

FDA Regulation of Electronic Source Data in Clinical Investigations

Q1 Productions Second Annual Innovations in Clinical Data Management Conference, Arlington, VA

Mahnu Davar

Presented on Oct. 28, 2014

Overview of the Final FDA eSource Guidance

- The Final eSource Guidance was published in Sept. 2013
 - “promotes capturing source data in electronic form”
 - “ensuring the reliability, quality, integrity, and traceability of electronic source data”
- The Final eSource Guidance reflects many practices already embraced by experienced industry clinical trialists
 - Clarifies key definitions and explains how they fit within existing GCP framework for IND and IDE trials
 - Meant to be read along with FDA Guidance on Computerized Systems Used in Clinical Investigations (Apr. 1999)

What Led FDA to Create Additional Guidance in this Area?

(3) Failure to maintain accurate, complete, and current information as required by 21 CFR 312.140 (b) .

Cypress failed to maintain adequate records of all on-site monitoring visits and activities. For example, the [REDACTED] monitoring/training visit was not documented on the monitoring logs for Dr. [REDACTED] site and, for Dr. [REDACTED] site, three additional site visits were not recorded. Also lacking were records of audits performed on [REDACTED] worksheets.

Cypress failed to have a system in place to verify the accuracy of data collected at laboratories not under their direct control. Transfer of data sets, including laboratory data from the contract laboratories to the CRO, to your firm and then transferred again to the contracted statistician resulted in discrepancies in what should have been identical data sets. Your current practice of submitting disks to different contractors and receiving disks from various locations does not address how an audit trail was maintained. Changes to data that are recorded and stored on electronic media require an audit trail in accordance with 21 CFR 11.10(e). For changes made at the research site, the documentation should indicate who made the change, when it was made, and a description of why the changes were necessary.



DEPARTMENT OF HEALTH & HUMAN SERVICES

FEDERAL EXPRESS

JUN 7 1999

WARNING LETTER

Mr. Jay Kranzner
Chief Executive Officer
Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, California 92121

Dear Mr. Kranzner:

During the period of November 2 through Mr. Victor Mo, an investigator with the Administration (FDA), Seattle District facility. The purpose of that visit was whether your firm's activities at the investigational study entitled [REDACTED]

[REDACTED] complied with applicable FDA product is a device as defined in section Federal Food, Drug, and Cosmetic Act.

Our review of the inspection report, a of FDA-conducted data audits at several investigator (CI) sites and the inspection research organization (CRO) who perform to support the marketing application of revealed violations of Title 21, Code Regulations (21 CFR), Part 312-Investigator Exemptions.

The findings from the FDA inspection of were listed on the form FDA-483, Inspection which was presented to and discussed a conclusion of the inspection. The following list of violations is not intended to be an all-inclusive list of the problems encountered during our review:

eSource and Good Clinical Practices

- Sponsors, CROs, and Investigators/Sites all have specific recordkeeping obligations under the IDE regulations at 21 C.F.R. Part 812
- If done right, capturing source data electronically and transmitting it to the eCRF can help ensure GCP compliance among the parties by eliminating unnecessary duplication, reducing potential for transcription errors, encouraging real-time entry and review, and facilitating remote monitoring
- The Final eSource Guidance provides FDA's position on how aspects of electronic data management systems fit into the existing GCP framework

FDA Enforcement Trends and Recordkeeping

BIMO Inspections Completed FY 2013

<u>Center</u>	<u>CI</u>	<u>IRB</u>	<u>Spon/CRO</u>	<u>GLP</u>	<u>Total</u>
CBER	91	8	4	1	104
CDER*	344	90	62	28	524
CDRH	193	76	53	10	332
CFSAN**	0	0	0	0	0
CVM	36	na	1	22	59
All Centers	664	174	120	61	1019

*3 IRB = RDRC; + 205 BEQ inspections (CDER specific) ⇒
total = 1224

**CFSAN's BIMO Program remains under reorganization

Non-compliance with recordkeeping requirements are among the most frequently cited deficiencies in FDA-regulated device trials, particular for investigators/trial sites

