August 16, 2017

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

RE: Docket No. FDA-2017-D-1105 for "Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11--Questions and Answers; Draft Guidance for Industry"

Dear Sir/Madam,

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually.

ACRO is pleased to provide these comments on "Use of Electronic Records and Electronic Signatures in Clinical Investigations under 21 CFR Part 11--Questions and Answers; Draft Guidance for Industry."

General Comments:

ACRO asks the Agency to consider updating the title of the document to include electronic systems (not just electronic records and electronic signatures) so that it reads: "Use of Electronic Records Systems and Electronic Signatures in Clinical Investigations under 21 CFR Part 11 – Questions and Answers."

Most modern computerized systems generate electronic records containing complex and extensive metadata. This requires the records to remain in their electronic, dynamic format to enable complete reconstruction and maintain data integrity. Q5 indicates that *"if simple screenshots or paper printouts are used to produce a report and that report fails to capture important metadata . . . that are recorded in the electronic system, such paper records would be regarded as incomplete unless the accompanying metadata are included."* Does the qualification of the criticality of metadata (i.e., 'important metadata') allow for an evaluation by the regulated entity to determine to what extent the metadata must be captured in a paper output (for example, via a documented risk assessment) and the potential to thus not retain the complete copy of the electronic record based on that assessment? Typically, the approach of using a static record such as paper in lieu of the original electronic record is quite onerous due to the difficulty in ensuring the complete ability to reconstruct the electronic record including all metadata. A risk-based approach towards the retention of metadata will reduce the burden of retaining records in non-native formats but may also decrease the extent to which the content and the meaning of the record is preserved.

Line-specific comments:

Lines 124-125
Could the Agency clarify whether the intent is for the electronic signature guidance to apply only to those records for which the predicate rule requires a signature or, alternatively, to those records that are required by predicate rule and are electronically signed (regardless of whether the predicate rule requires that the record be signed).

Lines 144-6
ACRO thanks the Agency for discussing the increasingly obsolete distinction of Closed vs Open systems. As the draft guidance seems to be calling for controls above and beyond those for 'Closed Systems,' it would be helpful for the Agency to further elaborate on suggested added controls (unless the intent is to treat systems as being 'Open' as far as control expectations are concerned.)

Lines 155-162
ACRO asks the Agency to consider expanding the examples list to include such systems as imaging systems and information management systems.

Lines 170-172
ACRO supports the principle referred to here. In addition, we would consider as equivalent (in virtualized environments) the capturing of baseline configurations at the time of validation. We recommend line 172 concludes with *"functions in the manner intended, in a consistent and repeatable fashion."*

Lines 180-181
Could the Agency clarify what is meant by the "attributes" of the electronic system. Also, are the "attributes" equivalent to the "nature of the system" in line 186? ACRO recommends providing examples such as COTS.

Line 182
ACRO asks the Agency to consider deleting "in general" as it opens the door for exceptions.

Line 186
ACRO asks the Agency to consider adding the following: *"and any collected data that would be needed to recreate the history of a patient's participation in a clinical trial."*

Lines 189-191
While the intent of this section will be clear to individuals familiar with computer system validation, it could be confusing to those who are not. They might interpret this to mean that spreadsheets (that perform critical functions) do not need to be validated. ACRO asks the Agency to consider adding a sentence that clarifies the distinction between the utilities and the use of these utilities as in the case of spreadsheets.

Lines 194-197
ACRO asks the Agency to consider the use of the phrase "critical records" in this statement in order to maintain consistency with language used throughout the draft guidance. ACRO proposes the following: *"For COTS systems that perform functions beyond office utilities and process or generate critical records, such as COTS EDC systems; validation should include . . . "*

Line 197
As the phrasing here repeats the phrasing in Line 172, ACRO also recommends for consistency that the sentence concludes with *"functions in the manner intended, in a consistent and repeatable fashion."*

Lines 199-200
ACRO asks the Agency to consider rewording this section as follows: *"systems that are configured or customized to meet a unique business need of a user."*

