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March 15, 2010

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

Re: FDA–2009–D–0605: Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: IRB Continuing Review After Clinical Investigation Approval

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the *Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: IRB Continuing Review After Clinical Investigation Approval.*

BIO represents more than 1,200 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

We have concerns that this guidance shifts the requirement of supplying study information to the Institutional Review Board (IRB) from the investigator to the sponsor, and does so by issuance of guidance rather than through a rulemaking process with opportunity to comment. The draft guidance fails to acknowledge that the primary interface with IRBs lies between the investigator and his or her IRB rather than the sponsor and the IRB. Further, current regulation as stated in 21 CFR 56 does not require that Sponsors provide information such as information on the test article, Data Monitoring Committee (DMC) reports, or information on the entire study to IRBs.

Additionally, this draft guidance would expand the role of the IRB to include technical and scientific assessments for which IRBs are not generally provided the resources or appropriate expertise to conduct. Further, expectations that individual IRBs engage in study oversight and data assessment undermines and conflicts with the role of Drug Monitoring and Safety Committees (DMCs), and other technical oversight Boards. We recommend that the guidance make a clear distinction of the roles of IRBs versus those of other oversight bodies such the DMC.

The draft guidance also does not clearly indicate the type of studies covered by the guidance. We recommend that the guidance clearly state that it is applicable to clinical investigations conducted under INDs, as opposed to observational studies. Further, the guidance does not provide specific language around the format, frequency, or content of reports that would be required to be submitted by Sponsors to IRBs under the draft guidance. This could result in individual IRBs receiving differing information from Sponsors responding to individual IRB requests and we recommend providing specific language for clarification.

SPECIFIC COMMENTS

BIO has provided specific comments on sections of the draft guidance in the chart below. In the left column of the table, we identify the page in the draft guidance; the next column contains the relative impact we view the item to have (C for a critical concern that must be addressed, M for a minor concern that should be addressed, and E for an editorial comment to the text); the next column contains BIO's comments and rationale to support our position; and the right column carries our suggested changes, where applicable. We would be pleased to provide further input or clarification of our comments, as needed.

*** Relative Impact** **C** = A critical concern that must be addressed
M = A minor concern that should be addressed
E = Editorial comment to text (change not necessarily required)

Specific Comments			
Citation Location Section/Page	**Relative Impact ***	**SPECIFIC Concern (short explanation)**	**Proposed Change / Suggestions for Rewording (if applicable)**
Pg1, Para 1	C	Please see general notes above	The paragraph should be reworded: "This draft guidance should also help clinical investigators and Sponsors better understand how they can support IRBs with performing their responsibilities."
2	C	The guidance summarizes the procedural aspects of the IRBs	Recommend incorporating the specific definition of IRB

		responsibilities but omits to state that the fundamental purpose of an IRB is to protect the rights and welfare of patients.	primary purpose from 21 CFR 56.102(g)
Pg 2, Para 3	C	It is not appropriate to provide regulatory specific documentation such as IND annual reports to IRBs. The purpose/content of IND annual reports goes beyond that of individual study continuing review. Such documents may cover multiple clinical studies covering multiple indications and investigational uses. Likewise such reports also document proprietary information pertaining to e.g. manufacturing/CMC information. FDA's statement that IRBs should obtain "reports for the entire study" is of concern to BIO. Sponsors already provide relevant documentation and data relating to safety and efficacy findings to investigators for IRB submission. Additional supporting documentation should be submitted annually or on an ad hoc basis dependent on new findings, or upon the specific request by an IRB. IRBs already express frustration at the high volume of data submitted to them for review. Providing redundant/duplicative data will not help or resolve existing IRB reviewing issues. Omit the term "reviewing" IRBs because this implies that certain IRBs may have a different role from others.	Recommend amending sentence as follows: "Sponsors of...are required by ...to submit annual reports to FDA...and should therefore be able to provide relevant periodic summary documentation to the IRBs.

Pg 3, Para 3	C	The Sponsor already submits information pertinent to the trial to the investigator (*e.g.*, memos regarding conduct of the trial, investigator brochure (IB), outcomes of DMC meetings). IRBs need to put in place processes to ensure that the investigator forwards this information to them in order to assist in the continuing review process. Again, we note that the primary point of contact for IRBs is the investigator. Sponsors do not typically communicate directly with IRBs. Please see our previous note on removal of the term "reviewing" IRBs. We request clarification that the guidance will apply only to studies conducted under the IND for investigational medicinal products, and not observational studies.	Suggest the following change "FDA recommends that information for review by IRBs be submitted by the Principal Investigators, provided by the study sponsor, to assist the IRB in conducting continuing review of research" [add CFR reference(s)] [1572] [21 CFR 56], and add the language, "These recommendations apply to studies conducted under the IND for investigational medicinal products. They do not apply to observational studies which are not conducted under an IND".
Pg 5	C	Sponsors already provide the latest IB, Protocol, and Informed Consent version when modified to the investigator for submission to the IRB. In addition Sponsors provide a summary of changes when requested. To avoid duplicative efforts we recommend that documents are not resubmitted when there are no further modifications. As noted previously the	Recommend revising the sentence as follows: "IRB should have the latest version of the IB, Protocol, and Informed Consent." Recommend the text be amended to distinguish responsibilities between the Investigator and IRBs, and to differentiate multi-site vs. single site studies.

