



May 15, 2023

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

RE: ACRO comment submission:
***Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations:
Q&A for Industry***
[Docket No. FDA-2017-D-1105]

Dear Ms. Kunkoski,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices, from pre-clinical, proof of concept, and first-in-human studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficacy, and safety of biomedical research.

We hope this ACRO feedback helps refine the final guidance to reflect the current industry usage of e-systems and e-records.

General comments

ACRO welcomes this draft guidance and the inclusion of especially valuable questions such as Question 13, which clarifies that it is not necessary to record every keystroke in an audit trail, and Question 23, which eloquently outlines the definition of eSource data.

This draft guidance revises the 2017 draft guidance; however, Question 26 from that draft was not included in the new one. Question 26 from the previous draft is an important clarification from the FDA that when a user logs into an electronic system using their username and password, it is not necessary to re-enter the same username when executing the first signature in that session. Having that recommendation available in FDA guidance was helpful as it clarifies the requirements surrounding Part 11.200(a)(1) which can be interpreted to mean the first signing should require the user to enter their username, even when entered upon session log in. We understand that the FDA still supports the stance in Question 26 from the 2017 guidance, and we ask the Agency to consider retaining Question 26 from the 2017 draft guidance in the current guidance for clarification of 11.200(a)(1).

ACRO notes that the concept of a “service provider” is promoted in the draft guidance and yet “vendor” appears throughout the document. Therefore, we ask the Agency to consider encouraging consistent terminology throughout the final guidance, with “service provider” replacing the phrase “vendor.”

Line-specific comments

Lines 106-119

The draft guidance states:

Q1. Are electronic records from real-world data sources submitted to FDA as part of a marketing application or under other predicate rules subject to part 11 requirements?

Yes. 21 CFR part 11 requirements apply to electronic records from real-world data (RWD) sources that were created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in FDA regulations or submitted to the Agency under requirements of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or the Public Health Service Act (PHS Act), even if such records are not specifically identified in FDA regulations.¹⁹ FDA acknowledges that there may be instances when electronic records from RWD sources were not originally created in part 11-compliant systems with the intention of being submitted to FDA as part of a marketing application, but such records can be used for that purpose. Sponsors that intend to rely on such data in support of a marketing application should ensure the quality and integrity of such electronic records.

ACRO asks the Agency to consider refining the final sentence of the answer to Question 1 as follows:

Sponsors that intend to rely on such data in support of a marketing application should ensure the quality and integrity of such electronic records by following general principles of data quality and integrity to ensure that all data – whether from the clinical investigation or from a real-world data source – is attributable, legible, contemporaneous, original, accurate, and complete.

Lines 155-156

When providing certified electronic or paper copies of electronic records, the associated metadata should be included, such as units of the data (e.g., mg). The description of metadata as including “units of data” indicates that such unit data is not, in itself, clinically relevant data which may be subject to analysis – this is an overextension of the usual definition of metadata.

ACRO recommends removing the phrase “units of data.”

Lines 186-187

The current draft guidance states:

“For example, records should be backed up regularly to prevent loss.”

ACRO recommends including a reference to mirroring and other redundancy as an option so that the final guidance reads: “For example, records should be backed up regularly and/or mirrored to prevent loss.”

Lines 194-198

The draft guidance states: *“FDA may request copies of these records and data in a human-readable form. Screenshots or paper printouts of electronic records should include metadata and audit trail information recorded in the electronic system. When systems are decommissioned and cannot be recommissioned, sponsors should ensure that files containing the metadata are retained before decommissioning and can be linked to each corresponding data element.”*

The statement that *“screenshots should include metadata”* is an unclear expectation.

ACRO recommends revising this section of the final guidance so that it reads:

FDA may request copies of screenshots or paper printouts of electronic data in a human-readable form. Metadata and audit trail information related to electronic data capture should be recorded in the electronic system. When systems are decommissioned and cannot be recommissioned, sponsors should ensure that files containing the metadata are retained before decommissioning and can be linked to each corresponding data element.

Lines 201-207

The draft guidance includes Question 6 and its answer:

Q6: Are electronic communication methods (e.g., email systems or text messages) for transmitting electronic records addressed by 21 CFR part 11?

Part 11 regulations do not address electronic communication methods used in the transmission of electronic records. When electronic records required by a predicate rule are transmitted via an electronic communication method, the regulated entity should ensure secure end-to-end transfer of that record. Audit trails in the sponsor’s electronic system should capture the date and time that electronic records are transferred and the originator of those records.

