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December 21, 2001

Dockets Management Branch (HFA-305)
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 00N-1543 - Draft Guidance for Industry: Electronic Records; Electronic Signatures, Glossary of Terms
Docket No. 00D-1538 - Draft Guidance for Industry: Electronic Records; Electronic Signatures, Validation

Dear Sir or Madam::

Attached please find the comments of Purdue Pharma L.P. to the referenced draft guidance documents issued by the FDA on September 24, 2001. Attachment 1 provides our comments to the Glossary of Terms document and Attachment 2 the comments to the draft Validation document.

We would like to commend the FDA team on the development of this guidance. We appreciate the hard work and effort required in preparing such guidance. We trust that our comments reflect the detailed review we have performed and can be incorporated to make the document even more useful to the industry.

Please be assured that Purdue Pharma L.P. welcomes the opportunity to work with the FDA in preparing and reviewing such guidance on complex issues like 21 CFR Part 11. If I can be of assistance with regard to these comments, please do not hesitate to contact me.

Sincerely,

Albert W. Stockalis
Director, Information Systems Quality Assurance
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00D-1543 C16

Dedicated to Physician and Patient

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Attachments

cc: Dr. Theresa Muchnick, Vice President, Corporate QA,
Purdue Pharma L.P.
Dr. Anthony C. Santopolo, Vice President, Regulatory Affairs
Purdue Pharma L.P.

Attachment 1 – Comments on "Guidance for Industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms – Draft Guidance" Docket No. 00N-1543

1. Purpose

a. To add clarity to the cross referencing, it should be noted that this document is a supplement to the Glossary of Computerized Systems and Software Development Terminology (Reference #5).
b. People are only subject to Part 11 as a result of the data and records they create or control. Suggest rewording the second sentence as "It is intended to assist persons responsible for the management and control of records subject to Part 11." Likewise, reword the final sentence as "It may also assist FDA staff who apply Part 11 to processes, procedures, operations and systems subject to the regulation."

2. Scope

a. In the first paragraph the phrase "current thinking" appears. This is standard wording in many guidance documents. Is the intent that the thinking will change moving forward in time? The industry is seeking guidance on implementing the regulation with specific rules to follow. When will a final interpretation or guidance be available?
b. In the Guidance on Validation, the term authentic was used. For the sake of consistency, in the second sentence, replace the word 'trustworthy' with 'authentic' (this change should be made throughout the document).
c. For clarity, recommend the second sentence be changed to read, "We intend to provide information on acceptable ways of meeting Part 11 requirements to ensure that electronic records and electronic signatures are authentic and reliable."

2.1 Applicability

No comments.

2.2 Audience

a. People are only subject to Part 11 as a result of the data and records they create or control. Recommend rewording the first bullet as "Persons responsible for the management and control of records subject to Part 11."
b. Recommend changing the second bullet to "Persons who create, modify, maintain, archive, retrieve, or transmit electronic records or electronic signatures".
c. To include individuals making changes to existing products, reword the third bullet as "Persons who develop or modify products or provide services to enable the implementation of Part 11 requirements."
d. Reword the final sentence as "This draft guidance may also assist FDA staff who apply Part 11 to processes, procedures, operations and systems subject to the regulation."

e. For the sake of clarity, it would be useful to provide a list of examples of the 'persons' being referred to in this section. (e.g. users, DBAs, developers, ...)

3. Definitions

a. To add additional information to the Glossary and provide guidance on areas questioned by the industry in interpreting the Part 11 regulation, it is suggested that the following be added and defined in the Glossary: authenticity, integrity, confidentiality, dynamic testing, accuracy, encryption, compatibility, code review, verification, validation procedures, testing (white box, black box), configuration management, change control (software and documentation), traceability matrix, SDLC, automated test tool (with an indication of validation required), qualification, user requirements, functional requirements, functional specifications, structural testing, functional testing, implementation, and test plan.

b. The definition of Computer System Validation is confusing. It refers to several items that are not defined raising several questions. Are user needs to be treated as intended uses? Is it intended that system specifications conform to user needs and to intended uses or should the computer system conform to user needs and intended uses?

c. The definition of Regression Analysis and Testing refers to verification and validation tasks. What is intended as the difference between verification and validation in this context?

