March 26, 2013

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

Re: Docket No. FDA–2010-D-0643: Draft Guidance for Industry on Electronic Source Data in Clinical Investigations; Availability

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the "Draft Guidance for Industry on Electronic Source Data in Clinical Investigations."

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.

GENERAL COMMENTS:

BIO supports FDA efforts to address the need for guidance in response to evolving technology available for electronic data capture. BIO supports the ongoing integration of electronic health records into the healthcare delivery system and industry adoption of electronic data capture systems. We are hopeful these systems will introduce new capabilities and efficiencies into the clinical trial enterprise. BIO commends the FDA for providing this revised and updated draft guidance in response to stakeholder concerns to the draft guidance of the same title released in January 2011. While draft guidance addresses many issues raised by BIO's previous comments[1] by presenting a more linear perspective to the capture and management of electronic source data in clinical investigations, BIO requests further clarification relating to the scope of the guidance and the recommendations regarding data review.

[1] BIO comments on the FDA "Draft Guidance for Industry on Electronic Source Documentation in Clinical Investigations", April 7, 2011, http://www.bio.org/sites/default/files/20110407_ecrf_comments.pdf

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I. Scope of Guidance

We request that FDA clarify that the guidance applies only to source data that are initially collected electronically. The title of the guidance, "electronic source data," implies a limited focus – the capture and management of electronic source data that populates the pre-defined fields in an electronic case report form (eCRF) - however the guidance content addresses the role of the eCRF even when it is expressly not considered the data source (see lines 162-183). Accordingly, BIO recommends the following revisions:

- Lines 21-22: "This guidance addresses source data from clinical investigations captured for the first time in ~~used to fill~~ the predefined fields in an electronic case report form (eCRF), according to the protocol."

- Line 162: "~~Transcription of~~ Source Data ~~from Paper or Electronic Sources to~~ in the eCRF"

- Lines 162–183: Frame the discussion under a new heading titled "Source Data Captured Prior to eCRF"

- Lines 343-346: Amend the definition of eCRF to recognize that the eCRF in this guidance document represents a logical construct and in practical terms may encompass information stored in multiple distinct computer systems (*i.e.,* that the capture, review, management, analysis, and reporting, does not occur in any single system.

In addition, and especially if the guidance is meant to be broader in scope, BIO requests greater clarity relating to how best to identify "source data". Since identification carries with it associated follow-on Sponsor and investigator responsibilities to maintain and make available for inspection supportive, electronic, or paper records greater clarity, including definitions of "automatic transmission", "intervening process", and "supportive information," would, at the very least, help ensure investigator and Sponsor compliance and advance the goals of the guidance.

II. Data Review

BIO requests that the guidance reflect Agency understanding and recognition that it is not practicable or feasible to audit trail every "view" access of records by an investigator, especially because noting a "view" does not necessary indicate deliberate data review. Systems typically capture an explicit action of the investigator attesting to their periodic review (*i.e.*, review one or more times) of data with a signature. This attestation is often an independent record stored in the system and is not necessarily stored in the audit trail itself as indicated in the guidance (see lines 237-238). Moreover, that act of signing may reference a large amount of data, but each individual piece of data (data

element) is generally not "tagged" with the investigator's signature as indicated by the guidance (see lines 240-242).

Please clarify that the guidance refers to the use of individual "data elements" and "tagging" as an emerging best practice, as the current design of most electronic data capture systems do not accommodate such practices. Please further clarify your understanding that traditional relational data base designs and audit trails are acceptable even if they do not individually tag discrete data elements. Otherwise, Sponsors would be required to extend time and capital to make huge design changes to most of their current data capture and reporting systems, which would also likely undermine the Agency goal of encouraging the adoption of electronic source.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Electronic Source Data 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/

Ruth DeLuca
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Biotechnology Industry Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. **ELECTRONIC SOURCE DATA**		
A. DATA CAPTURE		
1. Electronic Source Data Origination		
Lines: 113-115	"For each protocol, a list of authorized data originators (*i.e.*, persons, systems, devices, and instruments) should be co-developed and maintained by the sponsor and the investigator for each site." The phrase "for each protocol" creates confusion whether a single list is associated with the protocol when it really should be an individual list associated with each clinical investigation site.	BIO recommends deleting the phrase "for each protocol," so that the list be will clearly associated with each site and not the protocol. "~~For each protocol, a~~ A list of authorized data originators (i.e., persons, systems, devices, and instruments) should be co-developed and maintained by the sponsor and the investigator for each site."
Lines: 115-122	"The list should include unique identifiers (*e.g.*, user name or in the case of study subjects, a unique subject identification number) and the period of time for which data originator authorization was given. The list should be maintained to reflect staff changes that occur during the conduct of the investigation. The list should identify the systems, devices, and instruments that transmit data elements directly in the electronic case report form (eCRF). In the case of electronic patient diaries, the subject should be listed as the originator."	Please clarify whether the guidance applies to individual analytical instruments (*e.g.*, plate readers) that are housed in a central laboratory or if the guidance only applies to instruments at the clinical site. BIO suggests that the guidance should only apply to instruments at the clinical site.

SECTION	ISSUE	PROPOSED CHANGE
3. Data Element Identifiers		
Lines: 187-202	The use of individual data elements and tagging them with metadata represents one approach to capturing and representing data. It should not preclude the use of relational databases which underpin many existing eCRF commercial solutions.	Please clarify that the logical notion of tagging an individual data element with metadata may be implemented in a variety of manners and does not constrict the implementation of computerized systems to a system that physically stores each items of data as a unique element that aggregates data over its lifetime. Without such clarity, the tabular structure of many existing relational database models might be considered unacceptable to the Agency and, therefore, may discourage the capture of electronic source data until such systems are restructured.
B. DATA REVIEW		
1. Investigator		
Lines: 232-234	"[I]nvestigators should review and electronically sign the eCRF for each subject before the data are archived or submitted to FDA."	While this requirement is reasonable and expected for studies that are complete prior to sending data to FDA, the guidance does not address the many situations where interim data are used in submissions to the FDA where eCRFs have not been signed at the interim data lock of the study.
Lines:236-238	"Periodic review and electronic signing of the eCRF by the investigator during the conduct of the clinical investigation and evidence of this review should be contained in the audit trail."	Please clarify the acceptability of alternative approaches, such as periodic review and signing as subjects complete or discontinue, prematurely or otherwise, from the study, or periodic review notated in the audit trail, with a

SECTION	ISSUE	PROPOSED CHANGE
	Periodic review and electronic signing are not the current practice and there may be systems related limitations to the practice.	full electronic signature of the primary investigator at the end of the study, or an electronic signature which attests to the review of the complete eCRF.
D. DATA ACCESS		
Lines: 287-290	"We encourage viewing the data to allow early detection of study-related problems (*e.g.*, safety concerns, protocol violations and problems with conducting the study (*e.g.*, missing data, data discrepancies). Any interim analyses based on ongoing electronic review should be pre-specified in the protocol."	Please clarify if data review is being considered as data analysis; and if yes, to what detail need those analyses be described in the protocol.