Warning Letter to a Device Company (2006)

2. Failure to maintain accurate, complete, and current records relating to an investigation [21 CFR 812.140(b)(6)].

As per regulation, a sponsor shall maintain any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigation or a particular investigation. You failed to adhere to the above stated regulation; examples of this failure include but are not limited to the following:

- a. You failed to obtain copies of IRB approved protocols from [REDACTED] and the [REDACTED] Review Board.
- b. You failed to obtain copies of the investigator site visit reports for [REDACTED] ([REDACTED]) and [REDACTED] ([REDACTED]).
- c. You failed to obtain copies of the annual reports from [REDACTED] ([REDACTED]).

This Warning Letter is to inform you of objectionable Food and Drug Administration (FDA) inspection observations from August 7 through August 10, 2006, by an investigator at the District Office. The purpose of this inspection was to determine if you, as sponsor of the clinical study titled [REDACTED], complied with the requirements of 21 CFR 312.63. [REDACTED] is a device under 21(h) of the Federal Food, Drug, and Cosmetic Act. This letter also requests prompt corrective action to address the violations.

The inspection was conducted under a program designed to ensure that the information contained in requests for Investigational New Drug (IND) applications, Premarket Approval (PMA) applications, and Premarket Approval (PMA) applications (510(k)) are scientifically valid and accurate. Another purpose of the program is to ensure that human subjects are protected from undue risk in scientific investigations.

Our review of the inspection report prepared by the violations of Title 21, Code of Federal Regulations (21 CFR) Device Exemptions. At the close of the inspection, the inspection observations form FDA 483 for your review and discussed the observations listed on the form with you. You did not submit a response to the form FDA 483 consequently, only the deviations noted on the FDA 483 are discussed below:

1. Failure to accurately document device shipment records [21 CFR 812.140(b)(2)].

Pursuant to 21 CFR 812.140(b)(2), a sponsor shall maintain accurate, complete and current records relating to shipment and disposition of the device. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition

483 Observations from a CRO Inspection (2010)

1. Falsified source records

Records for the extraction of subject samples in numerous studies were falsified. Specifically, laboratory technicians identified as conducting the work were not present in the facility at the documented time of the study event. Electronic records of card key building entry time indicate that laboratory technicians arrived onsite only after the documented start time of sample extraction in at least 1900 instances over the period of April 15, 2005 through June 30, 2009. The falsification involves data from multiple studies for multiple sponsors.

DISTRICT ADDRESS AND PHONE NUMBER
4040 North Central Expressway, Suite 1000
Dallas, Texas 75204
Tel: 214 253-5200

NAME OF INDIVIDUAL TO WHOM REPORT
TO: Christopher Parnell, Ph.D., President
Cetero Research
Cetero Research
CITY AND STATE (If Cetero)
Houston TX 77099

DURING AN INSPECTION OF YOUR FIRM
This document lists observations made
during the inspection, and do not represent a
finding of non-compliance, or have implemented,
or action with the FDA representative.
questions, please contact FDA at the phone number and address above.

The following observations 1 and 2 pertain to Cetero's internal investigation of complaint allegations initially reported to FDA in June 2009.

1. Falsified source records

Records for the extraction of subject samples in numerous studies were falsified. Specifically, laboratory technicians identified as conducting the work were not present in the facility at the documented time of the study event. Electronic records of card key building entry time indicate that laboratory technicians arrived onsite only after the documented start time of sample extraction in at least 1900 instances over the period of April 15, 2005 through June 30, 2009.

2. Failure to document procedures for and identity of "prep" run injections

Electronic records of chromatography acquisition for subject sample analysis include a "prep" folder in addition to the study folder of final results. Cetero's internal investigation reported more than (b)(4) "prep" runs for about (b)(4) studies over the period of April 2005 through June 2009. There are no written procedures to describe the selection, evaluation, and reporting of such sample "prep" injections. Aside from the details in the chromatography acquisition software, there is no documentation to confirm the actual identity of the samples saved in the "prep" folder and laboratory staff did not record the injection of "prep" runs in the instrument log book.

