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Dockets Management Branch (HFA-305)
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Re: Comments on, "Guidance for Industry: Part 11, Electronic Records; Electronic Signatures -- Scope and Application", Docket Nos. 03D-0060, 99D-1458, 00D-1538, 00D-1543, 00D-1542, and 00D-1539

Dear Sir or Madam:

SEC Associates, Inc. (SEC) is pleased to have the opportunity to provide comments on the above-referenced draft guidance.

We see positive benefits resulting from this guidance and the planned re-examination of Part 11. Chief among these benefits are the ability to apply a science- and risk-based approach to compliance, as well as the clarification of confusing issues and "folklore" that have evolved since Part 11 was enacted. However, we also see the potential for further confusion and misinterpretations due to questions left unanswered by the draft guidance. We believe certain issues merit further clarification in order to maximize the benefits of this "re-direction", while at the same time assuring that safety, efficacy, and quality are not compromised in the process.

Our comments and suggestions are attached. Thank you again for the opportunity to express our views.

Very truly yours,
SEC ASSOCIATES, INC.

John C McKenney Sr

John C. McKenney, Sr.
President

attachment

99D-1458

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Line(s)	Comment	Recommendation
33-35	The draft guidance states that Part 11 scope will be narrowly interpreted during the re-examination period. Industry is left not knowing how long the re-examination period will last, nor how FDA will interpret Part 11 after the period ends. This may have unintended consequences, such as delaying the purchase of new technology while industry awaits the final interpretation.	Because of the uncertainty this creates for industry, it is recommended that FDA expedite the re-examination period.
36-39	The draft guidance shifts much of the compliance burden back on the predicate rules, without acknowledging that most predicate regulations were written before the widespread use of computerized systems in GXP operations. Most predicate rules do not address important controls and safeguards needed for electronic record systems. For example, the GCPs do not explicitly require validation of computer systems used in clinical trials. Reliance on the predicate rules, therefore, may fall short of what is needed to assure data integrity and reliability. Furthermore, it may lead to widely varying interpretations in industry and FDA, thereby resulting in subjective enforcement practices that would not benefit industry, FDA, or the public.	FDA should provide guidance documents, and consider revising the GCPs and drug GMPs to address computerized system and quality system requirements (analogous to the Quality System Regulation and "General Principles of Software Validation" guidance from CDRH). In the meantime, FDA should take an active role in educating industry on its predicate rule expectations for e-record systems.

Line(s)	Comment	Recommendation
41-44 236-239	Virtually all systems in operation before August 20, 1997, have undergone hardware, firmware, and/or software upgrades, leaving many of these systems substantially different from their pre-Part 11 state. The wording in the guidance, however, seems to imply that FDA will overlook any changes, regardless of how significant, in exempting pre-Part 11 systems. This view runs counter to FDA's stated goal of applying a risk- and science-based approach to GMP systems, since it disregards the potential for high-risk modifications and removes the requirement for scientific analysis that should be applied to the evaluation of system modifications.	Clarify the intent with respect to legacy systems. State that changes to legacy systems should be evaluated using a "justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety and record integrity (lines 208-209)." Require that the risk assessment be the determining factor in whether a legacy system should be brought into compliance with Part 11.
41-44 236-239	A primary objective of the draft guidance is to remove barriers to innovation and technological advances. By exempting legacy systems from Part 11 compliance, however, the new guidance may have the unintended consequence of encouraging retention of legacy systems (to avoid Part 11), rather than replacing them with technologically advanced systems that would need to comply with Part 11.	As explained above, do not extend a blanket Part 11 exemption to all legacy systems. Instead, require a risk and science-based approach for determining whether legacy systems should be brought into Part 11 compliance.
98-100	In the "Guidance for the Use of Computerized Systems in Clinical Trials", there are several Part 11 related issues that are now in conflict with (or at least out of sync with) the new guidance, such as the guidance on audit trails, time stamps, data tags, retrieval of data, and reconstruction of a study. This will send confusing and/or conflicting messages to industry and FDA investigators.	Synchronize the "Guidance for the Use of Computerized Systems in Clinical Trials" with the final Scope and Application guidance.

