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21 CFR Part 11 Electronic Records; Electronic Signatures Guidance for Industry – Scope of Application Position Paper: A Summary and Interpretation of the Guidance

Note: This document has been prepared based on information released by FDA plus ABB's experience gained from working with a wide range of clients in the regulated industries. ABB cannot be held responsible for the accuracy of interpretation or implementation of the recommendations – this document is issued purely as help for the industry.

Throughout this paper specific references are made to the FDA guidance document [1], quoting line numbers from the document in superscript.

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Executive Summary

FDA issued on 20 February 2003 a significant draft guidance document on the scope and application of 21 CFR Part 11. This new guidance will allow industry to adopt a much more pragmatic approach to Part 11. In some cases the FDA will not enforce the rule or aspects of the rule, e.g. legacy systems in operation before 20 August 1997 will no longer be subject to Part 11 inspections.

ABB has with this paper set out to provide a summary of the new guidance document, plus an interpretation of the restated requirements. A summary of recommendations is included, and industry can draw noteworthy benefits from implementing the guidance, without neglecting compliance with 21 CFR Part 11.

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Background

21 CFR Part 11 (henceforth referred to as 'Part 11' or 'the rule') has become one of the most significant pieces of recent FDA regulation. At the same time it is the regulation that has attracted the most criticism and caused immense confusion and costs for industry. Increasingly the cost of complying with Part 11 has outstripped any risk reduction to public health.

In August 2002 FDA announced a 'risk based' approach to enforcement of cGMP, and specifically included Part 11 in this new initiative. The Agency has also taken industry complaints to heart, as evidence has mounted on the difficulties in complying with the letter of the law. Accordingly, on 20 February 2003 FDA issued new draft guidance to industry on the scope and application of Part 11.

ABB has with this paper set out to provide a summary of the new guidance document, plus an interpretation of the restated requirements, as well as a set of recommended actions to follow. ABB welcomes any comments on this paper, which can be directed to the person at the end of the document. This document is copyright protected, and may not be copied or distributed without the written consent of ABB.

Summary of Guidance

In summary the guidance provides for:

- Reinforce the enforcement of predicate rules (Parts 58, 211, 820, etc.)
- Promote a 'risk based' approach to GMP. As part of developing this approach, Part 11 will be re-examined, which may result in changes to the rule.

Whilst this review takes place, the following guidance will apply:

- The definition of electronic records and signatures that fall under Part 11 has been clarified and in many cases narrowed.
- Enforcement discretion will be exercised, particularly in the following areas:
    - Legacy systems
    - Validation
    - Record copying
    - Record retention
    - Audit trail
- The remaining sections of Part 11 will continue to be fully enforced as per the rule wording.

In addition the Agency announces that:

- Already issued guidance to industry documents are withdrawn (all in draft and covering glossary of terms, validation, time stamps, maintenance of records and electronic copies of electronic records).
- The compliance policy guide CPG 7153.17 enforcement policy is withdrawn.

The details of the guidance are discussed in the following sections.

Status of Guidance

This guidance has been labelled as “draft – not for implementation”, and comments can be forwarded to the FDA until 20 April 2003. This rationale has been emphasised by the introductory statement that agency guidance, including this document, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.[46] Later, however, it is stated that this guidance has been issued “to describe how we intend to exercise enforcement discretion with regard to certain Part 11 requirements during re-examination of Part 11”[106]. This would suggest that this draft guidance contains important information and announcements, which industry can and should act on immediately. Even though a re-examination of the Part 11 regulation itself is referred to, it is not likely that the approach taken by the FDA will dramatically change further.

General Interpretation of Guidance

The guidance represents a major shift in FDA approach and enforcement policy.

