



Merck KGaA · Frankfurter Straße 250 · 64293 Darmstadt

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room IQ61
Rockville, MD 20852

Datum Nov-11-2002
Bereich/Abt. ISA/QA
Zuständig Dr. Jörg Schwamberger
Tel. +49(0)6151/72-8384
Fax +49(0)6151/72-91 8384
E-Mail joerg.schwamberger@merck.de

Reference: [Docket Number 00D-1539] "FDA Draft Guidance for Industry – 21 CFR Part 11; Electronic records; Electronic signatures; Maintenance of electronic records"

Dear Madams, Dear Sirs,

Merck KGaA (not linked to Merck & Co) appreciates the FDA's effort to provide guidance on 21 CFR Part 11, and the opportunity to provide comments on this new guidance document.

Please find enclosed our comments on the Draft Guidance for Industry – 21 CFR Part 11; Electronic records; Electronic signatures; Maintenance of electronic records, Docket Number 00D-1539.

For questions please refer to:

Dr. Joerg Schwamberger
Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt
Germany
Phone +49-6151-72 8384
Fax +49-6151-72 91 8384
Email joerg.schwamberger@merck.de

Sincerely,

Dr. Joerg Schwamberger
Manager Quality Assurance IS, ISA/QA

00D-1539

C17



In general the guideline should reflect that there are no guaranteed permanent technical solutions and limited commercially available solutions to meet the long-term retention requirement.

Further, we would appreciate to receive more guidance about FDA's current thinking on ways to achieve a migration without unnecessary costs to industry.

2. Scope

1st paragraph: We intend to provide information with respect to FDA's current thinking on acceptable ways of meeting part 11 requirements to ensure that electronic records and electronic signatures are trustworthy, reliable, and compatible with FDA's public health responsibilities.

Comment: The underlined wording is not equivalent to the wording in the original rule thus creating new areas of debate on interpretation.

Suggested change: The underlined wording should be changed to "generally equivalent to paper records and handwritten signatures executed on paper".

4.1 What Does Part 11 Require?

2nd paragraph, 5th bullet point: Accordingly, the signature manifestation information, associated with an electronic record that is subject to this requirement, must be maintained for the duration of the record retention period.

Comment: The guideline should clearly define the signature manifestation information.

Suggested change: Substitute "signature manifestation information" for "printed name of the signer, the date and time signing and what the signature means".

3rd paragraph: Implementation of these and other part 11 controls will help to ensure that your maintained electronic records will be trustworthy, reliable, authentic, and compatible with FDA's public health responsibilities.

Suggested change: The underlined wording is not equivalent to the wording in the original rule thus creating new areas of debate on interpretation.

Suggested change: The underlined wording should be changed to "trustworthy, and generally equivalent to paper records and handwritten signatures executed on paper".

5.2 Factors That Might Affect The Reliability

First paragraph, 3rd bullet point: You should identify and control factors that could potentially affect the reliability of electronic records during their records retention periods.

Comment: the guideline should take into account that not all factors identified may be controllable.

Suggested change: Substitute the sentence for "You should identify and, to the extent possible, control factors that could potentially affect the reliability of electronic records during their records retention periods.

5.3 Continued availability [...]

General comment: The guideline should also reflect the benefits of 'Technology Neutral Formats'.

Suggested change: Insert the following text "For the purpose of long term retention, electronic records may be retained in a format that differs from the original, which may include a format that offers independence on technology and offers a broader probability for readability". Otherwise more detailed guidance on this specific issue is needed.

1st paragraph: You should periodically access a representative number of electronic records to ensure that record contents can still be read and evaluated throughout the records retention period.

Comment: The guideline should clearly state that 'accessing an electronic record' does not mean 'checking the content of an electronic record'.

Suggested change: Add the following sentence "Accessing an electronic record does not mean a check of the content of an electronic record".

Last paragraph: Because electronic records are generally more perishable than traditional paper records, you should make back up electronic copies of your most important electronic records and store them separately from the primary electronic records. For example, we believe it would not be prudent to store both primary and backup electronic records on the same computer hard drive because both could be lost if the hard drive fails.