Line(s)	Comment	Recommendation
124	What are the expectations for records that a company keeps as proof that a predicate rule activity was performed, but where the predicate does not specifically require a record? For example, 312.50 and 312.56 require sponsors to monitor the progress of clinical investigations, yet no records are specifically mentioned. Would electronic records that a sponsor or CRO keep to provide evidence of monitoring fall under Part 11?	Please provide FDA expectations.
151-156	The phrase "merely incidental use of computers" has the potential to be broadly interpreted and enforced. This potential for inconsistency will be problematic for both industry and FDA.	Clearly define, with examples, the phrase "merely incidental use of computers". Ensure that the definition does not inadvertently encourage the avoidance of important security and integrity controls simply by relying (or appearing to rely) on the printed output of critical systems. The information on the paper may be unreliable without appropriate Part 11 controls for the underlying computer system.
160-161 191-192	Do these lines imply that FDA may limit the application of Part 11 requirements to <u>just the E-signatures</u> within a given system, if the e-records in that system are not subject to predicate rules? Lines 160-161 state "...Part 11 [is] applicable to...electronic signatures...". Is FDA intentionally limiting the scope to just the E-signatures (for signed, non-predicate records), or should this read "electronic signature systems"?	Clarify the intent of these lines with respect to electronically signed e-records that are not required by predicate rule.
165-167	In the past, FDA has held companies accountable for what is required by the company's SOPs, including records that the company indicates that it must keep, even when such records are not required by predicate rule. However, lines 165-167 in the draft guidance seem to imply that this will no longer be the case. Is this a correct interpretation?	Clearly state in the final guidance whether or not records required by a firm's SOP, but not explicitly by predicate rule, must be Part 11 compliant if maintained and used electronically.

Line(s)	Comment	Recommendation
168-183	This is the "merely incidental" issue described above, i.e., firms may rely on paper records in order to avoid the necessary controls and validation of the underlying electronic record system that generated the paper. This may result in unwarranted confidence in the printed record, without having the proper controls and procedures to assure the integrity of the data in the system that generated the printout.	Clearly define, with examples, the phrase "merely incidental use of computers". Ensure that the definition does not inadvertently encourage the avoidance of important security and integrity controls simply by relying (or appearing to rely) on the printed output of critical systems. The information on the paper may be unreliable without appropriate Part 11 controls for the underlying computer system.
184-190	This section states that records that make up a submission are not subject to Part 11 unless they are required by predicate rules. This seems to be a gap that may allow for potentially significant data integrity problems in records that are used to provide the conclusions and claims in an NDA. For instance, case histories are required by predicate rule. However the clinical data management system and subsequent multiple iterations of records created and manipulated to provide the tables and analyses in an NDA are not explicitly covered by predicate rules. Would a company be considered in compliance if they did not validate or implement proper access and audit trail controls for these types of systems? It would seem that significant errors and data adjustments could occur, which could lead to erroneous conclusions and claims in the final submission.	Because the current GCP predicate rules do not adequately address the many systems that may manipulate critical data in the submission life cycle, FDA should advocate a risk-based approach, requiring (at a minimum) a "justified and documented risk assessment and a determination of the potential of the system to affect [data] quality and safety and record integrity (lines 208-209)." This approach should be required for all systems that can affect quality, safety, and record integrity, regardless of whether or not a given system or record is explicitly addressed in the existing predicate regulations.

Line(s)	Comment	Recommendation
200-201	In order for FDA to enforce validation requirements, is it necessary for the predicate rule(s) to specifically use the word "validation"? Or, can FDA claim that validation is required in order to demonstrate compliance with record requirements such as "accurate and complete", or "accurate and adequate"? If the answer to the first question is "yes", then many critical record systems (such as most GCP record systems) will go unvalidated. On the other hand, if the answer to the second question is "yes", then we are left with a highly subjective approach for determining which record systems must be validated. Neither situation is desirable.	Ideal long-term solution: Update the GCPs, GLPs, and drug GMPs to explicitly state which records (or record systems) must be validated. This could be accomplished in a manner similar to that used in the Quality System Regulation section 820.70(i) which states, "When computers or automated data processing systems are used as part of production *or the quality system*, the manufacturer shall validate computer software for its intended use according to an established protocol." Short-term solution: Help industry understand FDA's expectations in this area through published guidance and public presentations.
218-232	This section starts by essentially backing off of the Part 11 audit trail requirement. It ends, however, by saying that "Audit trails are particularly important where the users are expected to create, modify, or delete regulated records during normal operation." Since this expectation (e.g., operator entries and actions) was already stated in Part 11.10(e), this sends a confusing and contradictory message about audit trails.	Either state that audit trails are not required, or state that a documented, risk-based approach must be used for determining whether or not audit trails are needed.
236-239	Electronic signature systems were not in compliance with predicate rules prior to August 20, 1997, since electronic signatures were not explicitly legal. By extension, does this mean that legacy electronic signature systems are not exempt from Part 11 requirements?	Clarify FDA's position with regard to legacy systems that were not in compliance with predicate regulations pre-Part 11.

Line(s)	Comment	Recommendation
N/A	General Comment: In our opinion, Part 11 requirements in large measure represented good information security and integrity practices. There were, however, areas where Part 11 had taken on interpretations that went beyond good practice, and were in some cases impractical. In the effort to define a clear scope for Part 11, and in the absence of clear predicate computer requirements for e-record and e-signature systems, FDA should proceed cautiously so as not to halt (or worse, to reverse) the positive progress made in the past 5 years to increase information security and integrity. Despite the problems, much good has resulted from Part 11. To use an old phrase, let's be careful not to "throw the baby out with the bathwater".	