4. References

No Comments.

Attachment 2 – Comments on "Guidance for Industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Validation – Draft Guidance" Docket No. 00D-1538

1. Purpose

a. People are only subject to Part 11 as a result of the data and records they create or control. Suggest rewording the second sentence as "It is intended to assist persons responsible for the management and control of records subject to Part 11." Likewise, reword the final sentence as "It may also assist FDA staff who apply Part 11 to processes, procedures, operations and systems subject to the regulation."

2. Scope

a. In the first paragraph the phrase "current thinking" appears. This is standard wording in many guidance documents. Is the intent that the thinking will change moving forward in time? The industry is seeking guidance on implementing the regulation with specific rules to follow. When will a final interpretation or guidance be available?

b. In the Guidance on Validation, the term authentic was used. For the sake of consistency, in the second sentence of the first paragraph, replace the word 'trustworthy' with 'authentic' (this change should be made throughout the document).

c. For clarity, recommend the second sentence of the first paragraph be changed to read, "We intend to provide information on acceptable ways of meeting Part 11 requirements to ensure that electronic records and electronic signatures are authentic and reliable."

d. The second sentence of the second paragraph indicates that the document "identifies key validation principles" when in fact this goal is unmet. For example, the document does not discuss development life cycles that are generally thought to be key in any validation activity. Rather than identify the key or minimum principles that must be met, the document refers you to seventy-six reference documents for guidance.

e. The second paragraph makes use of the term "key" validation principles. Recommend that the term "fundamental" be used instead. The implication here is that these are basic requirements upon which further layers can be added as appropriate. Given the context within which this guide is written, this term better fits the requirement.

2.1 Applicability

a. The document is intended to provide guidance on validation, not electronic records and signatures. Recommend rewording the first sentence to read, "This draft guidance applies to validation of computerized systems that enable electronic records and electronic signatures to be created, modified, maintained, archived, retrieved, or transmitted under the ...".

2.2 Audience

a. People are only subject to Part 11 as a result of the data and records they create or control. Recommend rewording the first bullet as "Persons responsible for the management and control of records subject to Part 11."
b. To include individuals making changes to existing products, reword the third bullet as "Persons who develop or modify products or provide services to enable the implementation of Part 11 requirements."
c. Reword the final sentence as "This draft guidance may also assist FDA staff who apply Part 11 to processes, procedures, operations and systems subject to the regulation."
d. For the sake of clarity, it would be useful to provide a list of examples of the 'persons' being referred to in this section. (e.g. users, DBAs, developers, ...)

3. Definitions and Terminology

a. The first sentence indicates that 'all' terms used are defined in the draft document "Guidance for Industry, 21 CFR Part 11; Electronic Records; Electronic Signatures, Glossary of Terms. This is clearly not the case. Trustworthy, compatible, confidentiality, authenticity, and integrity of electronic records are just a few of the terms used and not defined in the glossary. Suggest adding these and other undefined terms to the glossary.
b. To add clarity and a reference to the defined terms, it would be helpful if the defined terms were highlighted in bold.

4. Regulatory Requirements; What Does Part 11 Require?

a. The paragraph needs additional wording to indicate that there are additional specific requirements beyond the broad requirements stated in Part 11, Section 11.10.
b. The first sentence makes use of the phrase "confidentiality of electronic records". What is the intended meaning in the use of this phrase? Is this a reference to the encryption of data in open systems? If so, it is recommended that it be stated as an example along with any other examples to add clarity.
c. The term 'accuracy' is used in the last sentence. Please define in the glossary what is intended as the meaning of the term in the context of these documents.

5. Key Principles

a. Recommend renaming this section as 'Fundamental Principles' to avoid confusion implying these are the minimum set required as opposed to something to be built upon.
b. The guideline implies the need for a structured methodology although it is not defined or mentioned. Recommend replacing the opening sentence with "The successful validation of computer systems (i.e. purchased off-the-shelf and substantially configured by the user) requires the satisfaction

of several fundamental principles. First amongst these is that any successful implementation strategy must involve the use of a System Development Life Cycle (SDLC) methodology. There are many such documented methodologies, but whichever is adopted must include the following as a minimum."

