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April 7, 2011

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2010–D–0643: Electronic Source Documentation in Clinical Investigations

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations; Availability." BIO commends the FDA for providing this Draft Guidance and supports FDA efforts to address the need for additional guidance in response to evolving technology available for electronic data capture. However, BIO feels the guidance as written has significant shortfalls, particularly regarding the unclear scope of the guidance and the responsibility of an investigator to a Sponsor, and BIO requests clarification as detailed in this submission.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO supports the ongoing integration of electronic health records (EHR) into the healthcare delivery system and industry adoption of electronic data capture (EDC) systems, and we are hopeful that these systems will introduce new capabilities and efficiencies into the clinical trial enterprise. The majority of BIO members are small

companies that do not yet have a product on the market, but are at the forefront of biomedical innovation. BIO members welcome technological advances that will assist them in conducting clinical investigations in a more efficient manner. In fact, smaller emerging companies not burdened by legacy systems and practices may have greater flexibility and willingness to adopt new EDC systems. However, while BIO appreciates the principles outlined in the Draft Guidance, many of the responsibilities placed on the investigator remain ambiguous, and may create more potential burdens and uncertainty than clarification for biotech companies involved in clinical investigations.

GENERAL COMMENTS:

I. Please Clarify Scope of Guidance

We request that FDA clarify whether the Draft Guidance applies only to source data that are initially collected electronically, or if it also applies to data collected via alternative means and transcribed to electronic case report forms (eCRF). BIO suggests that it apply to the former only. To avoid confusion, we request that the guidance should explicitly exclude eCRF data when the eCRF is not used as the source.

If the guidance does not apply only to eCRFs used as the source, then other parts of the Guidance are difficult to interpret in that (1) the investigator or subinvestigator is the individual populating the eCRF, and (2) the investigator or subinvestigator can sign off on the data prior to its transmission to the Sponsor.

However, if the Guidance is not limited to eCRFs used as the source, then it is incorrect to state that investigators typically review data prior to every time that data are sent to the Sponsor. Rather these data are transmitted on an ongoing basis and sign off occurs at database lock; these data are not reviewed prior to every time they are sent to the Sponsor (Lines 132, 339, 359, and 410).

In addition, the title of the Draft Guidance does not imply that it provides guidance to general eCRF completion, but lines 339-355 seem to state that the Guidance applies to the eCRF in general. If the scope is larger than only when the eCRF data is the source, then we ask that the title of the Guidance reflect this.

However, as noted above, we request that the Guidance should exclude eCRF data when the eCRF is not used as the source.

Finally, the Draft Guidance does not address data recorded by patients in electronic devices (e.g. electronic diaries). We suggest this exclusion makes sense and should be explicitly noted.

II. Please Clarify Maintenance of the eCRF Systems

While we understand and appreciate the clinical investigator's responsibilities for conduct of the study and review/ approval of eCRF records, we feel that the Draft Guidance is ambiguous in two areas:

1. Support that can be provided by the Sponsor for the eCRF system used in the study, and

2. The timing and sequence for review, approval, archive and transmission of eCRF data between the investigator and Sponsor.

The Draft Guidance implies that the investigator collects, reviews, approves, archives and then transmits CRF data to the Sponsors. It is unclear if Sponsors can still maintain the eCRF systems directly and provide access to the investigators, and suggests the possibility of third party management of these eCRF systems. BIO feels that such a situation would not be the most efficient for either the Sponsor or the investigator. Such a situation could increase costs and the need for transmission of data, thereby increasing risk.

BIO recommends that the Guidance be clarified to provide the flexibility needed by all parties identified in the tiered approach such that it is clear that Sponsors can host and support the eCRF system directly and that Sponsors can manage access to the eCRF data in parallel with investigator review and approval to aid with quality review, archive and retention.

In order to allow flexibility and promote use of contemporary technology to advance clinical trial programs and make these programs available to patients worldwide, we recommend that FDA consider modifying the language within the Draft Guidance to make it clear that Sponsor hosted eCRF systems, managed in compliance with 21 CFR Part 11 and good clinical practice regulations, are appropriate and acceptable.

We also recommend that this Draft Guidance support the previously issued 1996 International Conference of Harmonsation (ICH) published Guidance for Industry: E6 GCP Consolidated Guidance.

III. Availability of Vendor EDC Offerings

BIO appreciates the principles outlined in the Draft Guidance regarding investigator responsibilities, including assembly and control of data, but we believe the data model outlined utilizing the eCRF as a central platform to assemble, review and archive data is not currently available among vendor EDC offerings. There are no or very few scenarios where data created centrally (central labs, electrocardiograms (ECG), imaging, database management systems (DBMS)) is transmitted to the Sponsor via the site. The most common scenarios usually involve immediate disclosure by such third parties to the

investigator and either live or batch transmissions from the third party to the Sponsor, with the third party being considered as the source owner or originator.

