November 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: FDA Draft Guidance for Industry on "Oversight of Clinical Investigations: A Risk-based Approach to Monitoring" [Docket No. FDA–2011–D–0597]

Dear Sir/Madam:

Pfizer Inc is providing comments on the FDA (Agency) draft guidance for industry on *Oversight of Clinical Investigations: A Risk-based Approach to Monitoring* that was published in the *Federal Register* of August 29, 2011 (76 Fed. Reg. 53683-53685).

We appreciate the opportunity to comment on this draft guidance and trust that the Agency will take these comments into consideration. Accordingly, please refer to the attached table of comments/recommendations.

Please do not hesitate to contact the undersigned if there are any questions or if clarification is needed.

Sincerely,

Lorraine Waring
Senior Director, Site Monitoring Process Owner
Pfizer Inc
860 441 3072

Attachment

November 28, 2011

SUBMISSION OF COMMENTS ON FDA DRAFT GUIDANCE ON "OVERSIGHT OF CLINICAL INVESTIGATIONS: A RISK-BASED APPROACH TO MONITORING" [DOCKET NO. FDA–2011–D–0597]

COMMENTS FROM: PFIZER INC

1. GENERAL COMMENTS

Pfizer appreciates the issuance of this draft guidance. We agree with the concept of a risk-based approach to monitoring and have utilized centralized monitoring methods where appropriate. However, we believe the final guidance should include specific guidance on the development and utilization of a risk assessment plan, which is the cornerstone of utilizing a risk-based approach, and include appropriate examples of risk mitigation. The inclusion of risk management tools and examples, along with potential applications for using risk-based monitoring strategies would help facilitate the implementation of such risk-based approaches and further ensure that expectations are consistent amongst all stakeholders. In addition, although we support the use of centralized monitoring methods, Pfizer believes that the final guidance should give equal emphasis to the fact that other monitoring methods may also be appropriate, and should also not create any new expectations for monitoring beyond what is required under current regulations.

Pfizer also agrees with FDA's position "encourag[ing] sponsors to tailor monitoring plans to the needs of the trial"[1] and believes that the final guidance should continue to emphasize that monitoring plans be tailored to the needs of the trial, taking into account the study phase and experience of the sponsor with the study drug. Consistent with the principles of quality risk management,[2] sponsors should be encouraged to use monitoring approaches commensurate with the perceived level of risk. The final guidance should also recognize that other factors should also be considered with regards to using on-site monitoring or centralized monitoring or a combination thereof for a particular clinical trial, including the availability and accessibility of appropriate technologies to both sponsors and investigators, and the applicability of any local laws (including privacy laws) and regulatory requirements.

[1] FDA, Draft, Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, Aug. 2011, at ln. 188-89, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf.

[2] FDA, Guidance for Industry: Q9 Quality Risk Management, June 2006, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf.

2. SPECIFIC COMMENTS ON TEXT

Line Number(s)	Comment and Rationale	Proposed change (if applicable)
66-71	The draft guidance states: "We are aware that the term *monitoring* is used in different ways in the clinical trial context. It can refer to the assessment of clinical investigator conduct, oversight, and reporting of findings of a clinical trial; the ongoing evaluation of safety data and the emerging risk-benefit profile of an investigational product by a medical monitor; and the monitoring of internal sponsor and CRO processes and systems integral to proposing, designing, performing, recording, supervising, reviewing, or reporting clinical investigations." For completeness, we would recommend the inclusion of data-management and statistics, since these groups may also be involved in the monitoring of clinical data, e.g., with regards to data capture and interim data analyses, depending on the monitoring plan.	"…It can refer to the assessment of clinical investigator conduct, oversight, and reporting of findings of a clinical trial; ***the review of clinical trial data by data management personnel or a statistician in connection with data capture activities or an interim data analysis***; the ongoing evaluation of safety data and the emerging risk-benefit profile of an investigational product by a medical monitor…"
156-159	It would be useful to add examples of the use of centralized monitoring versus on-site monitoring and their potential outcome (e.g., the use of centralized monitoring to perform statistical analyses to identify data trends) in addition to footnoting the three publications suggesting that data anomalies may be more readily detected by centralized monitoring than by on-site monitoring.	
159-163	With regards to centralized monitoring and electronic data capture (EDC), please provide examples or references on how "both trial data and source data" [e.g., informed consent, medical histories] "typically become part of the central submission."	
176-179 and 182-184	This section describes steps that the Agency is taking to facilitate the wider use of alternative monitoring approaches. Please clarify the timing for the following steps:	In the meantime, we encourage the Agency to work proactively with sponsors and other stakeholders on the development and implementation of risk-based monitoring plans, when appropriate.