5.1 System Requirements Specifications

a. In the third sentence of the first paragraph the words "...you should obtain evidence..." occur. The fundamentals of validation are requirements and as such are 'must be done' not 'should be done'. Recommend making this change throughout the document when referring to the fundamentals of validation.
b. In the second sentence of the first paragraph the words "...intend uses..." is used. Does this refer to the requirements of the system or the intended operator use?
c. In the first paragraph, the terms 'specifications' and 'requirements' seem to be used interchangeably. Is this intent? If not, the difference should be defined in the glossary.
d. In the second bullet of the second paragraph, the term 'scalability' is used. In its operational mode, we are really concerned with the performance of the system. Scaling factors may be used to simulate or predict performance but performance of the system is the issue here. Recommend changing 'scalability' to 'performance'.
e. In the last sentence of the first paragraph, the term 'document encryption' is used. Please add the definition to the glossary.

5.2 Documentation of Validation Activity

5.2.1 Validation Plan

a. Recommend rewording the last sentence as "The plan should be reviewed and approved by suitably qualified personnel prior to validation test execution." The use of the term 'management' is too restrictive compared to what will happen in practice. Also, 'designated' does not imply that they are necessarily the correct individuals to perform that task.
b. To add clarity and allow for complex validation plans having multiple components, recommend changing the first sentence to "The validation plan is a strategic document or set of documents that state what is to be done..."

5.2.2 Validation Procedures

a. Recommend adding detail to this paragraph to address the handling of deviations during the execution of the procedure.
b. For completeness, recommend adding discussion about change control procedures and requirement traceability to this section.
c. Add the term 'validation procedures' to the glossary.
d. Recommend rewording the last sentence as "The procedures should be reviewed and approved by suitably qualified personnel prior to validation

test execution." The use of the term 'management' is too restrictive compared to what will happen in practice. Also, 'designated' does not imply that they are necessarily the correct individuals to perform that task.

5.2.3 Validation Report

a. To add clarity and allow for complex validation reports having multiple components, recommend changing the first sentence to "The validation report or set of reports should document ...".
b. Delete the second sentence of this paragraph. It is a duplicate of section 5.4.3.
c. Recommend rewording the last sentence as "The report should be reviewed and approved by suitably qualified personnel." The use of the term 'management' is too restrictive compared to what will happen in practice. Also, 'designated' does not imply that they are necessarily the correct individuals to perform that task.
d. Recommend adding a discussion of test failures in the validation report. The validation report should include: problems, investigation, analysis, and corrective action. It should also include a procedure for documenting whether the system can be used in spite of open issues and allows for documentation of those requirements not met. Testing to verify manual procedures should also be included.

5.3 Equipment Installation

a. To add clarity to when testing of equipment is to take place and ensure that all stages of implementation are controlled and documented, recommend changing the first sentence to read: "Prior to functional testing, you must confirm via completion of a documented qualification process, that all hardware and software are properly installed and, where necessary, adjusted and calibrated to meet specifications."
b. If the term 'qualification' is adopted, it should be defined in the glossary.

5.4 Dynamic Testing

a. Recommend adding a discussion of test planning to this section.

5.4.1 Key Testing Considerations

a. The third bullet refers to 'live, user-site tests'. What is meant by the use of this phrase? Is this intended to mean parallel testing? The document requires clarification as to whether the FDA expects 'parallel operation or is comfortable with the more European approach of conducting the 'live' user testing over several stages. Extended performance qualification under 'live' conditions implies that the performance qualification extends into normal operations. Recommend adding specificity to this paragraph as to its intent or deleting the word 'live'.

5.4.2 Software testing should include:

a. In the last sentence of the first bullet, recommend replacing the word 'walkthrough' with 'source code review'. This term is more widely used and understood.
b. Recommend renaming the third bullet as 'Software Integration Testing'. This term is more typically used and understood.