For example, given the recurring theme of eCRF as repository in this Draft Guidance, we recommend that the Agency consider a central data repository or Sponsor clinical database as a potential definition for Tier 1 data entry or data capture.

Additionally, the capabilities outlined in the document presumably would need to support real-time Sponsor monitoring for patient safety, adaptive trial and related purposes.

Lastly, the term "release" as used in the Draft Guidance is unclear. Although most Sponsors require some nature of investigator approval for any analyses/reporting/unbinding activities, the Sponsors could not execute standard data management reconciliation/data review activities or medical monitoring across subjects and sites in "live" fashion. Therefore, we request clarification around the concept of "release."

We believe FDA should consider current EDC vendor – Sponsor data flow models that provide for investigator review and control without physically requiring eCRF as central platform.

IV. Issues with Tier Approach

In general, we believe the process flow illustrated in Figure 1 seems overly prescriptive in its 3-tier approach. Specifically, Figure 1 and the accompanying text depict all e-Source data flowing through the Clinical Investigator to the Tier 3 parties.

It is imperative to understand that this is not the current arrangement for all trials, *e.g.*, some e-Source data is currently flowing directly to Sponsor. Further, the elements in Figure 1 may cause a number of practical and technological problems if followed by Sponsors. For example, in the case of Electronic Patient Reported Outcomes (ePRO), the model where the patient transmits the data directly to the service provider will no longer be acceptable. The new model will require patients to either transmit the data to the investigator (which poses technological problems) or return the ePRO device to the investigator for review prior to transmission of the data to the service provider.

Later in the document, the language in the Draft Guidance becomes even more rigorous: "In exceptional circumstances, the protocol may require that certain data elements be hidden from the investigator. Concurrence with this procedure should be obtained from FDA review divisions. Such data elements may be forwarded directly to parties in Tier 3 without investigator sign off." (Line 352).

In the data model outlined, it is not clear who owns the data, particularly data not sourced by the investigator. More importantly, the implications of the "data originator" concept are not clear. In a web-based EDC setting, it would be difficult to demonstrate that the data is in direct control of the investigator.

Figure 1 also assumes that the subject can be granted identity credentials, which does not appear to be addressed here or related guidance.

We suggest that the Agency:

- Revise the 3-tier approach to be less prescriptive and allow for a wider range of data flow models.

- Expand Footnote 6 to indicate that there may be other circumstances where data may not flow through the Clinical Investigator.

- Consider current practices that allow source data to be forwarded to tier-3 without going through the Clinical Investigator.

- Clarify what it would expect from Sponsors and investigators to demonstrate that the source is under adequate control of the investigator to comply with established Good Clinical Practices (GCPs).

V. Originators of Data Elements

Given industry-wide lack of capabilities as outlined in the document, the Guidance as written places a significant burden on the investigator. For example, reference is made to maintenance on site of prospectively determined originators of data elements authorized to transmit data elements to the eCRF, inclusive of on-site devices and instruments and that should be co-developed by the Sponsor and clinical investigator.

Further, it is important to note that such data may not always be available prospectively for all devices and/or instruments.

Lastly, there does not seem to be an immediate benefit of including systems in this list.

While we believe that the Final Guidance should require that clinical sites should continue to maintain a list of all authorized data originators respective to their own site, we suggest that the Final Guidance indicate that sites are not required to maintain a copy of cross-site global lists of authorized data originators, which historically has been the obligation of the Sponsor.

VI. Impracticality of Some Recommendations

Given that data are collected many times over the life of a study, including a detailed written description of the timing and procedure for obtaining information from investigative site(s) would be impractical. At best, if deemed necessary by FDA, the Sponsor could provide a general description of this process in the protocol (Lines 361-364) with more details recorded in-house and available to FDA upon request.

In addition, study investigators are not typically responsible for creating study archives of eCRFs. Rather, it is industry practice for the Sponsor to create the archive and distribute a copy to each site (Lines 375-381). In addition, it would not be practical for the Sponsor to describe the location/logistics of where each investigator stores his/her archived copy as this will change over time and is beyond the Sponsor's control (Lines 380-381). The same problem occurs with the requirements for storage of the "web based repository" (Lines 390-400), as this may also change over time.