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	• "[FDA] [w]ill 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." • "[FDA] [w]ill consider establishing processes within CDER for sponsors to voluntarily and prospectively submit and receive feedback on proposed monitoring plans…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."	
192-196	The draft guidance states: "FDA believes it is reasonable to conclude that the flexibility described in ICH E6 was intended to permit innovative new approaches to improve the effectiveness of monitoring: notably, the advancement in EDC systems enabling centralized access to both trial and source data and the growing appreciation of the ability of statistical assessments to identify clinical sites that require additional training and/or monitoring." Please clarify the expectations regarding the capturing of source data by EDC as mentioned above. Specifically, the final guidance should recognize that the remote capture and monitoring of source data is only possible when the original record (or a certified copy thereof) is initially captured electronically and in accordance with local privacy laws and requirements.	"…notably, the advancement in EDC systems enabling centralized access to ***the original records or certified copies*** of both trial and source data***, where appropriate and in accordance with local laws and requirements***…"
205-209	The draft guidance states: "The most important tool for ensuring human subject protection and high-quality data is a well-designed and articulated protocol." However, the next sentence introduces a second tool, *the case report form (CRF)*, along with the *protocol* as documents that "may introduce systemic errors" if they are "poorly designed or ambiguous." For consistency with the second sentence, we suggest that the first sentence be	"~~The most~~ ***Two*** important tool***s*** for ensuring human subject protection and high-quality data ~~is~~ ***are*** a well-designed and articulated protocol ***and case report form (CRF)***. ***When these documents are*** poorly designed or ambiguous***, they*** may introduce systemic errors…"

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	modified to reference the CRF too.	
251-253	It may be helpful to clarify the term *early* or provide examples, with regards to the sentence, "On-site monitoring is particularly critical early in a study, especially if the protocol is complex, and includes novel procedures with which investigators may be unfamiliar."	"…early ***(as determined by the risk assessment and study complexity)***…"
258-260	The draft guidance states: "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." For clarity, we suggest the use of the qualifying term *assigned* since the personnel may vary depending on the monitoring plan, and placing *clinical monitors* before *data management personnel, statisticians* since that may represent a more logical progression.	Centralized monitoring is a remote evaluation carried out by ***assigned*** sponsor personnel or representatives (e.g., ***clinical monitors,*** data management personnel, ***and/or*** statisticians, ***etc.***~~, or clinical monitors~~) at a location other than the site(s) at which the clinical investigation is being conducted."
277-278	Among other points the draft guidance states: "Centralized monitoring processes should be used to the extent appropriate and feasible to achieve the following:" • "Verify source data remotely, provided that both source data and CRFs can be accessed remotely" We suggest emphasizing that this scenario would generally be an exception, since it is presently uncommon for source data such as signed informed consents and/or medical records to be accessible remotely for clinical trials. Also, for global studies, remote access of source data may not be permitted due to local privacy laws and requirements.	• "Verify source data remotely, ***provided that both*** source data and CRFs can be accessed remotely***, and in accordance with local privacy laws and requirements***."
297	This section introduces the term *risk assessment* with regards to clinical monitoring. We recommend that the FDA issue additional draft guidance for comment regarding the Agency's expectations and recommendations for	We propose that the final guidance should include a detailed appendix, providing guidance on risk factors and risk adaptive approaches, and recommend that the draft appendix

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	developing and implementing such risk assessments. We suggest the introduction of risk assessment much earlier in this guidance which would then frame the discussion of appropriate monitoring approaches that could be used to mitigate the identified risks. We would also suggest adding an appendix providing further detailed guidance on items to consider in the development of a risk assessment; similar to the October 2011 Medicines and Healthcare products Regulatory Agency (MHRA) paper on risk-based approaches.[3] In the spirit of global harmonization with respect to clinical trial monitoring processes, we would also encourage coordinating approaches with the guidance provided by the MHRA, where possible.	should be released for public comment and stakeholder input.
302-306	The draft guidance states: "Sponsors should consider the findings of the risk assessment when developing a monitoring plan. There is increasing recognition that some types of errors in a clinical trial are more important than others. .., a low, but non-zero rate of errors in capturing certain baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will not, in general, have a significant effect on study results." These examples may be better understood in context of a late phase non-interventional study. For additional clarity, can the Agency provide some examples and/or cited references concerning the "increasing recognition that some types of errors in a clinical trial are more important than others"?	
348	An additional factor to consider when developing a monitoring plan is *prior clinical experience with the investigational product and the phase of clinical development*. For example, the use of a centralized monitoring approach for phase IV trials.	Propose expansion of this section to add prior clinical experience with the investigational product as a factor.

[3] MHRA, MRC/DH/MHRA Joint Project: Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products, Oct. 10, 2011, at 6-18, available at http://www.mhra.gov.uk/home/groups/l-ctu/documents/websiteresources/con111784.pdf.

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357	With regards to the *complexity of the study design* as a factor to consider when developing a monitoring plan, examples are provided of studies that may require more intensive monitoring approaches (e.g., *increased frequency of review and/or multiple monitoring approaches*). For further clarity with regards to utilizing a risk-based approach towards monitoring, examples of studies where less intensive monitoring approaches may be appropriate would also be useful. Possible examples include non-complex studies utilizing a conventional study design (while taking into account the other factors to be considered) and phase IV non-interventional studies.	
407-410	The draft guidance states: "All sponsor and CRO personnel who may be involved with monitoring, including those who review and/or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan." Rather than *All* Sponsor and CRO personnel, we believe the scope should be limited to protocol specific personnel only i.e., "**are** involved" rather than "**may be** involved". In addition, clarity is requested regarding the phrase "should review the monitoring plan." Is the Agency referring to familiarity with one's assigned responsibilities under a monitoring plan versus a review of the entire monitoring plan by all involved Sponsor and CRO personnel, regardless of their assigned roles?	
487-489	The draft guidance states: "CDER intends to evaluate potential processes through which sponsors could voluntarily submit their monitoring plans to the appropriate review division and request feedback from the clinical trial oversight component for the Center."	As mentioned earlier, we encourage the Agency to work proactively with sponsors and other stakeholders on the development and implementation of risk-based monitoring plans, when appropriate.