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November 28, 2011

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

Re: Docket No. FDA–2011-D-0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring; Availability

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring."

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 goals of the guidance to assist sponsors of clinical investigations in developing risk-based monitoring strategies and to enhance human subject protection and the quality of clinical trial data. Biotechnology companies are at the forefront of biomedical innovation and welcome proposed strategies for monitoring activities that will assist them in conducting clinical investigations in a more modern, risk-based manner.

As an active member of the Clinical Trials Transformation Initiative (CTTI), BIO commends the work that the Agency and CTTI have done to survey current monitoring practices while compiling recommendations. BIO looks forward to continuing to

articulate and build support for these concepts through CTTI and among clinical trial stakeholders, including industry, contract research organizations, academia, and regulators.

Approaches such as centralized clinical trial monitoring and a focus on the most critical data elements can help Sponsors and FDA to deploy resources to the areas that will best promote the integrity and quality of clinical trial data. Conceptually, the approaches detailed in the guidance should enhance the efficiency and effectiveness of clinical trial monitoring, but great care should be taken in implementation of these approaches to reduce the potential for duplicative or burdensome monitoring requirements.

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring." 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
II. BACKGROUND		
Line: 134	"as long as the adequacy of the scientific evidence can be assured."	We recommend clarifying and elaborating on this statement.
Lines: 156-158	"Several publications suggest that data anomalies (e.g., fraud, including fabrication of data, and other non-random data distributions) may be more readily detected by centralized monitoring techniques than by on-site monitoring."	We request that the Agency provide examples of centralized monitoring techniques to identify data anomalies. We also recommend that the Agency include language stating that sponsors should establish criteria for on-site monitoring. These criteria and examples should clarify the expectation that Industry would provide to the regulatory agencies a detailed monitoring plan, including type of monitoring; intervals in which it would occur; and exact data to be monitored, and would reach agreement with the agencies on the outlined plan before the study begins enrolling patients. It is also the expectation that the Agency and industry would agree on data that would be inspected at a site visit, as this would potentially affect the monitoring plan, to assure that expectations between industry and regulatory agencies are clear.
Lines : 182-183	"Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans…"	While BIO agrees that a process for sponsors to prospectively submit a detailed monitoring plan should be established within CDER, we request that the Agency include a clearer definition and explanation of what will be the focus and intent of CDER's review. In addition, for this review to be a value added exercise for both CDER and sponsors, it would be beneficial to have CDER staff in the reviewing position that had previous experience at sites with monitoring.

III. FACTORS THAT INFLUENCE STUDY QUALITY AND INTEGRITY		
Lines : 245-248	"On-site monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate delegation of study tasks, and appropriate investigator supervision of site staff performing critical study functions)." Informed consent by the subject may be implicit in the sentence that begins on line 242 that states: "… provide assurance that study documentation exists…"	We believe that informed consent should be explicitly included in this list. Equally, in the list of tasks that can be performed remotely, remote training could be included.
Lines: 249-251	"Therefore, on-site monitoring ordinarily should be devoted to assessing the critical study data and processes and evaluating significant risks and potential site non-compliance identified through other sponsor oversight activities."	In addition, on site monitoring should be used to assess critical study data that cannot be assessed remotely (such as valid consent and appropriate consent procedures).
Lines: 258-260	Centralized monitoring is defined beginning on line 258: "Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) at which the clinical investigation is being conducted."	We believe that the Agency needs to be clear about the intent of the centralized monitoring. Additionally, we suggest additional wording: "Centralized monitoring could be considered to ensure more timely feedback and identification of protocol deviators and completeness and accuracy of data. It also allows identification of issues at sites."
Lines: 271-276	"Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data	Data management, clinical science, and other functions may be well placed to facilitate the analysis of data trends. We suggest including the following:

	trends not easily detected by on-site monitoring)" and "Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at a site"	"Data management, clinical science, and other functions may be able to facilitate this type of process working with a centralized monitoring group."
Lines: 277	"Verify source data remotely, provided that both source data…"	We suggest rewording the statement to read: "Verify CRF data from source data remotely, provided that both source data and CRFs can be accessed remotely."
Lines: 279-280	"Conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness"	We suggest changing the statement to read: ~~"Conduct aggregate statistical analyses of study data to~~ Identify sites that are outliers by evaluating the site data statistically ~~relative to others and to evaluate individual subject data for plausibility and completeness~~."
Lines: 322-323	"A sponsor's monitoring activities should focus on these critical measurements and on preventing important and likely sources of error in their collection and reporting."	We suggest editing the statement to read: "A sponsor's Monitoring Plan should focus on these critical measurements and on preventing important and likely sources of error in their collection and reporting of study data."
Lines: 353-355	"…versus targeted or random review of certain data (less than 100% data verification) of monitoring activities will depend to some extent on a range of factors, considered during the risk assessment, including the following"	The phrase "considered during the risk assessment" is redundant per lines 350 and 351: "A monitoring plan ordinarily should focus on the critical data and processes identified by the risk assessment." We suggest deleting "considered during the risk assessment" so the statement reads: "…versus targeted or random review of certain data (less than 100%

		data verification) of monitoring activities will depend to some extent on a range of factors ~~considered during the risk assessment,~~ including the following."
Lines: 375-377	"Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established…"	Please add "where" so the statement reads: "Sites in geographic areas where there are differences in standards of medical practice or subject demographics, or where there is a less established…"
Lines: 375-377	"Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established clinical trial infrastructure may require more intensive monitoring, including some level of on-site monitoring."	We request the statement be edited to read: "Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established clinical trial infrastructure may require more intensive monitoring, including a greater level of on-site monitoring."
Lines: 422-423	"For example, if it is determined that an investigator deviates significantly from other sites in making safety-related findings or other key safety metrics, the site should be considered for targeted on-site visits. …"	Investigators do not deviate from sites, but rather from other investigators. We request the statement be edited to read: "For example, if the safety findings at a particular site deviate significantly from safety findings at other sites, a targeted on-site monitoring visit to the outlier site should be considered."
Lines: 427-428	"Identification of possible deviations or failures that would be critical to study integrity and how these are to be recorded and reported"	This is unclear. Would this include failures and/or errors? Please provide clarification. We suggest adding the following text: "Any site that has been identified to be collecting information that in any way adversely affects the study integrity would need a full evaluation. The results of this evaluation would need to be collated and reported."
Lines: 433-434	"The study monitoring plan should also describe how various monitoring activities will be documented, regardless of whether	We suggest changing "centralized" to "centrally" so the statement reads:

	conducted on-site or centralized.”	"The study monitoring plan should also describe how various monitoring activities will be documented, regardless of whether conducted on-site or centrally."
Lines: 493-496	“Sponsors should consider what events may require review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity, could result in a change to the monitoring plan.”	We agree that the sponsor needs specific ways to alter a monitoring plan after a study is underway. We suggest that CDER also needs a process to review and approve such changes in an expedited manner.
V. DOCUMENTING MONITORING ACTIVITIES		
Lines: 510-511	“Monitoring documentation should be provided to appropriate management in a timely manner for review or, as necessary, follow-up.”	Please remove “as necessary” so the statement reads as follows: "Monitoring documentation should be provided to appropriate management in a timely manner for review or~~, as necessary~~ follow-up."