5.4.3 How test results should be expressed.

a. The second sentence uses the phrase '... independent evaluation of the test results.' Is the recommended implementation through the use of screen prints or through the use of tester recorded values? Is the implication that tester observations alone are not valid?
b. Recommend deleting the first word of the paragraph 'Quantifiable'. It is superfluous and it is used later in the same sentence.
c. To include and highlight the need for the application of quality assurance to the process, it is recommended that the second sentence be reworded as: "Quantified results allow for subsequent independent Quality Assurance review and evaluation of test results."

5.5 Static Verification Techniques

a. The term 'dynamic testing' is undefined in the glossary. For the sake of clarity, please add the definition to the glossary document.

5.6 Extent of Validation

a. The third bullet refers to a 'more comprehensive validation effort'. Please add further clarification as to which aspects of a comprehensive validation effort would not be included and/or considered appropriate for a normal validation effort.

5.7 Independence of Review

a. It is recommended that this paragraph contain further clarification (i.e. would it be appropriate for the person(s) executing the test scripts to also perform the test acceptance review?)
b. To add clarity please reword item (1) of the last sentence to read: "engaging a third party, such as an independent quality organization: and, ..."

5.8 Change Control (Configuration Management)

No comments.

6.0 Special Considerations

6.1 Commercial, Off-the-Shelf Software

No comments.

6.1.1 End User Requirements Specification

No comments.

6.1.2 Software Structural Integrity

a. Recommend rewording the first sentence to read, "Where source code is not available for examination, end users should infer the adequacy of the software structural integrity through the use of the following:" Committing to all three actions is not a realistic approach in some cases, although if possible, then all three could be done.

6.1.3 Functional Testing of Software

No comments.

6.2 The Internet

a. The Internet is a transport mechanism like intranet and email. The document is silent on WANs/LANs and other transport mechanisms (i.e. floppy disks, CD ROM). Recommend changing the heading of this section to "Internet / Intranet / Email / and other transport mechanisms".

6.2.1 Internet Validation

a. The second paragraph discusses the 'validation of both the source and destination computing systems'. If a browser is being used, does this include the qualification of a site's computer or the validation of the workstation? For example, remote data capture systems in which a physician connects to a link on our server using a browser. Would we expect the physician's workstation be fully validated and documented?
b. For clarity and completeness recommend adding a bullet point to show 'data encryption' as part of the suggested measures.

Appendix A

a. Recommend updating the reference to the new version of GAMP4, which will be released in December 2001 at the ISPE Amsterdam Conference.
b. Recommend adding a reference to the "Good Practice and Compliance for Electronic Records and Signatures; Part 2 – Complying with 21 CFR Part 11, Electronic Records and Electronic Signatures, Version 1, September 2001. This is a document produced jointly by ISPE and PDA, published in October 2001.

STERIS Corporation's comments on document, **"Guidance for Industry 21 CFR Part 11; Electronic Records; Electronic Signatures - Glossary of Terms" and "Validation."**

Section 2.1 Applicability

General Comment: The guidance document should specifically exclude the creation of records using electronic means when the record is printed out, approved via hand signature and maintained "manually" as the quality record. In essence, the computers are simply used as typewriters and calculators, with the results verified and approved through traditional means. This may be best clarified in the definition of "Electronic Record."

STERIS Corporation's comments on document, **"Guidance for Industry 21 CFR Part 11; Electronic Records; Electronic Signatures - Validation".**

Section 5.2.3 & 5.4.3 How test results should be expressed

FDA Guidance: *"Quantifiable test results should be recorded in quantified rather than qualified (e.g.,pass/fail) terms." Quantified results allow for subsequent review and independent evaluation of the test results.*

STERIS's Comments: FDA should give further guidance on what constitutes "quantifiable" test results, to help industry know what is acceptable to an investigator.

Section 5.5 Static Verification Techniques

FDA Guidance: Midway through the paragraph, *" ...static analyses such as document and code inspections, walk-throughs, and technical reviews."*

STERIS's Comments: FDA should expand on these concepts, since many industry regulatory and a large number of engineering personnel are not familiar with these concepts. This would help industry to evaluate whether or not an outside consultant or someone internal to the organization was actually doing acceptable verification activities.

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