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Clinical Research Regulatory Update:

FDA Proposes Updates To Informed Consent Regulations, Issues Guidance On IRB Continuing Review

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The U.S. Food and Drug Administration (**"FDA"**) continues to focus on clinical research activities. In this regard, FDA recently has taken two additional actions to regulate the conduct of clinical trials: (1) publishing a proposed rule updating informed consent regulations; and (2) issuing a draft guidance addressing Institutional Review Board (**"IRB"**) continuing review requirements. This Client Alert provides a high level summary of these recent FDA regulatory developments in the clinical research area.

Sponsors, IRBs, investigators, and clinical research institutions will want to evaluate the potential impact of these recent FDA actions on their operations and review and update policies and template documents as needed. These entities also have the opportunity to comment on both the proposed rule (by March 1, 2010) and draft guidance (by March 15, 2010).

I. Proposed Rule Amending Informed Consent Regulations

On December 29, 2009, FDA released a proposed rule that would amend the informed consent requirements in 21 C.F.R. §50.25(a) to require, for the first time, informed consent documents to disclose that the clinical trial has been or will be registered and the results will be published in the National Institutes of Health/National Library of Medicine clinical trials database (www.clinicaltrials.gov).[1] (**The "Proposed Rule."**)[2] **Public comments on the Proposed Rule must be received by March 1, 2010.**

More specifically, if finalized, the Proposed Rule would require the inclusion of specific disclosure language to be included verbatim in the informed consent document:

> Information, that does not include personally identifiable information, concerning this clinical trial has been or will be submitted, at the appropriate and required time, to the government operated clinical trial registry data bank, which contains registration, results,

> and other information about registered clinical trials. This data bank can be accessed by you and the general public at www.ClinicalTrials.gov. Federal law requires clinical trial information for certain clinical trials to be submitted to the data bank.

Although additional information regarding the clinical trials registry may be included, the required disclosure may not be altered.[3]

The Proposed Rule is intended to satisfy a mandate in the Food and Drug Administration Amendments Act of 2007 (**"FDAAA"**), which requires FDA to update its informed consent regulations "to require that the informed consent documents and processes for certain clinical investigations include a statement that clinical trial information for such investigations has been or will be submitted for inclusion in the clinical trial registry databank."[4] Of note, this particular provision of FDAAA amended Section 505(i) of the Federal Food, Drug, and Cosmetic Act (**"FDCA"**) which applies only to *new drugs*; it did not include a similar amendment to provisions of the FDCA relating to *investigational medical devices*.[5] Nonetheless, the Proposed Rule would amend the informed consent regulations so that these new requirements are applicable to clinical trials of investigational drugs, biologics and medical devices. FDA justified the application to medical device clinical trials, stating that: "[h]uman subject protection applies to all clinical trials, regardless of the type of treatment being studied, and FDA can find no justification for a scheme that would result in device trials having different or lesser requirements for human subject protection and informed consent."[6]

Affected entities engaged in clinical research should monitor the progress of the Proposed Rule and any guidance or final rules that are issued. Further, this Proposed Rule represents just one step in the ultimate implementation of the FDAAA's requirements for registering clinical trials and reporting clinical trial results.

II. Draft Guidance on IRB Continuing Review

On January 13, 2010, FDA released a draft guidance entitled, "Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval" (**"Draft Guidance"**).[7] The Draft Guidance addresses the continuing review obligations of an IRB set forth at 21 CFR § 56.109(f).[8] When final, the Draft Guidance is intended to supersede previous guidance set forth in the Information Sheet, "Continuing Review After Study Approval"[9] (September 1998, Office of Health Affairs, Food and Drug Administration). ***Comments on the Draft Guidance are due by March 15, 2010.***

The Draft Guidance describes the applicable standard for continuing review and includes detailed recommendations for the processes IRBs should employ to fulfill continuing review obligations. It also addresses sponsors' role in continuing review and with respect to providing relevant and complete information to IRBs to aid in their reviews. We summarize below some of the key parts of the Draft Guidance; however, entities engaged in clinical research should review the entire Draft Guidance carefully to assess the particular impact on their operations.

The Draft Guidance outlines the criteria applicable to an IRB's continuing review of an

ongoing clinical trial. At a high level, an IRB should determine whether any new information is available that would affect the IRB's prior finding that the research meets each of the criteria required for initial approval.[10] More specifically, continuing review should include an assessment of any changes in the study that may impact the risks and anticipated benefits of the study, the adequacy of the process for obtaining informed consent, any local issues applicable to the study, and the progress of the study.[11] The informed consent document currently in use should be reviewed to confirm that it is the most recently approved version, that it contains each of the necessary elements of informed consent, and that it has been appropriately updated to address any new information that has been obtained. The IRB may determine that human subjects need to be provided with additional information as a result of this review.[12]

Consistent with past FDA guidance, the Draft Guidance expressly endorses the use of cooperative review arrangements and other mechanisms for sharing continuing review obligations when multiple IRBs are responsible for review of a single study. It emphasizes, however, the need for each IRB to obtain and review information from across the study, not only from a single site.[13]

