[redacted]

From: CDER SBIA <CDERSBIA@fda.hhs.gov>
Sent: 13 Jul 2021 18:42
To: [redacted]
Subject: RE: [EXTERNAL] 21CFR11 - Compliance Requirements by Third Parties

Dear [redacted],

Thank you for your inquiry. SOPs, validation documentation, training records and other documents that are part of an internal quality management system are generally not regarded as required records of clinical investigations. These documents would not be subject to 21 CFR 11, including electronic signature requirements.

The information provided in response to this inquiry does not address any specific product or trial. Follow-up questions regarding specific products or trials should be directed to the appropriate FDA review division by the sponsor.

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Renu Lal, PharmD
Lieutenant Commander, United States Public Health Service Commissioned Corps

Division of Drug Information | CDER Small Business and Industry Assistance (SBIA)
Office of Communications
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Tel: 240-753-3395; 301-796-4687
Renu.Lal@fda.hhs.gov

From: [redacted]
Sent: Tuesday, July 13, 2021 11:24 AM
To: CDER SBIA <CDERSBIA@fda.hhs.gov>
Subject: RE: [EXTERNAL] 21CFR11 - Compliance Requirements by Third Parties

Hi,

This is a just a follow-up to see if there has been any progress on assessing and providing a response to my 21CR11-related query below. I would be happy to jump on a call if there is any clarification required. Thank you.

Kind regards,
[redacted]

From: [redacted]
Sent: 07 May 2021 09:34
To: CDER SBIA <CDERSBIA@fda.hhs.gov>
Subject: RE: [EXTERNAL] 21CFR11 - Compliance Requirements by Third Parties

Thank you for your response below to my query concerning 21CFR11. May I ask a follow-up question just to ensure there is no remaining ambiguity.

I have a very good understanding of validation requirements and have no concerns regarding compliance for organizations such as ours that provide services to clinical trial sponsors. I also understand that when vendors such as ourselves develop computerized systems that manage records subject to FDA regulations (e.g. the TMF), then those systems must also comply with 21CFR11 for the records to be accepted in lieu of paper records.

My query is very specifically about how third-party vendors **electronically sign** other supporting records. For example, a clinical trial sponsor might outsource storage of clinical trial records to Iron Mountain. Is there an expectation that the electronic signatures used by Iron Mountain (for SOPs, training records, agreements etc) comply with every requirement in 21CFR11? A clinical trial sponsor might contract with a training consultant to provide GCP training. Is there an expectation that the supporting records generated by the training consultant comply fully with 21CFR11 (e.g. CV of the trainer, SOPs, agreements).

In our specific case as a third-party vendor supporting clinical trial sponsors, we have an internal quality management system that includes deviations, SOPs, validation documentation, training records etc. The systems and processes are designed to be compliant with ICH GCP requirements. My understanding is that we should use an advanced electronic signature when we sign documents electronically but that there is not a requirement for our supporting documents as part of the QMS are signed using a system that MUST comply with every requirement contained in 21CFR11.

Can you please confirm that the requirement to comply with 21CFR11, **specifically for electronically signed electronic documents that are NOT clinical trial documents**, does not extend to third parties such as ourselves. Thank you.

Kind regards,
[redacted]

[redacted]

From: CDER SBIA <CDERSBIA@fda.hhs.gov>
Sent: 05 May 2021 21:02
To: [redacted]
Subject: RE: [EXTERNAL] 21CFR11 - Compliance Requirements by Third Parties

Dear [redacted]

Thank you for writing to the Division of Drug Information, Small Business and Industry Assistance (SBIA), in the FDA's Center for Drug Evaluation and Research (CDER).

Electronic systems used to produce required records (e.g., eTMF) are required to comply with 21 CFR 11 in order to ensure data attributably, access controls, etc. The responsibility for compliance is not the subcontractor or third-party vendor's responsibility, but the sponsor's to ensure the systems they use are reliable for regulatory purposes. Service level agreements may be used to ensure that the electronic system satisfies Part 11 requirements. The sponsor is also responsible for ensuring that training of users is provided when needed.

Validation is critical to ensure that the electronic system is correctly performing its intended function. A risk-based approach should be used for validating electronic systems owned or controlled by sponsors or other regulated entities. When using a risk-based approach for validating electronic systems, sponsors and other regulated entities should consider the risk that the system poses to the integrity, reliability, authenticity, and confidentiality of the study data and records.

Factors to consider when using a risk-based approach for validation include the following:

- The nature of the electronic system (e.g., commercial off-the-shelf (COTS) systems, customized electronic systems)
- The intended use of the electronic system (e.g., used to process records that are essential to the clinical investigation)
- The purpose and significance of the record and the criticality of the data (e.g., the extent of error that can be tolerated without compromising the reliability and utility of the record and data for its regulatory purpose)

Validation is critical when electronic systems are used for activities such as clinical trial management, data integration, data analysis, recording or processing adverse events, trial endpoints, drug dispensation, administration, and accountability. The following cases illustrate this risk-based approach. For COTS office utility software such as word processing, spreadsheet and portable document format (PDF) tools, the extent of validation should be guided by the organization's internal business practices and the intended use of the software in the clinical investigation. Validation may not be necessary for COTS office utility software used as intended by the manufacturer.

We hope this information is helpful.

If in the future you have additional questions, please feel free to contact us again at CDERSBIA@fda.hhs.gov.

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Best regards,

Renu
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CDERSBIA@fda.hhs.gov

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U.S. FOOD & DRUG ADMINISTRATION

From: [redacted]
Sent: Monday, April 26, 2021 6:02 AM
To: CDER DRUG INFO <DRUGINFO@fda.hhs.gov>
Subject: [EXTERNAL] 21CFR11 - Compliance Requirements by Third Parties

Dear FDA

There appears to be a growing misunderstanding about the extent to which compliance with 21CFR11 is expected. This query relates specifically to those involved directly or indirectly with clinical trials for new investigative drugs.

It is clear that any clinical trial sponsor must comply with 21CFR11 with respect to trial records that are generated during the conduct of a clinical trial (aka "the trial master file") and for their supporting systems. However, there now seems to be a growing expectation from those sponsors that sub-contractors and

other third-parties are also expected to comply with 21CFR11, even though their records are never submitted to the FDA and are extremely unlikely to ever be reviewed by the FDA.

For example, consider the case of a commercial software developer who develops document management software (an eTMF) that the sponsor may use to assist with the management of trial documents. Is there a requirement that the software company complies with 21CFR11 for their electronic validation records, electronic training records, electronic signing of their SOPs, etc? These records are not submitted to the FDA. The records will not be reviewed by the FDA. It seems that whilst the software company needs to meet GCP requirements for these records, there is no specific requirement to comply with 21CFR11. Is this correct?

Kind regards,

[redacted]

[redacted]

[redacted]