Comment: This paragraph creates confusion about the requirement for backups of already archived electronic records - if the original application is already decommissioned and the electronic records are properly preserved in archives this paragraph leads to the impression that one has to create electronic backup copies of the archive

for a redundant storage. Additionally, the criteria for “most important electronic record” have to be defined within the guideline.

Suggested change: Substitute the underlined wording by the following wording “Because maintained electronic records are generally more perishable than traditional paper records, you should consider protection of the maintained electronic records on a risk-based approach”.

5.4 Electronic Records Should Be Stored Under Appropriate Environmental Conditions.

1st paragraph: [...] You should monitor the conditions under which the electronic records are stored. [...]

Comment: In general recording media can be stored safely under a wider range of environmental conditions (esp. regarding temperature, humidity etc.) than pharmaceutical products. Also the question is raised if electronically monitored environmental data are electronic records by the means of 21 CFR Part 11. If yes, these records would also have to be stored under appropriate environmental conditions that would have to be monitored and so on.

Suggested change: Replace the sentence with “You should consider monitoring of the conditions under which the electronic records are stored on a risk-based approach”.

5.5 The Ability To Process An Electronic Record's Information Throughout Its Records Retention Period Should Be Preserved.

1st paragraph: Throughout the records retention period, the ability to process information in an electronic record should not diminish. By being able to process the information, you would maintain the ability, for example, [...] to improve product quality, safety, and effectiveness.

Comment: This is a substantial new requirement that is not covered by the original rule as the requirements for electronic records are defined according to 11.10 (b) as “the ability to generate accurate and complete [electronic] copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency”.

Suggested change: Substitute the underlined wording to “Throughout the records retention period, electronic records should be maintained in a way that allows generation of accurate and complete copies in both human and computer readable form that are suitable for FDA inspection, review, and copying”. Delete all the following sentences within this paragraph. Change the heading to “The Ability To Generate Copies Of An



Electronic Record's Information Throughout Its Records Retention Period Should Be Preserved".

2nd paragraph; Original Text: [...] Accordingly, where you could use computer technologies to search, sort, or manipulate information in an original electronic record, you should be able to use computer technologies to perform the same kinds of processing on information in the maintained electronic record. For example, if you could automatically search for words in the text of an electronic record, sort or find values in a table, or perform calculations in a spreadsheet, you should be able to process information in a like manner for the electronic record over the entire records retention period. This ability (or functionality) derives largely from the hardware and software used to extract information from the electronic record, as well as the electronic record format itself. You should include this ability among your specifications in your procedures and controls.

Comment: The described functionalities are substantial new requirements that are not covered by the original rule as the requirements for electronic records are defined according to 11.10 (b) as "the ability to generate accurate and complete [electronic] copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency." It is our understanding that this does not imply processing capability for maintained electronic records throughout the required record retention period. Acceptable alternatives are addressed in the predicate rules. For example in the GMPs section 211.180 (d) and the GLPs section 58.195 (g), the rule states "Records required by this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records." This clearly shows the intent to retain the information and does not require reprocessing." Requirement for reprocessing should be limited to those stated in a predicate rule (e.g. GLP, Part 58.3 (k)) and not introduced through Part 11 guidance(s).

Suggested change: Substitute the paragraph for "Throughout the records retention period, electronic records should be maintained in a way that allows generation of accurate and complete copies in both human and computer readable form that are suitable for FDA inspection, review, and copying".



6.2.1.3 Electronic Record Integrity Attributes Should Be Preserved

1st paragraph: Where a migration, in effect, creates a new electronic record (by transforming the old electronic record) then, per section 11.10(e), the audit trail for the migrated electronic record would have to cover this creation.

Comment: Given the migration from the old and new systems is documented this appears to be an unnecessary step thus adding to the effort and cost of migration with limited incremental value. Also commercially available software is typically not supporting this functionality.

Suggested change: Substitute the underlined wording for "this transformation shall be documented in a comprehensible way".

