Biotechnology Industry Organization

February 19, 2013

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

Re: Docket No. FDA–2012-D-1168: Draft Guidance for Industry on Providing Submissions in Electronic Format – Summary Level Clinical Site Data for Center for Drug Evaluation and Research's Inspection Planning; 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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the "Draft Guidance for Industry on Providing Submissions in Electronic Format – Summary Level Clinical Site Data for Center for Drug Evaluation and Research's Inspection Planning." BIO supports the release of this draft Guidance as FDA and Industry work together to implement the Prescription Drug User Fee Agreement (PDUFA) V Agreement (the Agreement).

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 the Agency's efforts to implement a risk-based approach to inspections, to plan inspections efficiently and effectively, and to meet PDUFA goal dates, which will be facilitated by the early submission of electronic summary level clinical site data to the Office of Scientific Investigations (OSI). The consistency, predictability, and clarity of data requests from OSI is essential as Sponsors prepare to provide complete clinical site information predicated under the PDUFA V New Molecular Entity (NME) Review Program.

In order to improve the efficiency of the drug review process, the PDUFA V Agreement sets a timeline for mandatory electronic submission and lays out a process for the development and adoption of the standards and format of the electronic submissions. BIO believes that PDUFA V governs OSI electronic data requests for selection of clinical sites for pre-approval inspections. Accordingly, the Notice and Guidance should reference the PDUFA V implementation timeframe and specify the required standards, formats, and specifications. Alternatively, this Guidance should be issued as an

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addendum to the recently released *Draft Guidance for Industry Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, issued in accordance with the Food and Drug Administration Safety and Innovation Act (FDASIA) (Pub. L. 112-144), which describes how FDA plans to implement the requirements for the electronic submission of applications for certain human pharmaceutical products.

BIO also believes that the requirement for specificity necessitates more than reference to the publication of a data standard on the FDA Data Standards Resources webpage. Reference to the FDA website for technical specifications documents and other resources that are subject to change without notice, not only undermines the intent and spirit of the PDUFA V Agreement, but also hinders the successful implementation of data standardization efforts by removing the security that comes with clear and transparent requirements and requests. Without such security, both industry and FDA are inhibited from undertaking long-term planning decisions and making the necessary technology investments that truly improve the efficiency of the review process.

It is BIO's understanding that OSI has developed a three part standard information request, which is currently distributed to Sponsors prior to, or during Pre-NDA/Pre-BLA meetings, and that this Guidance only addresses the third part of such request. BIO requests OSI make the standard information request publicly available, and address the voluntary nature of the request and its relationship to the PDUFA V Agreement. We also request FDA issue guidance on Parts I and II of the standard information request under the PDUFA V framework. Without the public release of the standard information request and associated formal guidance it is difficult for Sponsors to satisfy the requirements for submission of complete and timely clinical site information, electronically or otherwise, without incurring significant resource burdens.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Providing Submissions in Electronic Format – Summary Level Clinical Site Data for Center for Drug Evaluation and Research's Inspection Planning." Specific, detailed comments to the Guidance and the technical specifications, which are incorporated into the Guidance by reference, but not otherwise subject to a public review process, 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
Manager, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. DESCRIPTION OF SUMMARY LEVEL CLINICAL SITE DATASET		
Lines:113-114, 155-156	The cited specifications document is missing a version identifier. This is critical for industry to know when the specifications have changed and thus fulfill the commitments of the PDUFA V Agreement as discussed in the General Comments above.	Please cite a specific version of the referenced technical specifications document from within the Guidance or include the specifications within this Guidance document.
Lines: 113-114, 155-156	FDA is referencing internally generated ad-hoc specifications instead of leveraging industry standards developed in an open, consensus based standards development organization. This behavior burdens Sponsors by requiring duplicative information be submitted in multiple formats within the same application.	FDA should prioritize this work within the CDER Data Standards Program to advance industry recognized standards specifications so that the information can be submitted once in a consistent format in an application and FDA can effectively extract and use it for the multiple purposes they require. Once the required information is specified by industry standards and required by FDA for electronic submission in that industry standard format, all requirements to include the same information duplicatively in other parts of the application should be waived.

SECTION	ISSUE	PROPOSED CHANGE
V. CREATING AND SUBMITTING THE DATA FILE: "SPECIFICATIONS FOR PREPARING AND SUBMITTING SUMMARY LEVEL CLINICAL SITE DATA FOR CDER'S INSPECTION PLANNING"[1]		
Section II	It is unclear whether the values in the variable Treatment Efficacy Endpoint (TRTEFFE) should be simple summary statistics (mean, median, percent, count, etc.) for the efficacy endpoint. It is also unclear whether it is recognized and understood that these values would not necessarily be generated using the same statistical method as the primary statistical analysis as the site level data may not be sufficient to apply the formal statistical analysis method used for the entire study population.	Please include an additional statement in the draft Guidance clarifying that values in variable TRTEFFE should be simple summary statistics for the efficacy endpoint and that such values may be generating using statistical analysis tools applied to the entire study population.
Section II	We request clarity on how Sponsors should handle subjects that do not contribute data for the primary endpoint (*e.g.*, week twenty-four visit value is defined as primary and the subject discontinues prior to week twenty-four).	Please clarify.
Section II	In Section II Censored Observations (CENSOR) is described as "the number of censored observations for the given site and treatment," and Sponsors are directed to record the data element as missing if a study does not contain a time-to-event endpoint. In the Appendix variable index number 22 CENSOR is described	Please make the descriptions and associated directions of the variable CENSOR consistent.

[1] The Draft Guidance incorporates by reference the "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning," available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf).

SECTION	ISSUE	PROPOSED CHANGE
	as "number of censored observations given at a site by treatment arm," and Sponsors are directed enter -1 if the variable is not applicable.	
Appendix 1, Variables 29,30,31	It is a cumbersome effort to verify that the Investigator First, Middle and Last name in the Part III dataset matches character for character the name as reported on form 1572.	Please clarify if an exact character for character match is absolutely required for FDA analysis purposes or a small amount of variability is tolerable (such as difference between specifying a middle initial versus a middle name).
Appendix 1, Variables 27,28	Predicate regulations and ICH guidance specify limits above which financial disclosures are relevant to avoid significant expense of tracking insignificant amounts. Similar expectations should be specified for Maximum Financial Disclosure Amount (FINLMAX) & Financial Disclosure Amount (FINLDISC).	Recommend amending the instructions to include only those financial disclosures which are reportable following ICH guidelines.
Appendix 1	Many variables are requested that are not contained in the clinical database (see list below), and as such Sponsors will need to develop new processes and possibly Information Technology systems to gather these new data and combine with the clinical study data. Variables not contained in the clinical database: Study Title, Sponsor Number, IND Number, Under IND, NDA Number, BLA Number, Supplement Number, Maximum Financial Disclosure Amount, Financial Disclosure Amount, Investigator Phone Number, Investigator Fax Number, Investigator E-mail	

SECTION	ISSUE	PROPOSED CHANGE
	Address, State, City, Postal Code, Street Address	
Repeated references throughout the Guidance and accompanying technical specification	The description of which studies to include OSI data listings and datasets varies within the Guidance and the referenced specifications.	All references to "pivotal" should be defined similarly to the referenced specifications which target the "pivotal Phase 3" studies. Similarly, footnote 9 in the Guidance should be scoped to require additional OSI data submissions only if the new data is from a pivotal Phase 3 clinical study used to support the initial application.