3. Study (b)(4) and the two related (b)(4) and AP LCM/S

A. Records for the extraction of samples were falsified as described in (b)(4).
B. Records for the extraction of samples as described in item 1 above. For (b)(4).
C. Stability was not demonstrated for (b)(4) or (b)(4).

SEE
REVISION
OF THIS
PAGE
FORM FDA 483 (09/00) PREVIOUS EDITIONS

Electronic records of chromatography acquisition for subject sample analysis include a "prep" folder in addition to the study folder of final results. Cetero's internal investigation reported more than (b)(4) "prep" runs for about (b)(4) studies over the period of April 2005 through June 2009. There are no written procedures to describe the selection, evaluation, and reporting of such sample "prep" injections. Aside from the details in the chromatography acquisition software, there is no documentation to confirm the actual identity of the samples saved in the "prep" folder and laboratory staff did not record the injection of "prep" runs in the instrument log book. Cetero's written correspondence to FDA for the "prep" runs does not reveal the lack of written procedures and documentation of the identity of the "prep" injections. Despite the above, the firm's investigation plan claims that the allegation of "fixing" runs to obtain a passing result can be addressed by reviewing the "prep" injections.

Warning Letter to an Investigator (2004)

5. Failure to maintain accurate, complete, and current study records (21 CFR 812.140(a)(2) and 812.140(a)(3))

FDA regulations require CIs to maintain accurate, complete, and current records of receipt, use, or disposition of the investigational device, and each subject's case history and exposure to the device pursuant to 21 CFR 812.140(a)(2) and 812.140(a)(3).

You failed to satisfy these requirements. Examples of this failure include but are not limited to the following:

- There are no records of receipt or disposition of the investigational devices.
- The IRC contingency approval memorandum, dated May 3, 2002, was not maintained.
- From July 2002 through July 2003, the case report forms (CRFs) do not have any totals for the [REDACTED]
- Subject [REDACTED]'s name is missing from the informed consent form.
- The CRFs for Subjects [REDACTED] and [REDACTED] are incomplete, unsigned, or undated by the investigator.
- The early post-op follow-up x-ray evaluation CRFs are missing from the files for Subject [REDACTED]
- Subject [REDACTED] early post-op visit CRF is dated October 30, 2002, which is prior to the actual office visit on November 11, 2002.



Timothy P. Mar, M.D.
2801 K Street, Suite 330
Sacramento, California 95816

Dear Dr. Mar:

This Warning Letter informs you of objectionable conduct by the Drug Administration (FDA) inspection conducted at [REDACTED] on March 25, 2004, and/or respond to the noted violations. Your response process of reviewing each item listed on the Form FD-362 response within 30 days of the date of your letter, how written response which indicates the corrective and preventive actions taken or will take. This letter requests that you implement the violations cited. Mr. Jeffrey W. Shriver, an Investigator in the District Office, conducted the inspection from March 25, 2004, to determine if your activities as a [REDACTED] study complied with applicable regulations. [REDACTED] is a device defined in Section 201(j) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321 (j)].

The FDA conducted the inspection under a program of information contained in requests for Investigational Device Exemptions (IDEs), Premarket Approval Applications (PMAs), and Premarket submissions are scientifically valid and accurate. The subjects are protected from undue hazard or risk during the study.