6.2.1.4 The Ability To Process Information In Electronic Records Should Be Preserved

1st paragraph: The importance of being able to process information in an electronic record, using computer technologies, is explained above. In the migration approach, the new computer system should enable you to search, sort and process information in the migrated electronic record at least at the same level as what you could attain in the old system (even though the new system may employ different hardware and software). For example, if you could sort a table of values using the old system, you should be able to sort those values in the migrated electronic record using the new system, and achieve the same results. Some new systems can, by emulating older systems, process information in a very similar way.

Comment: While there may be similarities between old and new computer systems this is a substantial new requirement that is not covered by the original rule as the requirements for electronic records are defined according to 11.10 (b) as "the ability to generate accurate and complete [electronic] copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency".

Suggested change: Change the heading to "The Ability To Generate Copies Of An Electronic Record's Information Should Be Preserved". Change the paragraph to "In the migration approach, the new computer system should be capable of making copies of the electronic records in human and computer readable form suitable for inspection, review, and copying by the agency".

6.2.1.5 Unavoidable Differences And Losses Should Be Accounted For and Explained In The Migrated Electronic Record Or New System Documentation

1st paragraph: When electronic records are migrated from one system to another, we recognize that there might be unavoidable losses or changes in certain information or record attributes that do not diminish the reliability of information that is preserved and presented.

Comment: To preserve the meaning of the information migrated is the fundamental objective of a migration. It is our understanding that the meaning of the information migrated shall not change and therefore only information relevant to this meaning needs to be migrated. This should be reflected in the guideline.

Suggested change: Insert the following sentence "The fundamental objective of the migration is to preserve the meaning of the information as judged by experts in the field to be equivalent to the original in the context of its stated, actual or intended use."

1st paragraph, 2nd to 4th bullet point:

- Just prior to performing the electronic record migration a trusted third party from outside of the organization that has some responsibility for the electronic record verifies the digital signature using the old system methods;
- Under supervision of the above trusted third party, the signed electronic record is migrated to the new system; and,
- The above trusted third party then applies a new digital signature (using technologies appropriate to the new system) to the migrated electronic record. The same third party also prepares and applies a digital signature to a new separate electronic record (or to an addition to the migrated electronic record) that explains the migration. In this situation, although you would no longer be able to verify the old digital signature directly, you should nonetheless be able to demonstrate continuity of record integrity by verifying the newly digitally signed migrated electronic record and explanatory statement.

Comment: The requirement to involve trusted third parties in the migration approach is a substantial new requirement that is not covered by the original rule and is not required for the original signing of electronic records. Thus involvement of trusted third parties should not be mandatory - instead an appropriate check during validation by the company itself should be suggested. The guideline should clearly state that not the signature itself is migrated, but the representation of the fact of the signature is migrated and a new signature of testimony by a responsible person is added afterwards.

Suggested change: Complete revision of the 1st paragraph and the bullet points 2 to 4 to reflect the issues raised in the comment.

1st paragraph, 5th bullet point: [...] An electronic record that supplements the migrated electronic record should explain the correlation between old and new color representations, so that the reader would correctly interpret the information. [...]

Comment: Given the differences between the old and new systems are documented this appears to be an unnecessary step and one that is not typically supported by commercial software. Thus adding to the effort and cost of migration and offering limited incremental value. Also commercially available software is typically not supporting this functionality.

Suggested change: Substitute the underlined wording for “A comprehensible documentation that supplements the migration process should explain the correlation between old and new color representations, so that the reader would correctly interpret the information”.

1st paragraph, 5th bullet point: [...] However, text (that referred to the colors) in the migrated electronic record should not be altered because doing so would change the record content and authenticity.

Comment: Transcribing of the text to refer to the new colors is required to preserve the meaning of the record in a manner that is easily understood. Requiring literal text be preserved and to be understood by humans in a convoluted fashion, especially after multiple migrations, could lead to human error of serious consequence. Migrations of text need not to be any more literal than migrations of numbers that may change in literal representation from one system to the next. The key determining factor should be whether the migrated record preserves the meaning of the original record, i.e. judged by experts in the field to be equivalent to the original in the context of its stated, actual or intended use. Any such transcription can be documented as part of the migration process.

Suggested change: Complete revision of the 5th bullet point to reflect the issues raised in the comment.