The original purpose, as requested by industry, was to define the conditions under which electronic records and signatures would be acceptable to the FDA. This in turn would enable the gainful employment of fully electronic systems in drug development and manufacture. The stated purpose of the guidance is to make Part 11 more pragmatic and manageable, and to remove the majority of instances of misguided cases of interpretation.[81] In particular, enforcement of specific clauses of the rule became paramount and almost disconnected from the intent of those clauses, i.e. a reduction in the risk to public health. The draft guidance does enable a much more pragmatic approach to Part 11, which should result in fewer non-compliances, and hopefully promote the use of the provisions that Part 11 provide.

It is important to realise, however, that the guidance does not go the whole way towards a pragmatic risk based approach. Clauses of Part 11 that are not specifically mentioned in the guidance are not subject to enforcement discretion.[125] This includes access controls §11.10(d)(g), operational checks §11.10(f), device checks §11.10(h), competence checks §11.10(i), documentation controls §11.10(k), open systems §11.30, and all clauses related to handwritten and electronic signatures §11.50, §11.70, §11.100, §11.200, §11.300.[126] It is true that these clauses have caused less concern to industry, but a pragmatic risk based approach is still beneficial in these cases.

In addition, this guidance, while clearly narrowing and better defining the scope of Part 11, is still open to interpretation, even in such fundamental areas as to what constitutes an electronic record.

Specific Comments

Definition of Electronic Records[158]

The definition of a Part 11 electronic record has been clarified to state that the rule applies to:

- Regulated records that are maintained in electronic format in place of paper format.[163]
- Regulated records that are maintained in electronic and paper format, where the electronic format is used for regulated activities.[168]

Regulated records are those documents / records that are identified by the applicable predicate rules (Parts 58, 211, 820, etc.) and need to be maintained. Regulated activities are those actions identified in the predicate rules.

Paper records that are generated by computers, that are merely incidental to the record generation process, do not fall under the rule[154]. This definition is helpful, and does not differ from ABB practice. An example is a word processor that is used for the generation of a submission. This is then presented to the FDA and maintained in paper format, and the computer-generated data is not used for any other regulated activities. In this case Part 11 does not apply.[151] Should the same records be distributed electronically for regulatory purposes, e.g. as an SOP, then Part 11 does apply because you are now relying on the integrity of the electronic record.[171]

It may not always be easy to determine the exact records required under predicate rules (regulated records). Predicate rules do not necessarily reflect current practice, e.g. Part 211 defines GMP not cGMP, and additional guidance may need to be consulted, such as FDA Guidance on General Principles of Software Validation [2], the GAMP guide [3] and ISPE Baseline guides [4]. Note that it is still the case that electronic records that are submitted in addition to those identified in regulations, also potentially fall under the Part 11 regulation.[184]

The guidance recommends that each predicate record is defined as either paper record or electronic record (and hence within scope of Part 11), and that this is documented in an SOP.[179] It is industry practice to identify all relevant electronic records as part of system assessment. It is also ABB's practice to define the electronic records in the system description or user SOP or similar document.

Definition of Electronic Signatures[191]

The definition of a Part 11 electronic signature is limited to those instances where an electronic signature is used to replace a signature or initial identified in the predicate rules. This is interpreted to include those instances that state 'verified' in the predicate rules. Electronic signatures that are not identified in the predicate rules do not fall under Part 11. It should be noted, however, that the security and use of any such signature could be questioned under the predicate rules.

Legacy Systems[234]

Enforcement of Part 11 will be limited to systems that have been put into operation after 20 August 1997. The applicable predicate rules, however, still apply to all systems used for regulated work, and the guidance states specifically that all systems must be fit for purpose.

ABB would support this revision in policy, as many of the Part 11 requirements have proved difficult to implement for these older systems, so the main impact of this exemption is to enable companies to retain the systems as long as they are safe and trustworthy. In a few years time most of these systems are likely to be replaced as part of the scheduled capital spend.

Note that the exemption only applies to systems more than 6 years old, so that many current systems will still be within the scope of Part 11.

Also, note that no exemption is applied to any system using electronic signatures, since legally these could not be employed before 20 March 1997.