Our review of the inspection report prepared by the investigator identified violations of Title 21, Code of Federal Regulations (CFR) Part 312.61, (a)(1) and (a)(2), 21 CFR Part 312.62, (a)(1) and (a)(2), and 21 CFR Part 312.63, (a)(1) and (a)(2). At the conclusion of the inspection, Mr. Shriver noted the observations listed on the Form FDA-483. The violations noted on the Form FDA-483 and our subsequent report are discussed below:

Ensuring Quality in an eSource System

- Apr. 1999 FDA Guidance on Computerized Systems Used in Clinical Trials makes clear FDA/BIMO's expectation that electronic records must be subjected to the same quality and regulatory controls as conventional trial documentation
- "ALCOA" principles endure for electronic records; data must be:
 - **A**ttributable
 - **L**egible
 - **C**ontemporaneous
 - **O**riginal
 - **A**ccurate

What is an Electronic Record?

- Electronic records can be any combination of text, graphics, data, audio, pictorial, or other information represented in a digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system. *See also* 21 C.F.R. 11.3(b)(6).
 - An electronic case report form (eCRF) is an example

What is Source Data?

- Source data includes all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation
- Source data is composed of data elements, which are the smallest unit of an observation captured for a subject in a clinical investigation, such as race, white blood cell count, pain severity measurement, or other observations

Who can be a Data Originator?

- Clinical investigators and delegated clinical study staff
- Clinical investigation subjects or their legally authorized representatives
- Consulting services (e.g., radiologists reading a CT scan)
- Medical devices (e.g., an ECG machine or other medical instruments)
- Electronic Health Records (EHRs)
- Automated laboratory reporting systems (e.g., from central labs)
- Other technology

Controls over Data Originators

- The sponsor must develop and maintain a list of all authorized data originators (i.e. persons, systems, and instruments)
 - In the case of electronic, patient-reported outcome (PRO) measures, the subject (using the unique subject identifier) should be listed as the originator
 - Where log-in is required, controls must be employed to ensure security and integrity of authorized user names and passwords (same goes for biometrics)
 - This list should be shared with each trial site and can be part of a broader data management plan document
- All eSource systems must produce a unique, traceable data element identifier that identifies the data originator
 - e.g., if an ECG machine automatically transmits to the eCRF, a data element identifier should be generated that identifies the ECG as the originator

Approaches to Data Capture Covered by the Final Guidance

- FDA permits data to be entered into the eCRF manually or electronically as set forth in five scenarios:
 1. Direct entry of data into the eCRF
 2. Automatic transmission into the eCRF
 3. Transcription from paper or electronic sources into the eCRF
 4. Direct transmission from an EHR system into the eCRF
 5. Transmission of data from PRO instruments into the eCRF

1. Direct Entry into the eCRF

- Direct entry into the eCRF can eliminate errors by not using a paper transcription step
 - In such instances, the eCRF is considered the source
 - In the event of an inspection, FDA can (and likely will) request other documentation to corroborate an eCRF entry during an inspection, such as evidence that a particular test was run to corroborate an entered diagnosis
- If a paper transcription step is still used, then the paper must be retained as an inspectable record

1. Direct Entry into the eCRF (cont'd)

- What does the Final Guidance say about images?
 - Images, such as CT scans, are not included as an eCRF data element, rather the interpretation of the image is a predefined field
 - If the image (e.g., CT scan) is sent to a central reading center for interpretation and a radiologist is authorized to enter data directly into the eCRF (e.g., “normal”), then the radiologist is the originator and the CT scan is the record
 - However, where the protocol requires the radiologist to send the report to a clinical investigator who then enters the data, the investigator is the originator and the radiologist’s report is the record

2. Automatic Transmission into the eCRF

- When a device or instrument is the originator (e.g., glucometer) and data are automatically transmitted directly to the eCRF, the eCRF is considered the source
- If the data are first transmitted to a service provider's database or EHR system, then either the database or the EHR would be the source
- **Note FDA does not intend to regulate EHRs under Part 11, though privacy and other laws still apply

3. Transcription from Paper or Electronic Sources

- Data elements may be transcribed into the eCRF from paper or other eSource documents
- The authorized person transcribing the data from the source documents is considered the data originator and the documents from which the data is transcribed is the source
- These data must be maintained by the clinical investigator as inspectable records under 21 C.F.R. 812.140(a)(3)

