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November 28, 2011

FDA Dockets Management Branch (HFA305)
Food & Drug Administration
5630Fishers Lane
Rockville, MD 20852

Docket No. FDA-2011-D-0597: Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring

Dear Sir or Madam

Please find attached comments from Novartis Pharmaceuticals Corporation ("Novartis") on the Food and Drug Administration (FDA) **Draft Guidance for Industry on Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring.**

Overall, Novartis fully supports and commends FDA on recognizing the value of alternative monitoring approaches and proposing a risk-adapted Monitoring Plan to determine the intensity, frequency and focus/scope of the monitoring activities, while ensuring patient protection, protocol and regulatory adherence, as well as data accuracy and integrity. Novartis has implemented risk-based monitoring approaches, as appropriate, for its trials and finds this Draft Guidance important and timely.

Novartis appreciates the opportunity to provide comments and respectfully requests that consideration be given to our comments and recommendations.

Kind regards,

Nancy Hutchinson, PhD
Head Drug Regulatory Affairs
- North America

Attachment

Submission of Comments For:

FDA Draft Guidance: Oversight of Clinical Trials - A Risk Based Approach to Monitoring

Comments Submitted by: Novartis Pharmaceuticals Corporation

Specific Comments		
Section / Line #	**Proposed content (regulation/guidance)**	**Novartis Comments**
I. Introduction ***(Lines 21-24)***	***"This guidance is intended to make clear that sponsors can use a variety of approaches to fulfill their responsibilities related to monitoring investigator conduct and the progress of investigational new drug (IND) or investigational device exemption (IDE) studies."***	It is suggested that the guidance be made applicable to any trial submitted to FDA. The Guidance specifically makes reference to IND and IDE clinical trials; however, there are many trials that are performed at the request of FDA as post approval trials. These studies are typically performed with a dose and patient population that is consistent with the approved labeling and as per the IND regulations would not meet the definition of investigational use of a drug, however maybe submitted to the IND.
II. D. Steps FDA is Taking to facilitate Wider Use of Alternative Monitoring Approaches ***(Lines 176-181)***	• ***"Will ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM 7348.810) and for clinical investigators and sponsor-investigators (CPGM 7348.811) are compatible with the approaches described in this guidance*** • ***"Will ensure that all affected program areas within FDA are aware of the goals and purposes of this guidance and its compatibility with current CPGMs"***	Sponsors that have already begun to employ alternative monitoring approaches often have questions raised during FDA inspections because these processes deviate from the "traditional" approach to monitoring. Therefore, it would be helpful for the Guidance to outline the additional changes and communications that will be made by FDA to ensure the FDA inspection program is in alignment with this the final Guidance. Defining/committing to timeframes for implementing these additional changes and communications with respect to the finalization of the guidance would help to facilitate more robust and seamless implementation by sponsors and FDA.

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IV. A. 2. Centralized Monitoring ***(Line 286-289)***	***"FDA encourages greater reliance on centralized monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring. The extent to which centralized monitoring practices can be employed will depend to some extent on accessibility of electronic records and EDC systems."***	Novartis agrees with the concept of greater reliance on central monitoring activities along with reduced on-site monitoring. However, recognizing the privacy issues related to accessing electronic medical records that would be need to be addressed to verify patient source data against the submitted information, it may be helpful to denote that the use of "centralized monitoring practices" to conduct remote source data verification (SDV) may not always be feasible. Thus on-site monitoring may still be required in most instances to confirm the accuracy, and identification, of any deviations that would primarily be found during the review of patient source data. The same would also be true for the verification of informed consent forms since they also contain personally identifiable medical information.
II. D. Steps FDA is Taking to facilitate Wider Use of Alternative Monitoring Approaches ***(Lines 182-184)*** ***and*** **IV. D. 4. Training and Study-Specific Information**	***"Will consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans (see section IV.D.4). Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH's Division of Bioresearch Monitoring."*** ***"CDER intends to evaluate potential processes through which sponsors could***	Novartis supports the FDA proposal to establish processes for sponsors to submit and obtain the review of proposed alternative monitoring plans based on a risk based approach, and recommends that a mechanism and/or guidance include provisions that allow the sponsor to submit, discuss and obtain feedback on detailed, protocol-specific risk based monitoring plans. This process should also be applicable for any significant revisions to an existing risk based monitoring plan.

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(Lines 487-489)	***voluntarily submit their monitoring plans to the appropriate review division and request feedback from the clinical trial oversight component for the Center."***	
IV. D. 1. Description of Monitoring Approaches ***(Line 420-421)***	***"Definitions of events or results that trigger changes in planned monitoring activities for a particular clinical investigator."***	The use of tolerance ranges or establishing acceptable variations has not been addressed in this Guidance document. It is recommended that tolerance ranges be established "per protocol" for trial procedures and data (based on statistical components). These in turn would act as a "trigger" to initiate increased monitoring activities. These Tolerance ranges have been proposed by the EMA (Draft EMA Reflection Paper on Risk Based Quality Management in Clinical Trials, dated 14 June 2011.
IV. D. Monitoring Plan **(Lines 436-460)**	***"2. Communication of Monitoring Results"*** ***and*** ***"3. Management of Noncompliance"***	Since many of the components of the monitoring plan recommendations in these two sections are often addressed in applicable Sponsor SOPs and written processes related to monitoring activities, it may be helpful to denote that these recommended components of the monitoring plan can be addressed within individual study monitoring plans or, more generally, in related sponsor SOPs or other written general monitoring processes.
III. D. 4. Training and	***"A monitoring plan may reference***	It is suggested that a statement be added denoting that if the sponsor

Study Specific Information *(Lines 482-485)*	***existing policies and procedures (e.g., a standard operating procedure describing issue investigation and resolution). In this case, the sponsor should take appropriate steps to ensure that monitors, whether sponsor or CRO employees, are aware of and are trained on these policies and procedures as well as on the monitoring plan."***	proposes to use the CRO's procedures, the sponsor should review and agree to the adequacy of those procedures prior to use
V. Documenting Monitoring Activities *(Line 501)*	***"Documentation of monitoring activities should include the following:*** • ***The date of the activity and the individual(s) conducting it*** • ***A summary of the data or activities reviewed*** • ***A description of any noncompliance, potential noncompliance, data irregularities, deficiencies identified*** • ***A description of any actions taken, to be taken, and/or recommended, including responsible for completing actions and the anticipated date of completion"***	The section for documenting monitoring activities appears to be focused on the typical "on-site" methods of monitoring. When using the "central" or "remote" monitoring method, we recommend the acknowledgement that the use of alternative electronic or automated documentation methods; to demonstrate and document data review activities and follow up actions should be acceptable provided they meet appropriate controls regarding access, back up and audit trails, which will ensure the data integrity and ability to retrieve the information using validated systems. Also since FDA inspectors are required to review monitoring logs during pre-approval inspections, the guidance should include a recommendation that both on-site monitoring and centralized monitoring activities are documented in some form of monitoring log.