Line 204
ACRO requests the Agency to consider adding *" . . . dynamic testing, and stress testing based upon documented requirements."*

Line 207
As the phrasing here repeats the phrasing in Line 172 and Line 197, ACRO also recommends for consistency that the sentence concludes with *"functions in the manner intended, in a consistent and repeatable fashion."*

Line 209
ACRO suggests that this be revised as follows: *"control changes to the electronic system and the environment in which it operates . . . "*

Lines 244-245
The principle of shared audits is helpful, as service providers are often assessed for many of the same controls by their clients resulting in much repetition and inefficiencies. We encourage the FDA to also refer to third party attestations as an additional option to achieving audit objectives across multiple stakeholders. This is already in place as evidenced by System and Organization Controls (1 and 2) reports as another option besides shared audits.
Please see
https://www.aicpa.org/InterestAreas/FRC/AssuranceAdvisoryServices/Pages/ServiceOrganization%27sManagement.aspx

Lines 288-289
Depending on the lifecycle of systems that may be referred to in this question, the systems may be retired and generally unavailable. ACRO asks the Agency to consider specifying any further guidance for this scenario where access is a practical option. If there is another manner (an alternative measure) in which metadata can be provided in the absence of -- or as an alternative to -- direct access to a system in question (such as retention of metadata in logs or other offline options), ACRO recommends that the regulated entity or the service provider be able to utilize that alternative measure to meet this requirement.

Lines 302-303
It would be helpful if the Agency explicitly accepted automated and validated methods of making certified electronic copies of paper records when automation is used. In this case, certifying signatures per record would be impractical (requiring individual signatures at the record level). ACRO recommends that the validated process or written processes to ensure the consistency of the certification process be considered acceptable in lieu of individual sign offs per copied record. This would also seem to be in alignment with the statements in Question 7 in the guidance.

Lines 333-335
As noted in ACRO's comments on Lines 288-289, if an inspection takes place after a system is retired, it may be difficult to provide live access to an offline and archived system. As such, does the Agency imply restoration of the original platform that generated the records (or, alternatively, is it simply referring to electronic methods of reviewing) in the following statement: *"During inspection, FDA may request to review and copy records in a human readable form using electronic system hardware"*?

Line 391
Traditional audit trails are well known to industry and the Agency. It is possible that alternatives or supplements to legacy audit trails may be even more robust as to demonstrating records integrity, such as Blockchain technology.

Line 394
ACRO agrees that encryption at rest and in transit are strong controls; however, it would be helpful if the Agency in its criteria would also view encryption as being "addressable" -- similar to the way in which the HIPAA Security Rule allows covered entities to adopt an alternative measure that achieves the purpose of the standard, if the alternative measure is reasonable and appropriate.

Line 429
This is helpful guidance, as the benefits of a distributed environment reduce the likelihood of failures in the event of outages or disasters.

Lines 454-465
ACRO would like to note the complexity that is sometimes involved in a risk-based approach. Do sponsors and other regulated entities need to review and test changes made by the electronic service vendor? If so, would this be true only for changes to the software/application, or would this also be true if due to a protocol amendment on a single study a patient diary is changed? The guidance states the need to apply a risk-based approach for validation, but does not really give any details regarding what this means.

Line 461
Sponsors should have reasonable access to documentation in order to make decisions regarding their validation processes of outsourced services. Extensive validation and testing outputs may be difficult to provide without notice and must be done in a controlled manner to ensure confidentiality of said documents. ACRO is concerned about the creation of a general expectation that users of such systems need to have a live stream library of SOPs and testing documentation. Due diligence exercises and audits that are agreed to by the vendor and clients should cover the objectives in Question 15.

Line 508
ACRO asks the Agency to consider deleting *"Where possible."* The statement holds true in all cases given that the items within the parentheses are examples and *"as appropriate"* is used in the sentence.

