word processing functions by incorporating it within an Electronic Document Management System (EDMS), this would be under Part 11, especially if electronic signatures were used. This system produces Part 11 electronic records and must be validated. Apart from word processing, no specific examples are discussed; however, in the laboratory not many systems would be excluded based on this approach. Document (in an SOP or system requirements specification) the records required by predicate rules and whether electronic or paper records are used to perform regulated activities. The best approach is to justify each system on a case-by-case basis if Part 11 applies and, if so, clarify what records are contained within the system. In many instances this will mean revisiting a number of systems in a laboratory’s Part 11 assessment and remediation programme to reassess how the system is being used and if records produced still fall under Part 11 or paper.
Let’s look at a specific example that occurs in many laboratories: a chromatography laboratory:
• This system is not incidental to the production of paper records, so don’t even start down this road; if you do, have the warning letter drafted to give when the inspector comes on site
• A single system for instrument control, data acquisition and reporting will be under 21 CFR 11 and validated according to predicate rule requirements; if electronic signatures are implemented, further validation and procedural controls will be required for this functionality
• In some laboratories, a central data system is responsible for data acquisition and reporting; instrument control is under the control of the original equipment manufacturer’s data system but only the instrument control features are used. In an earlier “Questions of Quality” article, I called this arrangement a hybrid electronic system as electronic records were contained in both systems. Under the new guidance, the narrow scope of Part 11 can be used to advantage: the instrument control workstation can be declared as incidental to the production of paper records providing that the procedural controls are in place for the production of paper records to meet records requirements of the predicate rules you work to.
Where Part 11 is not applicable: The FDA has stated that under the narrow interpretation of the regulation where 21 CFR 11 does not apply, that:
• Records (and any associated signatures) that are not required to be retained by predicate rules — but are nonetheless maintained in electronic format — are not Part 11 records
• 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 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 performed 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 performed. 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 these impact the computerized systems being used. This is not always the situation, in my 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’s 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 should we interpret the following for computerized systems in the chromatography laboratory:
• Adequate design
• Adequate size
• Suitably located?
As we look though the existing predicate rules there are sections giving no stated or explicit requirements for records, for example with 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 cGMP 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, Good Laboratory Practice (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.

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

Are the predicate rules up to snuff?

Several times in the guidance document there is the statement “even if there is not a predicate rule requirement, it may still be important to... validate a system or have an audit trail etc.”

One way of looking at this and the other similar statements is that the predicate rules, originally written in the 1970s, 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.

§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 §11.63 as highlighted above or the GLP equivalent under §58.61.

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 notes, validation and its extent should be based on a documented and justified risk assessment of the system.

In their only specific example of the entire 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.

§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 electronic 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 records are preserved. It is important to validate this before the inspector turns up on your front door, not during the inspection
- If your electronic records can be searched or trended then the copies supplied to the FDA should also be capable of this when 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.³⁹
- Using industry standard portable formats where possible, if the use of such formats brings more benefits than disadvantage.
- Using 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.

Gone is the poorly worded draft guidance phrase of “FDA does not normally intend to object” which was vague and subject to interpretation itself.

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. In the final version this is much improved.

Now we have 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 formats (the most common and best developed 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 US; furthermore the ICH requirement for the electronic Common Technical Document (eCTD) states that data must 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, but 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. Don’t 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.”¹³

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\(^1\)\(^4\) so that they can be accessed if required and the FDA have completed their Part 11 review.

\(\textit{§11.10(e) Audit Trail: To ensure enforcement discretion, computerized systems must still meet predicate rule requirements for date and time sequence of events. Allowable methods for this have expanded 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 using 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 life easier to monitor the creation, modification and deletion of records by users.

There is still a sting in the tail 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 20 August 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, suitable Part 11 controls would be required. Again for all systems this must be documented and approved.

For all other systems implemented since 20 August 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).

\(\textit{Impact on Hybrid Systems}
\)

Taken as a whole, the contents of the draft guidance document appear to make hybrid systems more acceptable — as long as the electronic records generated by them are trustworthy, reliable and meet 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.\(^1\)\(^5\)

\(\textit{Current Remediation Efforts}
\)

From a practical perspective, this means that Part 11 remediation programmes underway should begin a careful re-evaluation of the scope and inventory of systems in light of these changes. Not all sections of the draft guidance may make it to the final version, and it is very important that companies do not immediately change their direction or focus on 21 CFR 11. As noted in Table 1, the majority of Part 11 requirements have not changed and systems must comply with them.

The draft guidance also supports a move to a risk-based approach towards compliance. This approach will allow companies to analyse their own processes, identify and define critical records and signatures, and implement appropriate controls to mitigate risks. Companies will 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.

\(\textit{Current FDA validation guidance still available}
\)

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\(^1\)\(^6\)
- Compliance of Off-The-Shelf Software Use in Medical Devices CDRH, 1999\(^1\)\(^7\)
- General Principles of Software Validation, CDRH and CBER 2002.\(^1\)\(^8\)

\(\textit{Conclusions}
\)

The following conclusions can be drawn from the guidance on Part 11 scope and applicability:\(^1\)\(^0\)

- 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
- Doing nothing is not an option — progress towards an electronic
environment on business grounds alone is financially justified.

References
18. General Principles of Software Validation; Final Guidance for Industry and FDA Staff (FDA, Center for Devices and Radiological Health, Center for Biologies Evaluation and Research, 2002).

Bob McDowall is Principal of McDowall Consulting, Bromley, Kent, UK. He is also a member of the Editorial Advisory Board of LC•GC Europe.