



June 7, 2004

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

Reference Docket No. 2004N-0133

To Whom It May Concern:

META Solutions, Inc. wishes to submit the following presentation and responses to FDA's questions for discussion at the Agency's June 11, 2004 public meeting relating to the FDA's 21 CFR 11 regulations and guidance.

"A Consultant and Instructor Perspective on the 21 CFR 11 Regulations and Guidance"

This presentation is provided as a consultant and 21 CFR 11 instructor perspective on the request for information from the FDA regarding the "Part 11" regulations and the "Scope and Application Guidance". Specific responses to the FDA's questions are provided within this presentation and in writing, as submitted to the respective public docket. Thank you for this opportunity to present this perspective.

We believe that the Part 11 regulations should be modified to reflect the current industry environment and status, and to be able to more effectively prepare for rapid advances and adoption of new technology solutions. The concerns that are reflected in the existing regulations may have been appropriate at the time that they were conceived in the early to mid-1990's. However, the rapid acceptance of the PC, the Internet and e-commerce, the resultant improvements in security technology, and increased corporate and individual awareness of electronic security and responsibility, have dramatically changed over the last ten years. These improvements render many of the Part 11 regulations obsolete, or in many cases, inefficient and confusing.

We believe that Part 11 has discouraged innovation by 1) increasing the regulatory compliance uncertainty of making decisions to use new technology and processes, which usually results in no decision (or a "no" decision), 2) increasing the need for a conservative regulatory compliance approach, which increases cost and reduces the availability of already limited funding to try new technology, and 3) increasing the reluctance of company Management to try new approaches or to upgrade an existing system or technology.

We recommend that:

- ?? Part 11 should be rewritten to focus on minimum regulatory requirements for e-records/signatures
- ?? There should be less prescriptive regulation ("what" is required)
- ?? There should be more relevant guidance ("how" to comply)
- ?? There should be improved alignment between Part 11 and predicate rules

It is our opinion, and we believe the opinion of many of our clients, that the regulations are, in general, overly prescriptive and detailed. It is recommended that the focus of Part 11 should be on "minimum requirements" for e-records/signatures, rather than the agency's criteria for the trustworthiness, reliability and equivalence of e- and paper/handwritten records/signatures. These criteria have resulted in the overly broad scope and interpretation of Part 11 by both the FDA and industry. The expectation for trustworthiness and reliability of any records, whether electronic or not, should be expressed in predicate rules. It is recommended that Part 11 should be simplified to provide the minimum regulatory compliance requirements for the use of electronic records and signatures to replace their paper and manual equivalents. For example, we believe that the current Part 11 requirements for closed systems controls, including validation, audit trails, operational checks, authority checks, and device checks, are overly

prescriptive and may not apply in all situations. It is recommended that the regulations for system controls simply require that regulated computer systems be designed, tested and implemented to ensure that electronic records and signatures meet predicate rule requirements, including 1) documentation of operators' regulated entries and actions, 2) protection to ensure security and integrity during the record retention period, and 3) the ability to be *electronically* inspected, reviewed and copied by the agency. Further:

- ?? The use of an automated audit trail with specific safeguards may be appropriate for most computerized data management systems, but it is overly prescriptive and may not be appropriate for all situations, such as hybrid and low-risk systems. In some of these cases, printouts or procedural controls could adequately meet regulatory requirements regarding changes made to data without the need for an automated audit trail.
- ?? Similarly, Part 11 requirements for configuration and document management for system hardware and software would also be overly prescriptive, especially for smaller purchased applications. These requirements are more relevant for the more substantial computerized systems that are subject to periodic upgrade and modification. FDA expectations for these different categories of systems and their respective documentation controls would be more appropriately described in guidance.
- ?? The identification of specific mechanisms for this protection, including follow-up, would be overly prescriptive. Part 11 should require that electronic records be protected for security and integrity. Would these mechanisms be mandated if the records were maintained as paper records?