Finally, as equipment may vary by site and over time in a multinational long-term study, the requirement that information (manufacturer, model #, serial #, etc.) be recorded for electronic devices used to capture data in the eCRF is impractical (Lines 317-320). If FDA deems this information necessary, then BIO requests that the FDA specify the types of equipment for which it is most important and permit it to be documented by site.

Enabling the integration of numerous, non-standardized, site-based EHR systems to an EDC platform is not practical, nor possible in many instances. Currently, a standard for compliance does not exist to develop these systems and it would put Sponsors at risk to implement system integrations across clinical programs, as every EHR technology is unique and sometimes extensively customized at individual trial centers.

We commend the overall purpose of enabling integration from site-based EHR systems to EDC. However, the Draft Guidance does not indicate whether FDA will support this goal with the need to establish standardization/integration from EHR vendors.

VII. Validation:

FDA and Industry have both invested large amounts of effort and resource in defining the concepts and requirements for "Electronic Records," and establishing the discipline of Validation. The benefit and value from this guidance would be best assured by the consistent re-use of existing terminology and discipline of computerized system validation. This would help to clarify expectations/recommendations for properly documented system requirements and to test scripts developed to challenge the requirements with documented results of that system testing.

In several lines, this draft Guidance includes the recommendation that several new and very detailed pieces of information be captured and retained by the sponsor and/or Investigator. While each of the items seems to have real purpose and value, we are cautious that not all would be available during the creation and approval of the Study Protocol. We request that the FDA provide additional guidance regarding the appropriate place to capture and retain information below (presuming it is not desirable to delay study protocol approval until all details are available):

- Algorithms for data transfer from electronic health record systems to EDC or similar study specific system;
- Lists and unique identifiers for each data originator and equipment/system directly supplying data to the study;

- May not be known at creation and approval of the protocol… (Line 191) Different place, attachments/appendices, and at what level of detail/ what would require revision of this information systems;
- Sponsor's description of which data elements will be transmitted electronically, their origin and destination, when, etc (Lines 417-422);
- Lists and purpose or intended use of all computerized systems used in the clinical study (Lines 435,) as several computerized systems may not be known until after Contract Research Organization (CRO) & Site Selection and qualification….(Line 435);
- Description of system security measures for each system (Line 436-437);
- Detailed diagram and description of data transmission (Line 438);
- Information about electronic tools to detect events in eCRF such as inconsistencies, etc (Line 440-442);
- Logs from use of tools and issues detected (Line 443)

Many of the details on the use of computerized system, data transfer algorithms, lists of site equipment, etc. (above) are subject to change during the course of a multi-year, Phase II or Phase III study. While each of these changes would be prepared based on an approved Systems Change Control procedure, the result may also impact study records in addition to the system validation records. We ask that the FDA provide additional guidance about its expectations and recommendation for revision of this data within an approved Study Protocol or other study specific document set.

We believe the guidance could perhaps be more clearly written if the FDA were to harmonize terminology with the other, previously issued guidance documents referenced in both Section I: Introduction (Lines 28-31) and Section IV: Regulatory Review and Collaboration (Lines 431 – 433), as the objective for and rationale behind each of these guidance documents are the same.

VIII. Other Issues

a. <u>Secure Repositories:</u>

While we support FDA's efforts to enhance the process for maintaining electronic data sources, the means by which a regulatory inspector accesses the secure repositories is not discussed in this or related guidance. For example, it is not clear whether inspectors will be assigned individual accounts.

b. <u>Additional Documentation:</u>

The Draft Guidance indicates that FDA may request additional documentation to support eCRF direct entries – *e.g.* a hospital record to review for evidence of blood glucose to support underlying illness of diabetes, or a prescription record or pharmacy record to support concomitant therapy reported by patient.

We note that, for these two examples, routine expectation is that background illnesses and concomitant therapy is often patient-reported and collection of additional documentation by the investigator is not mandated by the Sponsor.

Therefore, we request that FDA provide specific guidance regarding the circumstances when additional documentation would be expected.

c. Lab Data:

The diagram on page 4 does not recognize that laboratory data are commonly sent to the Sponsor prior to/concurrent with lab reports being sent to the investigator. It is incorrect to presume that lab data are loaded into the eCRF at the site and then provided to the Sponsor after investigator signature. Many data types (*e.g.*, central reader, central lab, PRO, etc.) bypass the EDC system at the site and are captured directly in the Sponsor's clinical data management system. These data do not appear in the eCRF and are not stored there.

d. XML Format:

