



June 28th, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852
USA

Subject: Comments to Docket No. 2004N-0133 – Food and Drug Administration

Dear Sirs,

With respect to specific comments sought to Docket No. 2004N-0133:

A. Part 11 Subpart A –General Provisions

1. In our opinion, the current text of part 11 reflects in an adequate way the applicability of part 11 to electronic records and signatures to be maintained under predicate rules. However, if paper records are used as primary source of pharmaceutical information or decision making the non-applicability of part 11 to the equivalent e-records / signatures has to be derived implicitly. The current text does not address this explicitly. Therefore the Agency are encouraged to revise part 11 to implement the narrow interpretation described in the guidance.
2. No comments.
3. We would very welcome a clarification which records are required by predicate rules because the present text of part 11 leads to huge discussions whether or not part 11 applies to specific records. We could imagine that these records directly relate to the product and are relevant to public health and therefore address:
 - ?? Non-clinical and clinical research data
 - ?? Product batch data
 - ?? Product quality control data
 - ?? Product distribution data.

Data not directly related to the product itself (such as personnel qualification data) are less relevant and could be out of the scope of part 11.

B. Part 11 Subpart B—Electronic Records

1. The Agency are encouraged to consider extension of the risk based approach to all parts of part 11, except for some issues addressed below.
2. We would very welcome a clarification how predicate rule requirements could be fulfilled.
3. In our opinion, part 11 should not apply to copies of e-records that have been submitted to the agency. Before submission, the copy process as well as the records that are going to be submitted have to be validated. Copied records will have to be secured against loss of integrity, loss or modification, in an identical way as the original records. Once records have been submitted to the Agency they are not in the scope of part 11 anymore. So, in our opinion distinction should be made for records before and after submission.
4. In our opinion, the distinction between open and closed system adds little value because the intention of part 11 is to protect records against unauthorized access, creation, modification or

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deletion. It is not of interest whether threats come from within or outside a company. This issue should be considered when designing controls for protection and it is obvious that controls for outside threats have to be stricter than from internal. We feel that making a distinction in part 11 is not necessary. Providing examples or indications where controls have to be applied strictly (e.g. access via the internet, outsourcing to an external company of application hosting) could be advantageous.

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1. Basically, in our opinion each system that deals with records subject to predicate rules need to be validated. Application of a risk based approach for the requirement to validate a system has at least two serious disadvantages:
 - ?? The assessment of the likelihood of occurrence of an adverse event and the impact thereof is subjective.
 - ?? These subjective assessments will lead to discussions within a company and between a company and the Agency during inspections.Such subjective assessments tend to lead to different approaches throughout the industry and should be avoided as much as possible.
2. No comments.
3. Audit trail requirements should include controls designed and implemented to deter, prevent and document unauthorized record creation, modification and deletion. The nature and extent of such controls should be based on a documented risk assessment on the audit trail.
4. In our opinion, corruption or deletion of system documentation may have only an indirect effect on product quality and public health. For system hardware and software this might be different. Unauthorized modification or deletion of hardware or software components might result in unexpected system behavior. In addition to this, configuration and change management is the basis to keep a system in a validated state. Therefore, the Agency are encouraged to consider the incorporation of these concepts in part 11 for hardware and software but not for documentation.

C. Part 11 Subpart C—Electronic Signatures

The Agency are encouraged to include the handling (investigation, follow-up) of security breaches in part 11. The scope should not be limited to individuals but should include also virus attacks, etc.

D. Part 11 Additional Questions for Comment

1. Modifying part 11 will probably reduce unnecessary cost without compromising product quality and public health.
2. If feasible to do so, we would very welcome a clarification which records are required by predicate rules where those records are not specifically identified by predicate rules.
3. No comments.
4. The Agency are encouraged to consider incorporation in part 11 of the following lines of thinking:
 - ?? Part 11 should apply to e-records that replace paper records and that are used to base pharmaceutical decisions on.
 - ?? Part 11 should apply to records that are, explicitly or not, required by predicate rules.
 - ?? Part 11 should specify these records.
 - ?? Part 11 should ensure integrity and, when applicable, confidentiality of records.
 - ?? Adherence to part 11 with respect to the records specified in part 11 has to be mandatory unless a company carefully considers and documents not to (partly) do so, preferably based on a risk assessment. This approach will decrease discussions within companies on which records are subject to part 11, but will give companies the freedom to take a different direction. In such

cases, the Agency will have to assess whether such a different direction is acceptable and the company will take a risk that the Agency will not agree with this different direction.

- ?? Application of the risk assessment and mitigation concept is acceptable throughout part 11, except for the records specified (previous point) and the requirement to validate a system.
- ?? Part 11 should focus on **what** has to be achieved and not on **how** this can be done.

In general, we would welcome a mixture of proscriptive approach and the freedom for companies to take a different direction. We are very reluctant to leave the definition of the scope of part 11 and the interpretation of the predicate rules to individual companies. Doing so could lead to serious interpretation differences and to endless discussions within a company and between a company and the Agency.

5. See above comments.
6. We would welcome the application of the risk assessment and mitigation concept to legacy systems.
7. In our opinion, record conversion should be addressed because conversion is relevant for record retrieval, copying, retention and submission to the Agency. According to predicate rules, records may be required to be kept for a significant period and current technology may become outdated. In order to be able to retrieve records and to use new technology, record conversion may be required. In addition to this, conversion of records to a common data format may be required, e.g. for submission purposes. The conversion process should be validated and the converted records should have the same level of integrity and, when appropriate, confidentiality as the originals.
8. In our opinion, part 11 should state requirements that are independent of a specific technology. The requirements should focus on **what** has to be achieved and not on **how** this has to be done.

In our opinion, the provisions of 11.100(c)(1) add little to product quality and public health but involve a lot of unnecessary paperwork. The Agency are encouraged to remove this paragraph.

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