ACRO would like to connect the reference to email and text within the question to the reference to secure end-to-end transfers in the answer. We note that technology for electronic communication (such as email or text messaging) typically relies on infrastructure directly out of the control of sponsors or indeed investigational site personnel. Consequently, regulated entities may be constrained in their ability to secure end to end transfer. ACRO suggests that the guidance should acknowledge this and allow regulated entities to adopt reasonable risk-based measures to secure electronic records in transit. Therefore, we ask the Agency to consider the value of a risk-based approach here so that the final guidance answer to Q6 states:

Part 11 regulations do not address electronic communication methods used in the transmission of electronic records. When electronic records required by a predicate rule are transmitted via an electronic communication method, the regulated entity should ensure secure end-to-end transfer of that record. Audit trails in the sponsor’s electronic system should capture the date and time that electronic records are transferred and the originator of those records.

Technology for electronic communication (such as email or text messaging) typically relies on infrastructure directly out of the control of sponsors or indeed investigational site personnel. Consequently, regulated entities may be constrained in their ability to secure end to end transfer. We recommend that regulated entities adopt reasonable risk-based measures to secure electronic records in transit.

Line 228 and Lines 609-619

Both Question 6 and Question 18 of the draft guidance include “*electronic quality management systems*” as a bulleted example.

Because of the breadth of the QMS, in both instances, ACRO asks the Agency to consider modifying the phrase to read: “all relevant QMS procedures and documents.”

Lines 240-242

The bulleted example in the draft guidance lists:

Centralized, web-based portals that display, maintain, and archive essential data (i.e., electronic patient-reported outcomes (ePROs), electronic clinical outcome assessments (eCOAs), DHT-collected patient data (see section III.D), or eIC documents and records)

We believe that ePRO, eCOA and eIC systems should be differentiated from “web-based portals,” as portals are more typically considered as a sub-system of eCOA, ePRO (instead of the other way round). ACRO recommends adding separate bullets to provide examples of eCOA, ePRO and considering web portals (e.g., for sharing correspondence, materials with sites) as a separate, distinct item.

Lines 284-286

The draft guidance states: “*For new electronic systems that are custom-made or for existing systems that are customized (e.g., IRT system or eCRF system designed to meet the requirements of the protocol) . . .*”

Typically, such systems used to meet the requirements of a protocol would be considered configured rather than customized. ACRO recommends replacing “customized” with “configured” in line 285.

Lines 288-292

The draft guidance states: “*In addition, sponsors should perform user acceptance testing (UAT) and document the criteria for and results of testing to ensure that the electronic system fulfills its intended purpose. Alternatively, sponsors should review the vendor’s UAT and document that the UAT was reviewed and was found to be adequate.*”

As UAT is typically a User (i.e., a regulated entity), the sentence “UAT performed by the sponsor or vendor” needs amending. ACRO recommends deleting the last sentence starting “alternatively” or replacing it with “Alternatively, sponsors should consider the vendor’s product development verification documentation.” Our comment on Line 321 (below) is related.

Line 321

The draft guidance contains the bulleted example of “*UAT performed by the sponsor or vendor*”

As the UAT is typically a User (i.e., a regulated entity) the sentence “sponsors should review the vendor’s UAT” needs amending. ACRO suggests deleting “or vendor.”

Lines 377-379

The draft guidance states: *“The clinical investigator should retain this information for review during an FDA inspection so that FDA can assess whether such records contain information bearing on the sponsor’s adequate compliance with relevant requirements.”*

This requirement, as currently phrased, could exacerbate investigator burden. ACRO recommends amending this to read: *“The clinical investigator should retain (or be able to make available) this information for review during an FDA inspection.”*

Line 457

The draft guidance states: *“Security breaches that could affect the safety or privacy of clinical investigation participants and data should be reported to the IRB and FDA as soon as possible.”*

ACRO has two suggestions for the final guidance. First, because the requirement to report breaches to FDA is new (and not included in the 2017 draft), ACRO asks the Agency to consider including a short discussion of the origins and basis of this new expectation. Second, ACRO recommends revising the final guidance to read:

Security breaches which have been internally investigated and confirmed as impacting the safety or privacy of clinical investigation participants and data should be reported to the IRB and FDA in a timely manner and in accordance with institution, state and federal reporting obligations for such data.