		responsibility for providing documentation to the IRB lies with the investigator.	
Pg 5, Para 2	C	Observational studies do not require annual reports be provided by the sponsor to the FDA under 21 CFR 312.33. The current label that contains the most up to date information is currently required to be reported by Sponsors to study investigators conducting observational studies, and is sufficient.	Recommend adding the adding the additional language, "Sponsors of observational studies that are not conducted under an IND and therefore are not required to submit annual reports to FDA under 21 CFR 312.33, may provide the current label to the IRB".
Pg 5, 4th bullet	C	Please see our comments above. The provision of redundant/duplicative data should be avoided.	Recommend amending the text to: "the Investigator Brochure, if available, including any modifications, or notification there is no change to the last IB version."
Pg 5, 8th bullet	E	Please see our comments above relating to the role of the IRB (versus DMCs etc.). We note that the aggregate of subject withdrawals be provided for the total study, but the specific details of subject withdrawals be limited to that specific study site under the oversight of that particular IRB. The aggregate safety data including withdrawals for the overall study are reviewed by the DMCs.	Recommend amending the text to clarify summary withdrawal reports relevant to the specific site, and specific to safety.
Pg 5, 2nd paragraph	C	Please see our comments above. The provision of redundant/duplicative data should be avoided.	Recommend removing the paragraph: "Note that much of the above information is often included in annual reports prepared by study Sponsors. If the information is included in the annual report, the information

			may be provided by supplying the IRB with a copy of that report; a separate document need not be prepared." Recommend changing the word "reports" to "outcomes."
Pg 6	C	Please see note above. Sponsors typically provide information to the investigator to send to the IRB and do not interact directly with the IRB.	Recommend rewording text as follows: "For a multi-site study…that Sponsors provide investigators with pertinent information from the entire study such as: outcomes of DMC meetings…" Please also change "interim assessments of DMCs" to " interim outcomes of DMC meetings,"
Pg 6	M	It is not clear what FDA is recommending here. It is not common for an IRB to perform the initial review but delegate mid study to another IRB for continuing review purposes. Typically if there is a change in IRB for any reason, the new IRB does a complete initial review for approval and continues reviewing after this.	Recommend removing or clarifying the paragraph: "An IRB other than the IRB that conducted the initial review may perform continuing review of a study. However, an IRB that conducted the initial review may be best suited to conduct continuing review because of its familiarity with the study and/or previous review(s)."
Pg 6, Para 1	C	Clarification is needed that Sponsors are not required to undertake the responsibilities for Adverse Event reporting. Any change to regulatory requirements for notice to IRBs should be made through notice and comment rulemaking processes, not through issuance of guidance.	Recommend assuring there is no reference to the "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs-Improving Human Subject Protection" found in footnote 9.
7	C	Please see our notes above relating to provision of IND	Recommend removal of the text:

		annual reports and performance of technical safety analyses also conducted by DMCs, etc).	"…, including the sponsor's annual report, any analysis by the sponsor performed since then, …"
Pg 8, 2nd paragraph under item # 4	E	A distinction should be made between oversight of single site protocols and a multi-site protocols in terms of total number of subjects expected to be enrolled. A multi-site protocol would not contain site specific enrollment targets. Also, please see our note above relating to the role of individual IRBs' responsibilities for their own individual sites compared with the totality of the sites/study. We request that FDA provide clarification.	Recommend text is amended to provide clarity that recruitment review pertains to an individual site under the purview of that IRB i.e. 'their' particular site. Recommend amending the text as follows: "…more than the number allowed at that site…more than the protocol as submitted to the FDA." Replace "protocol" with "approval"
8-9	C	A proposal for scheduling should not be mandatory just because a drug produces psychoactive effects. Currently, there are psychoactive substances which are not scheduled.	Recommend revising or removing statements regarding the following IRB responsibilities: a) IRB analysis of viability of meeting study objectives based on enrollment rate at a study level, b) assessing justification to continue exposure to test article, as there would not be sufficient data to answer scientific question.
9	C	Please see our general comments above.	Recommend amending the text to address IRB responsibility at a local level, *i.e.*, low enrollment issues at the local site level.
9	C	Please see our General Comments above. Reassessment of the study to determine if the data are sufficient is not within the remit or expertise of an	Recommend removal of following paragraph: "Once the enrollment goals for the study have been reached, the study should be reassessed to

		individual IRB. This type of analysis/assessment is done by a DMC and/or steering committee in conjunction with a sponsor.	determine if data are indeed sufficient to answer the scientific question raised by the study. A sponsor is prohibited from unduly prolonging a study if the results of the investigation appear to establish sufficient data to support a marketing application."
10	E	The Sponsor typically drives the determination of when sites may be closed as there may be specific closure activities required of an investigator prior to this occurring.	Recommend clarifying that the final paragraph, regarding how to close out a study at particular sites, applies to the sponsor of the trial rather than the IRB.
15	C	Prompt notification to the Sponsor is important not only to ensure the Sponsor can meet its (global) regulatory reporting obligations but also so that it can work with the investigator to either transfer subjects to another site in the local area, find a replacement Principal Investigator at the site or ensure that the trial is terminated in an orderly manner.	Recommend that the Sponsor be added to the list of those notified promptly of study suspension or termination by the IRB.

Conclusion

Thank you for this opportunity to comment on the Guidance for Industry, IRB Continuing Review After Clinical Investigation Approval. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Sara Radcliffe

Vice President, Science & Regulatory Affairs

The Biotechnology Industry Organization (BIO)

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