It has been our experience that the effort and cost of Part 11 compliance has increased because of the need for conservative interpretation of the regulations, and because unnecessary controls are often implemented in order to meet the "letter of the law" with little real value to system owners or to the American public. For example, the Part 11 regulatory requirement for an "audit trail that documents time-sequenced development and maintenance of *systems documentation*" (21 CFR 11.10k) is a high-cost effort that has little practical benefit in assuring system security. The current Guidance statements are confusing and subject to interpretation. The Guidance refers the industry to predicate rules that do not explicitly state which records are required to be maintained. As a result, companies must conservatively assume that ANY records that are related to the predicate rules are required to conform to part 11.

The Part 11 regulations should identify "what" is necessary, and not prescribe "how" the requirement is to be met. Additional FDA guidance documents are useful to present the FDA current thinking on "how" to implement the regulations. It is suggested that future guidance could be organized by major regulatory domains, such as GLP, GCP, drug GMP, and device GMP "worlds" to describe the agency's current thinking in each area, and specifically describe whether and how they can be applied in other areas. This new guidance should include much more practical, current and specific industry examples than the ones that are usually given in FDA guidance. In many cases, past Part 11 guidance required even more interpretation than the 21 CFR 11 regulations. One example of this confusion was caused by the current guidance statement regarding the incidental use of computer systems to produce a paper record. This statement is confusing and does not reduce scope, because the computer system probably still requires validation, protection of source/raw data records, etc. under the predicate rule.

It is recommended that the regulations should require that the technical and procedural controls for any "regulated computer system" (now there's a needed definition) should be commensurate with the risks to the records and signatures, and guidance should present FDA's current thinking of what kind of controls are necessary for different situations. We believe that the industry should be encouraged to conceive and adopt their own "risk-based approaches" to determine when and how to implement these controls. We agree that this determination should be based on a justified and documented risk assessment that is approved by Management, and a formal implementation plan should be instituted and followed. However, the need for the risk-based approach should be provided as the Agency's "current thinking", in the form of guidance and not regulation. The standard risk statement from the Agency regarding product quality and safety, and record integrity is vague and subject to much interpretation, and has resulted in increased scope of effort.

We believe that there is insufficient alignment of the 21 CFR 11 regulations with predicate rules, especially in the preclinical (GLP) and clinical (GCP) research environments. As one example, the current, and predominant, industry standard is to require validation of computer systems that are used to support FDA-regulated data and activities. Although the Scope and Application Guidance focuses the industry's attention on predicate rule requirements for validation, the GCP and GLP requirements for data management system validation are currently broadly interpreted using non-specific regulations for "adequate and accurate case histories" (21 CFR 312.62b) or testing of "equipment

used for the generation, measurement or assessment of data" (21 CFR 58.63a), or from medical devices guidance. It has been our experience that the Part 11 regulations provides a valuable and consistent framework for GCP and GLP validation and other current industry standards regarding documentation, security and procedural controls. It is our opinion that the 21 CFR 11 regulations should either retain the requirements to test (or validate) a regulated computer system, or the predicate rules should be modified to include these requirements. We believe that much of the interpretation and increased scope has been caused by the lack of clarity in the predicate rule requirements.

In closing, we believe that the economic ramifications of changes to Part 11 could be significant if the changes resulted in greater clarification of FDA expectations, requiring less conservative interpretation using less-prescriptive regulations and more specific and relevant guidance that is regularly updated with the Agency's current thinking. Although for most regulated entities, much of the cost of validating or replacing primary data systems has already been spent, the benefit would be for future decision-making. For most companies, the major economic benefit would be a reduction in unnecessary efforts and controls caused by the need for conservative interpretation of the regulations. We believe that the implementation of these recommendations will ultimately encourage innovation and technical advances within the regulated industries.

Respectfully submitted,

META Solutions, Inc.