Line 471

The draft guidance states: *“Audit trails should be protected from modification and from being disabled.”*

ACRO recommends adding redaction of audit trail under tightly controlled circumstances by adding *“Audit trails may be redacted under tightly controlled circumstances where patient privacy is impacted (removing personally identifying information errantly entered in the underlying electronic record).”*

Lines 575-576

The bulleted line of the draft guidance reads: *“Ability of the IT service provider to provide secure, computer-generated, time-stamped audit trails of user’ actions and changes to data.”*

There should be a clear distinction between self service capabilities to create audit trail reports and use of the vendor to create such reports. ACRO recommends replacing the current text with *“Ability of the electronic system either directly or with service provider participation, to provide secure, computer-generated, time-stamped audit trails of user’ actions and changes to data.”*

Lines 589-591

The draft guidance states: *“FDA recommends that sponsors and other regulated entities have written service level agreements (SLAs) with IT service providers that describe how the IT services will meet the sponsor’s requirements.”*

ACRO notes that an SLA may not be the specific legal agreement that is put in place between IT service providers and regulated entities. The term SLA is a broad definition that is not defined by the regulations and would likely be fulfilled by many different types of contracts.

Because other contracts meet the requirements of SLAs, a clarification here would be helpful. Therefore, ACRO recommends the following additional, clarifying text in the final guidance:

“FDA recommends that sponsors and other regulated entities have written agreements, such as service level agreements (SLAs) with IT service providers that describe how the IT services will meet the sponsor’s requirements.”

Lines 616-622

The draft guidance contains these bullets:

- *SLAs and any other agreements that define the sponsor’s expectations of the IT service provider*
- *All quality or risk management procedures related to the IT service*
- *Documentation of ongoing oversight of IT services*

ACRO recommends refining the bullets in the Draft Guidance so that the following clarifications and additional text (bolded here) are added into the Final Guidance:

- SLAs **[financial terms redacted]** and any other agreements that define the sponsor’s expectations of the IT service provider
- All **[relevant]** quality or risk management procedures related to the IT service
- Documentation of ongoing oversight of IT services **[supplier audit reports excluded pursuant Q10]**

Lines 664-667

The draft guidance states: “The data originator may be a person, a computer system, a DHT, or an EHR that is authorized to enter, change, or transmit data elements via a secure protocol into a durable electronic data repository such as an EDC system, a clinical investigation site database, and/or a vendor database.”

While EDC systems may be in use for extended periods of time for long running clinical trials, the use of the word “durable” implies that they are themselves archiving solutions which is not the case in practice. ACRO recommends removing the word “durable.”

Lines 762-773

The draft guidance states:

In general, electronic signatures and their associated electronic records that meet all applicable requirements under part 11 will be considered to be equivalent to handwritten signatures. Part 11 specifies that signed electronic records must contain the printed name of the signer, the date and time when the signature was executed, and the meaning associated with the signature. In addition, electronic signatures must be linked to the respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means. In situations where electronic signatures cannot be placed in a specified signature block, a statement of testament (e.g., “I approved the contents of this document”) should be placed elsewhere in the document to state the meaning of the signature and link the signature to the electronic record.

ACRO would like to propose a modification/clarification for signatures often used as workflow for electronic records (versus signatures that are called for under the actual predicate rules). Alternatively, it would be good to see an articulation that general use signatures (outside of predicate rule signatures) are suggested to follow part 11 expectations, but the agency intends to be practical and treat part 11 narrowly on meeting the full requirements of part 11.

ACRO suggests adding a new sentence to line 771 that states:

While part 11 requirements should be met for signatures required under predicate rules, workflow signatures and other non-predicate rule signatures (often seen used in practice for sign offs of clinical trial related materials and records) do not require strict adherence to part 11 signature attributes and the agency intends to be practical so long as the signatures can be tied to a specific user, are tied to a record, and time/date are captured as evidence for work flow purposes.

Lines 827-828

The draft guidance states: *“Sponsors should work with COTS electronic signature service vendors to ensure compliance with part 11.”*

This sentence currently may be misinterpreted and read as prescriptive to use COTS as the only acceptable method. For consistency purposes with the earlier sections on electronic signatures, it is suggested to clarify that COTS electronic signature is one of the accepted options, and -- while all electronic methods need to be CFR part 11 compliant -- they do not have to be COTS, as would be consistent with Q24 lines 777-779.

ACRO recommends replacing current text with the following: *“sponsors should ensure electronic signatures are CFR part 11 compliant, irrespective of the electronic signatures in question being COTS or customized electronic systems if it is not COTS.”*

In conclusion, ACRO thanks the Agency for this opportunity to comment on this draft guidance. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can answer questions or provide additional information.

Respectfully submitted,

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ACRO