We suggest that the guidance should allow for multiple formats by which the eCRF may be stored beyond Extensible Markup Language (XML*)* (Lines 366-368). XML may not be an appropriate format for analytical instrument data, or other data that is generally graphical or consisting of digital images. We suggest that FDA consider updating this section in the Final Guidance to allow for the eCRF to be stored in other common formats (such as PDF). This is particularly true as new formats will be developed.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Kelly Lai
Director, Science & Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 15:	The Draft Guidance states "This document provides guidance to Sponsors, contract research organizations (CROs), data management centers, and clinical investigators on capturing, using, and archiving electronic data in FDA-regulated clinical investigations."	Is the reference to "data" here specific to source data, or all data associated with a clinical trial, including Sponsor analysis datasets, etc? See reference at line 43. Please clarify as to whether data is specific to source data or all data associated with a clinical trial.
II. BACKGROUND		
Line 51:	The Draft Guidance refers to "electronic case report forms (eCRF)."	This is a bit confusing, since the CRF or eCRF is usually never considered source, but more the data collection vehicle assuming the data from the true "source" has been transcribed or uploaded into the vehicle. Please clarify whether the Guidance is talking about direct entry into the eCRF, whereby the eCRF is both the source and the vehicle.
Lines 58 and 68:	These provisions state that "Access to source documents and source data is essential to inspection" and that the recommendation will help ensure that electronic source data "meet the regulatory requirements for recordkeeping and record retention."	Please clarify if these lines are intended as FDA's recommendation that such site equipment and systems which are used for, but not 100% dedicated to, gather clinical study data meet all the requirements of 21 CFR Part 11, or just the several sub-sections of Part-11 as enumerated within this guidance. Also, please clarify what standards and scope of inspection might apply to these eSource Systems and Records.

Lines 71:	The Draft Guidance states the "identification of the data element as the basic unit of information in the eCRF."	Please clarify if this guidance document is limited to eCRFs. The Guidance appears to be specific to electronic source data, regardless of whether the source feeds a paper CRF or an electronic CRF.
Lines 73-74:	The Draft Guidance states "Information about the electronic creation, modification, transmission, and storage of source data and documents."	It seems FDA is differentiating between source data and non-source data documents. This is confusing as this Guidance specifically addresses electronic source documents.
Lines 73-76:	This guidance discusses the following specific topics related to electronic source data: • Information about the electronic creation, modification, transmission, and storage of source data and documents • Investigator responsibilities with respect to reviewing and archiving data • Transmission of data to the sponsor and/or other designated parties	Please amend the lines to say the following: • Information about the electronic creation, modification, transmission, and storage of source data and electronic documents. • Investigator responsibilities with respect to reviewing and archiving ~~data~~ source documents. • Transmission of electronic data to the Sponsor and/or other designated parties.
III. ELECTRONIC SOURCE DOCUMENTS AND SOURCE DATA		
Lines 150-152:	A data element in an eCRF represents a single observation associated with a subject in a clinical study. Examples include birth date, white blood cell count, pain severity measurement, or other clinical observation made and documented during a study.	The draft guidance addresses "data elements," but does not address them as an electronic record. Individual data elements, such as 12 mg, 98.6° F, are generally not meaningful when isolated from the electronic record into which the data elements are being entered (date, patient number, patient parameter being measured, etc.).
Lines 131, 332-3:	The Tiers 1, 2, 3 outlined in Figure 1 conceive of a singular EDC Database and simplified	When the Investigator is at a site and some key evaluations are performed remotely, and only after data is transmitted to the off-site

	study data structure where all sources of data are centralized to this single Database. Often, studies rely on much more complex data relationships between Sites, Labs, Central Labs and Sponsors, etc. where this is not always the case (*e.g.*, remote radiologist(s) reading digital MRI at central lab(s) that is not contained with an EDC/eCRF).	Central Lab, what is the Site Investigator's responsibility for Access, Review and Sign-off on these data? See Lines 131, 332-333, Must systems be designed so that the "investigator" has access to the data at the central lab (*e.g.*, radiologist evaluation of digital images) even though these are not contained within primary EDC System and sign-off on these records prior to transfer on to Tier 2, 3 participants?
Lines 154-155:	The Draft Guidance reads "For each data element provided on a subject in a clinical study, there is an originator responsible for its entry into the eCRF."	Please clarify if this section should read "entry and/or transmission" into the eCRF. If so, please amend to state: For each data element provided on a subject in a clinical study, there is an originator responsible for its entry and/or transmission into the eCRF.
Lines 168-174:	This section identifies the need for assuring computerized systems or automated equipment operate accurately for their intended use, and, as such, could be more clearly stated if the FDA were to indicate that computerized systems should be validated.	Please clarify that computerized systems should be validated.
Line 176:	Transcription of Data Elements from Other Source Documents	It is unclear what "other source document" refers to, please clarify.
Lines 188-194:	This section identifies the need for documenting the reliability of data transfer and algorithms to facilitate the transfer, and as such, should indicate the need for development of proper system requirements and computerized system validation.	Please indicate the need for development of proper system requirements and computerized system validation.