4. Direct Transmission from an EHR System into the eCRF

- Data elements originating in an EHR system may be transmitted directly into the eCRF automatically
- Unlike a direct transmission to an eCRF from instruments or medical devices, EHRs can use intervening processes (e.g., data selection algorithms)
- For this reason, FDA requires that the EHR be the source and the pertinent data for the subjects in the study be maintained as an inspectable record

5. Transmission of Data from PRO Instruments into the eCRF

- When a PRO instrument is used by a subject to transmit data elements directly into the eCRF, the subject is considered the data originator and the eCRF is the source
- If a process is used by which the subject uses the instrument to transmit data to a technology service provider database, then the database is considered the source

Data Element Identifiers Are a Key Control

- According to FDA, the eCRF system should include the capability to record who entered or generated the data and when it was entered or generated without obscuring the audit trail
- Data element identifiers should be attached to each data element and contain, at a minimum:
 - Originators of the data element (including those data elements entered manually)
 - Date and time of entry into the eCRF (the audit trail begins at the time the data are transmitted to the eCRF)
 - Clinical investigation subjects to which the data element belongs

Modifications and Corrections to Data

- Only a clinical investigator or delegated staff should perform modifications or corrections to the eCRF
- As noted, each modification and correction must have data element identifiers which identify the time, date, originator, and reason for the change, and must not obscure previous entries
- A field should be provided allowing originators to describe the reason for the change (e.g., “transcription error”), which is critical to creating an auditable record
- Similarly, automatic transmissions should have traceability and controls via the audit trail to reflect the reason for the change

Prompts, Flags, and Data Quality Checks

- In the Final eSource Guidance, as well as the 1999 Computerized Systems Guidance, FDA has encouraged industry to use electronic flags, prompts, and data quality checks in the eCRF to minimize errors and omissions during data entry
- Investigators should have the ability to comment on the data they enter (e.g., in a comments field)
- Sponsors should describe (e.g., in a data management plan) the electronic prompts and other elements designed to address inconsistencies, missing data, and other potential data quality issues

Data Review Obligations for Clinical Investigators

- Under 21 C.F.R. 812.3(i), the clinical investigator is responsible for conducting the investigation and supervising his or her delegates, including in the creation of accurate, traceable records
- To comply with the requirement to maintain accurate case histories (812.140(a)(3)), investigators should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to FDA
- Masking of certain data elements from the investigator are permissible as required by the study; such elements should be noted in the sponsor's data management plan
- As noted, either originators or investigators may make traceable modifications to data elements; however the investigator must sign off on any modifications made in the eCRF subsequent to his or her signature

Record Retention and Monitoring

- Consistent with the requirements found at 21 C.F.R. 812.140(a)(3), FDA affirms that clinical investigators must retain control of the electronic records (e.g., completed and signed eCRF or certified copy) and provide FDA inspectors with access
 - Related paper records, or certified copies, must also be maintained as inspectable records
- Sponsors, CROs, data safety monitoring boards, and other authorized personnel should have access to view data in real-time
 - FDA encourages early review by sponsors to timely detect study-related problems

Data Management Plans

- The Final eSource Guidance encourages sponsors to develop a data management plan or similar document
 - Should list all current authorized data originators with eCRF access rights
 - FDA recommends these individuals receive documented training and be given unique log-ins and other authorizations
 - Log-ins and authorizations should be discontinued if an individual discontinues involvement
- The data management plan (or protocol, investigational plan, or another related document) should include descriptions of the systems to be used during the study, including attendant security measures employed to protect the data, and a description or diagram of the data flow

Legal Considerations

- Data management and quality agreements for CROs and other partners
- Remote data monitoring systems
- Data security and contractual indemnification for breaches
- System interoperability among sites, sponsors, monitors, and other parties

Questions?

Mahnu Davar

(202) 942 - 6172

mahnu.davar@aporter.com