Validation §11.10(a)[196]

The validation requirements shall be determined by the predicate rules, other existing FDA guidance (in particular General Principles of Software Validation [2]), GAMP 4 [3], and risk assessment (risk to product quality, product safety and record integrity).

The level of validation should be commensurate with the size, complexity, criticality, standardisation and quality of the computer system. This is consistent with ABB practice and current best industry practice.

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Copies of Records §11.10(b)[242]

The requirement to be able to provide electronic and readable copies of all electronic records has been reduced to giving the inspector reasonable and useful access to records, using standard system functions or commonly available tools / software / functions, as long as these are feasible to use. PDF is promoted as an acceptable format (because it can be universally read and searched), with the proviso that content, meaning and search / sort / trend functionality are preserved where possible.

This wording gives companies ample leeway to comply with §11.10(b). There is no mention of validating the copying procedure or the need to maintain all configuration and meta data. Configuration and meta data are not addressed by the guidance, and it is often difficult to obtain copies of these. The guidance recommends, however, that you ensure that the content and meaning of the record are preserved in the copying process.[256]

ABB recommends that companies document which records can be copied, and to what format the copying is done. Where copying cannot be done electronically, using readily available methods, paper copies may be generated and verified. These instances should be justified by a credible rationale.

Record Retention §11.10(c)[263]

The predicate rules determine what records need to be retained and for how long. It is no longer necessary to retain all electronic records and all record components, such as configuration and meta data, as long as the predicate rule requirements are met. This is an important concession, as comprehensive electronic record retention (as previously interpreted by FDA) over the lifespan of a record may be difficult to attain. The new guidance specifically states that the FDA will not normally object to the archiving of electronic records onto microfilm, microfiche or paper.[275] This reflects current best industry practice.

The guidance states that which records are to be kept should be justified.[271] Stored records must retain their content, meaning and context. Hybrid records, i.e. a mixture of paper and electronic components, are specifically allowed in the new guidance, something that represents current industry practice.

Audit Trail §11.10(e)[216]

The need for an audit trail is now to be determined by the predicate rules, other existing FDA guidance (in particular General Principles of Software Validation [2]), GAMP 4 [3], and risk assessment (risk to product quality, product safety and record integrity). This is consistent with ABB practice, but constitute a material change from what industry in general has been attempting to do.

The guidance recognises that an audit trail is only one way of reducing risk and ensuring record integrity. Alternatives are access controls (physical, logical), procedural controls, security and back-up of records.

Note that manual audit trails are not mentioned as a substitute to automated electronic ones. It has long been ABB policy that these are not credible alternatives for detecting unauthorised changes. On the other hand, manual controls for authorised changes, i.e. change control, can often be appropriate.

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Summary of Recommendations

Based on ABB's interpretation of the draft guidance and our experience from working with all aspects of the rule, our recommendations to industry are as follows:

- Companies must still comply with Part 11, which remains the law. What the FDA is now classing as "enforcement discretion" will only apply to some aspects of the rule. Part 11 rectification programmes should not therefore be terminated.
- Companies should take advantage of the fact that the guidance enables a much more pragmatic approach to be adopted.
- A risk based approach to Part 11, and computer system validation in general, should be implemented.
- Companies should continue to pay attention to the use and control of computer systems. The vast majority of 483 observations, which are issued with relation to computer systems, do not reference Part 11. The guidance enforces the stringent adherence to predicate rules.

Companies now have the opportunity to focus their remediation spend on the more critical systems. The above approach will enable cost savings to be made, without increasing the risk to public health or the inspection risk.

References

1. Guidance for Industry, Part 11, Electronic Records; Electronic Signatures – Scope and Application (US FDA; 20 Feb 2003)
2. Guidance for Industry and FDA Staff; General principles of Software Validation (US FDA; 11 Jan 2002)
3. GAMP v4 Guide for Validation of Automated Systems (ISPE; Dec 2001)
4. Baseline Guides; various volumes and editions (ISPE)

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