Lines 517-519
Regarding the statement *"sponsors should consider obtaining a signed declaration from the study participant"* can the Agency provide additional details as to how this can be obtained since the sponsor does not typically have direct contact with the study participant. Can this be done via the mobile app or via the

clinical investigator and stored with the investigator records? ACRO recommends adding clarity to this sentence as follows: *"sponsors should consider obtaining a signed declaration from the study participant by _____."*

Lines 538-542
As an alternative to EDC indicating a mobile device as a data originator, ACRO asks the Agency to consider it as equivalent when protocols (and or data management plans) indicate the data originator as a mobile device. Both methods of indicating the data originator would be acceptable.

Line 571 and Lines 584-588
Could the Agency clarify when the audit trail begins (e.g. at the time data are first recorded in a permanent manner -- not just when the data enter the sponsor's EDC system, but when the data enters any system in a permanent manner, e.g. LIMS, IVRS, CTMS, etc)

Lines 589-591
Devices often capture data multiple times a day and report summary data for analysis. For example, activity tracker data (as opposed to devices that only capture data in discrete time points throughout a day) can provide summary data including time points. In this case, the EDC time of receipt is likely to be in a summary format for a period of time (e.g., daily instead of every hour every day). Could the Agency clarify what it expects when device data recordation times may not be available on a measurement by measurement basis (summary data is entered into EDC via automated methods)?

Lines 608-628
There are two possible interpretations of Question 21. Could the Agency please clarify which one is correct. On one hand, the guidance states that sponsors should validate that mobile device values are accurately captured. On the other hand, the document states, in the second paragraph, that the performance of the measurement is beyond the scope of the guidance. While it (quality of the measurement) may be beyond the scope of Part 11, ACRO recommends that the first paragraph (Lines 611-618) should caveat the scope of part 11 with regards to measurement accuracy objectives cited in order to align with the second paragraph or omit the references to accuracy.

Lines 637
Encryption at rest on mobile sensors may not be needed given the limited nature of their connectivity and the access to such devices may be very limited via physical proximity through local means of communication such as Bluetooth. While encryption at rest is a reasonable control under many circumstances, ACRO recommends some flexibility here that can be justified with a risk assessment to highlight (in a preemptive fashion by the sponsor or selector of the mobile technology) the reasonably foreseeable risks to data integrity corresponding to devices that do not encrypt at rest.

Lines 647-653
These examples of controls may be perfectly reasonable in some contexts but highly intrusive in others. For instance, patients who are in a BYOD study or prefer BYOD are unlikely to accept intrusive software on their devices that may allow for remote wiping or other controls. These controls should be considered in light of added patient or other stakeholder burdens vs the added controls these technologies offer.

Line 755
ACRO asks the Agency to consider discussing alternatives to using traditional passwords when electronic signatures are being undertaken, as many systems today offer two-factor authentication and the ability to use other methods of authentication. For instance, entering a pin to e-sign that may differ from a password used to initially log on (the pin is, of course, a password itself) or using a biometric credential such as a thumbprint to e-sign as well. Please refer to Question 27.

Regarding Question 25 more generally, it would be helpful if the Agency indicated its views on an electronic system that captures an image of a handwritten signature (e.g., a stylus on a tablet or other device) that is associated with an electronic record; for instance, patients or researchers manually sign electronic records. This would not be an electronic signature per se, but a traditional signature captured electronically or as the Agency's 2016 Q&A on Use of Electronic Informed Consent refers to, *"handwritten signatures executed to electronic records."* In the case of handwritten signatures associated with an electronic record, could the Agency clarify that it does not expect a specific password challenge for the act of manually signing a record?

Line 757
It would be helpful to indicate that the meaning of the signature may be evidenced by metadata associated with the act of signing and/or by the context of the signature as explained in the form or on the display when the signature is called via workflow processes. For instance, an eCRF focused or titled on signing off by an investigator for a particular study milestone or study completion (including an attestation statement in the CRF) should make it obvious as to the meaning of a signature. As an alternative, if metadata explains the meaning of the signature, we urge acceptance as well.

ACRO thanks the Agency for the opportunity to comment on this draft guidance. Please do not hesitate to contact ACRO if we can provide additional information or answer any questions.

Respectfully submitted,

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