Kim Nitahara, CEO

Telephone: 908-791-1900

Facsimile: 908-791-9977

e-Mail: kim.nitahara@metasol.com

Background Information:

META Solutions, Inc. is a consulting company that has provided Part 11 and validation consulting services to over one hundred pharmaceutical, biotechnology, medical device and CRO companies in North America, Europe, Asia, Africa, South America and the Middle East. The company has provided Part 11 training to thousands of industry, academia and government participants at dozens of global industry meetings, including the primary Part 11 training sessions at the last six DIA Annual Meetings. The primary speaker also served as the Chairperson of the Society of Quality Assurance committee that responded to the Proposed Rule in 1994.

Responses to Agency Topics for Discussion and Comment

A. Part 11 Subpart A - General Provisions

Question: “We are interested in comments on FDA's interpretation of the narrow scope of part 11 as discussed in the part 11 guidance and whether part 11 should be revised to implement the narrow interpretation described in the guidance.”

Response: Part 11 should not be revised to implement the narrow interpretation described in the guidance. It is recommended that FDA's current thinking about the narrow scope of part 11 should be provided in the form of guidance only. The current guidance statements are confusing and subject to interpretation. The guidance refers the industry to predicate rules that do not explicitly state which records are required to be maintained. As a result, companies must conservatively assume that ANY records that are related to the predicate rules are required to conform to part 11. One example of confusion is caused by the current guidance statement regarding the incidental use of computer systems to produce a paper record. This statement is confusing and does not reduce scope, because the computer system usually still requires validation, protection of source/raw data records, etc. under the predicate rule.

Question: “We are interested in comments on whether revisions to definitions in part 11 would help clarify a narrow approach and suggestions for any such revisions.”

Response: As described in our other responses herein, there is no need for “open” and “closed systems” definitions. Other definitions should be further clarified to reduce opportunities for wide or conservative interpretation.

Question: “We are interested in comments on the need for clarification in part 11 regarding which records are required by predicate rules and are therefore required to be part 11 compliant?”

Response: Part 11 should not specifically identify which records are required by predicate rules. Part 11 should only state that it applies to any records in electronic form that are required to fulfill a predicate rule. This would include data records as well as event records, if they are needed to document predicate rule conformance. The current statement that ‘This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations’ is overly broad and subject to interpretation because 1) predicate rule records requirements are not always explicit, and 2) this has been interpreted to mean ANY electronic records that are created, modified, etc. during a regulated process regardless of significance or whether they are explicitly identified in a predicate rule.

B. Part 11 Subpart B - Electronic Records

Question: “We are interested in comments on whether there are other areas of part 11 that should incorporate the concept” [of basing the need to implement part 11 requirements on a “justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity.”]

Response: It is recommended that the focus of part 11 should be on “minimum requirements” for e-records/signatures rather than the agency's criteria for the trustworthiness, reliability and equivalence of e- and paper/handwritten records/signatures. These criteria have resulted in the overly broad scope and interpretation by the FDA and industry. The expectation for trustworthiness and reliability of any records, whether electronic or not, should be expressed in predicate rules. It is recommended that part 11 should be simplified to provide the minimum regulatory compliance requirements for the use of electronic records and signatures to replace their paper and manual equivalents. The specific approach and technology solution should be open to the state-of-the-art, and based on better guidance regarding the FDA's expectations and current thinking. The current part 11 requirements for closed systems controls, including validation, audit trails, operational checks, authority checks, and device checks, are overly prescriptive and may not apply in all situations. It is recommended that the regulations for system controls

simply require that regulated computer systems be designed, tested and implemented to ensure that electronic records and signatures meet predicate rule requirements, including 1) documentation of operator entries and actions, 2) protection during the record retention period, and 3) the ability to be electronically inspected, reviewed and copied by the agency. The standard agency risk statement regarding product quality and safety, and record integrity is vague and subject to much interpretation, and has resulted in increased scope of effort. The concept of a risk assessment should be clarified in guidance.

Question: “Is additional clarity needed regarding how predicate rule requirements related to subpart B can be fulfilled?”