Lines 191-192	Algorithms for data extraction should be described in the study protocol or in another document that includes data management details.	It is not clear what is exactly meant by this phrase and by the term extraction (term is not referred to in glossary).
Lines 200-204:	This section indicates the need for linking data elements to other information which give context to the data element.	This section could benefit by referring to this as an electronic record which is already described and accepted as consisting of the Data and Meta Data required to understand, interpret and otherwise make use of the data. As this section correctly indicates, individual data elements are generally not meaningful without the other information that was part of the electronic record. Consistency with other referenced Guidance, rather than trying to parse individual elements of the electronic record, would benefit the FDA's purpose and Industry's application of this guidance.
Lines 219-221:	The section on display of data element identifiers requires the system to "include a functionality that enables the user to reveal or access the data element identifiers related to each element […]". The current wording suggests that this requirement should be implemented in all systems and available to all users. While the ability to review data element identifiers might be useful, implementing it in each system (and for all users) will pose a significant burden and technological challenges.	We request that FDA consider updating the Final Guidance to state that "…the system should include a functionality that enables authorized users to review eCRF data element identifiers on the data entry system or another system that maintains (a copy of) the data".
Lines 227-228:	FDA recommends that clinical data be entered electronically by study site personnel	Does this statement mean that FDA prefers, when utilizing an eCRF, that the investigator enter into the eCRF the blood pressure, for

	at the time of the subject visit to avoid transcription from unnecessary paper records.	example, as opposed to taking the blood pressure, writing it down in the medical record, and then transcribing or entering it into the eCRF? Please clarify intent.
Lines 268-298:	This section provides a listing of data originators, including "[a]utomated laboratory reporting systems." Additionally, it states "Each study site should maintain a list of prospectively determined originators […]" and "For devices and instruments, the list should include any available unique identifier, the manufacturer, the model number, and the serial number".	We request that FDA consider revising the section to (1) limit the site documentation of data originators to users (that is, excluding systems), and (2) allow for the documentation of other originators to be maintained separately and under the control of other parties (such as the system administrator).
Lines 352-355:	This provision states that "In exceptional circumstances, the protocol may require that certain data elements be hidden from the investigator. Concurrence with this procedure should be obtained from FDA review divisions. Such data elements may be forwarded directly to parties in Tier 3 without investigator sign off."	This section refers to "exceptional circumstances" where data elements may be forwarded directly to parties in Tier 3 without investigator sign off. It would be helpful to Sponsors if examples were provided in the guidance document of such circumstances.
Line 361:	In multiple lines (Lines: 129, 131, 136, 341, 360, 375/376 & 411), the Draft Guidance signals a strict sequence of events where the Investigator "Signs Off" on a completed Case History prior to transmission of the data on to Tier 2 or Tier 3 participants.	In light of the Draft Guidance's emphasis that the investigator must sign-off and approve eCRF/Case histories prior to transmission on to Tier 2/Tier 3 parties, we request that the FDA provide greater clarity on which portions of the eCRF could be released to Tier 3 parties as the study progresses.
Lines 375-376:	This bullet states: "The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review	Does this recommendation mean specifically that the site has to generate the protected copy and the Sponsor can no longer provide this copy to the investigator/site?

	and sign off."	Please clarify.
Lines 380-381:	This bullet recommends that "The clinical investigator should generate a write-protected copy of the eCRF for the study archives following review and sign off."	How specific does the description of standard operating procedures (SOP) have to be? Is "archived by each site" adequate? If this refers to e-source (rather than eCRF in general), than this is again confusing as the e-source gets transferred to the Sponsor. Please clarify.
Lines 387-389:	The Draft Guidance states "When an investigator has transcribed data elements from paper documents in an eCRF, **the investigator must also retain the paper documents for review by FDA** (see 21 CFR 312.62(c) and 812.140(d))." (Emphasis added). In our experience, FDA has advised clinical sites that electronic copies of paper documents are acceptable as long as any corrections are able to be tracked.	We believe the Final Guidance should reflect FDA's historical advice to allow electronic copies of paper documents are acceptable as long as changes to the documents can be adequately tracked.
Lines 390-396:	"the laboratory should have access to the hemoglobin levels that it reports, just as the study subject should be able to review data reported in a patient-reported outcome tool or patient diary."	Please note that there are circumstances when a protocol requires that a patient does NOT have access to previous entries in order to de-link the responses from one visit to the next.