Response: Yes, much of the interpretation and increased scope has been caused by the lack of clarity in the predicate rule requirements. It is recommended that the predicate rules should be clarified to include the requirements, or there should be guidance for the major regulatory domains, such as GLP, GCP, drug GMP, and device GMP “worlds” to describe the agency’s current thinking in each area.

Question: “Should the requirements for electronic records submitted to FDA be separate from electronic records maintained to satisfy predicate rule requirements?”

Response: No, they should both be incorporated under part 11 to prevent a difference in the requirements for records that are both electronically maintained and submitted.

Question: “Should part 11 continue to differentiate between open systems and closed systems?”

Response: No. The definitions for open and closed systems have caused much unnecessary discussion and interpretation. It is recommended that the regulations should require that the technical and procedural controls for any “regulated computer system” (here’s a needed definition) should be commensurate with the risks to the records and signatures, and guidance should present FDA’s current thinking of what kind of controls are necessary for different situations.

Question: “Should we retain the validation provision under Sec. 11.10(b) required to ensure that a system meets predicate rule requirements for validation?”

Response: The provision should be modified because there is insufficient alignment of the part 11 regulations with predicate rules for validation, especially in the preclinical (GLP) and clinical (GCP) research environments. The current, and predominant, industry and agency standard is to require validation of computer systems that are used to support GxP-regulated data and activities. Although the Scope and Application Guidance focuses the industry’s attention on predicate rule requirements for validation, the GCP and GLP requirements for data management system validation are currently broadly interpreted using non-specific regulations for “adequate and accurate case histories” (21 CFR 312.62b) or testing of “equipment used for the generation, measurement or assessment of data” (21 CFR 58.63a), or from medical devices guidance. Part 11 regulations have provided a valuable and consistent framework for GCP and GLP validation and other current industry standards regarding documentation, security and procedural controls. It is recommended that the part 11 regulations should either retain the requirements to test (or validate) a regulated computer system, or the predicate rules should be modified to include these requirements.

Question: “Are there any related predicate rule requirements that you believe are necessary to preserve the content and meaning of records with respect to record copying and record retention? What requirements would preserve record security and integrity and ensure that records are suitable for inspection, review, and copying by the agency?”

Response: The predicate rules currently express these requirements for record copying and retention, including inspection, review and copying by the agency. The part 11 regulations only need to affirm that these requirements are necessary when the records are in electronic form.

Question: “Should audit trail requirements include safeguards designed and implemented to deter, prevent, and document unauthorized record creation, modification, and deletion?”

Response: No. The part 11 regulations should only require that the documentation of regulated entries and actions be maintained and protected to ensure security and integrity during the record retention period. The use of an automated audit trail with specific safeguards may be appropriate for most computerized data management systems, but it is overly prescriptive and may not be appropriate for all situations, such as hybrid and low-risk systems. In some of these cases, printouts or procedural controls could adequately meet regulatory requirements regarding changes made to data without the need for an automated audit trail.

Question: “Section 11.10(k) requires appropriate controls over systems documentation. In light of how technology has developed since part 11 became effective, should part 11 be modified to incorporate concepts, such as configuration and document management, for all of a system's software and hardware?”

Response: No. The part 11 regulations should not require controls over systems documentation, or configuration and document management for a system’s software and hardware. Predicate rules already require that personnel are adequately trained. It is up to the regulated entity to decide how to assure that personnel are trained, whether through SOPs, systems manuals, or on-the-job training. Part 11 requirements for configuration and document management would also be overly prescriptive, especially for smaller purchased applications. FDA expectations for controls over systems documentation would be more appropriately described in guidance, especially for the more substantial computerized systems that are subject to modification.

C. Part 11 Subpart C - Electronic Signatures

Question: “Section 11.10(d) requires that system access be limited to authorized individuals, but it does not address the handling of security breaches where an unauthorized individual accesses the system. Should part 11 address investigations and followup when these security breaches occur?”

Response: No. Part 11 should require that electronic records be protected for security and integrity, and the identification of specific mechanisms for this protection, including follow-up, would be overly prescriptive. Would these mechanisms be mandated if the records were maintained as paper records?

D. Additional Questions for Comment

Question: “What are the economic ramifications of modifying part 11 based on the issues raised in this document?”

Response: The economic ramifications could be significant if the changes to part 11 resulted in greater clarification and less interpretation using less-prescriptive regulations and more specific guidance. For most regulated entities, much of the cost of validating or replacing primary data systems has already been spent, and the benefit would be for future decision-making. For most companies, the major economic benefit would be a reduction in unnecessary efforts caused by the need for conservative interpretation of the regulations, and because unnecessary controls are often implemented in order to meet the "letter of the law" with little real value to system owners or to the American public.

Question: “Is there a need to clarify in part 11 which records are required by predicate rules where those records are not specifically identified in predicate rules? If so, how could this distinction be made?”

Response: There is no need to specifically identify records that are required by predicate rules. It would be useful to have a definition or a statement that part 11 applies to records in electronic form that documents an event or activity that is performed to meet any records requirements set forth in agency regulations.”

Question: “In what ways can part 11 discourage innovation?”

Response: Part 11 can, and has, discouraged innovation by 1) increasing the regulatory compliance uncertainty of making decisions to use new technology and processes, which usually results in “no” decision, 2) increasing the need for a conservative regulatory compliance approach, which increases cost and reduces the availability of already limited funding to try new technology, and 3) increasing the wariness of company Management to try new approaches or to upgrade an existing system or technology.

Question: “What potential changes to part 11 would encourage innovation and technical advances consistent with the agency's need to safeguard public health?”

Response: Narrowing the scope of part 11 and clarifying the regulations to reduce the uncertainty and the need for interpretation will encourage innovation and technical advances.

Question: “What risk-based approaches would help to ensure that electronic records have the appropriate levels of integrity and authenticity elements and that electronic signatures are legally binding and authentic?”

Response: An appropriate risk-based approach would enable a regulated entity to determine with reasonable certainty whether the FDA would accept the entity’s plans and controls, such as appropriate levels of integrity, authenticity elements, signature controls, and extent of validation. The industry must receive more detailed guidance about risk than previous FDA statements regarding product quality, patient safety and data integrity.

Question: “The part 11 guidance announced that the agency would exercise enforcement discretion (during our re-examination of part 11) with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997 (legacy systems), the effective date of part 11. What are stakeholder concerns in regards to modifications made to legacy systems in use as of August 1997?”

Response: The part 11 guidance statements regarding legacy systems were actually relatively meaningless to the industry because 1) strictly speaking, there are no legacy systems because virtually all systems have required some change since 1997, 2) most older systems were replaced during preparations for Y2K or because they were ready for retirement anyway during this period, and 3) companies that had legacy systems replaced or improved their systems to meet part 11 requirements because of their need for conservative interpretation of the regulations and the uncertainty and vagueness of part 11 guidance.

Question: “Can the use of risk mitigation and appropriate controls eliminate concerns regarding legacy systems?”

Response: Yes, the use of risk-based approaches to identify appropriate risk mitigation controls is an ideal mechanism regarding legacy systems.

Question: “Should part 11 address record conversion?”

Response: Yes, part 11 should address the conversion of electronic records because it is not as straight-forward as the duplication of paper records. For example, the guidance statement that “any copies of the required records should preserve their content and meaning” should be in the regulations because it identifies “what” is expected by the FDA. Additional guidance would then be necessary to describe “how” to meet this expectation in different situations.

Question: “Are there provisions of part 11 that should be augmented, modified, or deleted as a result of new technologies that have become available since part 11 was issued?”

Response: The increasing rate of new technology introduction is a reason for modifying the part 11 regulations to be less prescriptive, and for guidance to be regularly updated with the agency’s current thinking. It is our recommendation that the way to re-stimulate innovation is to improve clarity of FDA expectations to reduce opportunities for broad and conservative interpretation, and to provide more specific guidance.