Importantly, according to the Draft Guidance, sponsors are in the best position to provide study-wide information to IRBs; therefore, sponsors of multi-center clinical trials should provide reviewing IRBs with the information necessary to fulfill their continuing review obligations. In some cases, this information could be in the form of the sponsor's annual report to FDA. However, the Draft Guidance also includes a list of materials that IRBs should obtain and consider in performing continuing review. This list, which expands upon the list in comparable Office for Human Research Protections (**"OHRP"**) guidance,[14] may include more information than is currently reviewed by some IRBs during continuing review. It includes:

- the version of the protocol and informed consent document(s) in use at the site;
- any proposed modifications to the protocol and/or informed consent document;
- a written summary, if available, of amendments to the research since the last review;
- the Investigator's Brochure, if available, including any modifications;
- any new and relevant information, published or unpublished, especially information about risks associated with the research; for example, a summary of any unanticipated problems and available information regarding adverse events;
- aggregate information about relevant regulatory actions occurring during the past year that could affect safety and risk assessments (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls and device disposition required by 21 CFR 812.150(b)(6));
- any other significant information, such as reports from data monitoring committees (DMCs), if available;
- a summary of any subject withdrawals from the research since the last IRB review; and
- a summary of any complaints about the research from subjects enrolled at the local site since the last IRB review.[15]

The Draft Guidance also addresses the frequency of continuing review and the IRB's obligation to determine, based on the degree of risk of the study, whether review more frequently than annually is required. The Draft Guidance recommends the factors that should be considered in determining whether more frequent review is necessary and suggests that the frequency of review may require adjustment as a result of the outcome of the continuing review.[16] Notably, the Draft Guidance expressly states that the review of a protocol amendment following study approval does not constitute a full review of the research that would permit an extension of the date for the next continuing review.[17] Furthermore, continuing review should occur at a convened meeting of the IRB, unless the study involves no more than minimal risk and specifically qualifies for expedited review.[18] The Draft Guidance provides recommendations for determining whether expedited review is appropriate.

Finally, the Draft Guidance addresses lapse, suspension and termination of IRB approval. For example, although a lapse of IRB approval does not constitute a suspension or termination that must be reported to FDA, a failure of an investigator to meet continuing review obligations may be grounds for such a suspension or termination.[19] The Draft Guidance recommends that when IRB approval of a study lapses, the reviewing IRB should document the reason why the lapse occurred and the corrective actions undertaken to prevent future lapses.

In all, the recommendations in the Draft Guidance demonstrate FDA's heightened expectations for the depth of continuing review of ongoing research by IRBs that are likely to impact IRBs, sponsors, investigators and institutions engaged in clinical research activities. These entities should consider reviewing their policies and procedures to ensure that they have the recommended policies and procedures in place and that those procedures are consistent with FDA's expectations as set forth in the Draft Guidance. These same entities also may wish to file public comments, where appropriate.

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This Client Alert was authored by Amy Dow, Leah Kendall and Lee Rosebush. For additional information about the issues discussed in this Client Alert, please contact one of the authors or contributors or the EpsteinBeckerGreen attorney who regularly handles your legal matters.

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ENDNOTES:

[1] 74 Fed. Reg. at 68,753.

[2] 74 Fed. Reg. at 68,750.

[3] 74 Fed. Reg. at 68,756.

[4] 74 Fed. Reg. at 68,750. Section 801(b)(3)(A) of FDAAA amended section 505(i) of the Federal Food, Drug, and Cosmetic Act **("FDCA").** Section 505(i) of the FDCA is codified at 21 U.S.C. §355(i).

[5] 74 Fed. Reg. at 68,751. Section 520(g) of the FDCA is codified at 21 U.S.C. §360j(g).

[6] *Id.*

[7] FDA Draft Guidance for IRBs, Clinical Investigators, and Sponsors: IRB Continuing Review after Clinical Investigation Approval (January 2010).

[8] 21 CFR 56.109(f) provides that, "An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research."

[9] Information Sheet: Continuing Review After Study Approval (September 1998), Office of Health Affairs, Food and Drug Administration.

[10] *Id.* at 4. Criteria for IRB approval of research are set forth at 21 C.F.R. §56.111, and include: 1) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result; 2) Selection of subjects is equitable; 3)Informed consent will be sought and appropriately documented; 4) Where appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects; 5) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; 6) Appropriate additional safeguards are included to protect vulnerable subjects; and 7) Where the study involves children, the research complies with 21 C.F.R. Part 50, Subpart D.

[11] *Id.* at 6.

[12] *Id.* at 7.

[13] *Id.* At 3.

[14] *See, e.g.*, Office for Human Research Protections Guidance on Continuing Review (January 15, 2007), *available at*: http://www.hhs.gov/ohrp/humansubjects/guidance/contrev0107.htm.

[15] *Id.* at 5.

[16] These factors include: 1) the nature of and risks posed by the clinical investigation; 2) the degree of uncertainty regarding the risks involved; 3) the vulnerability of the subject population; 4) the experience of the clinical investigator in conducting clinical research; 5) the IRB's previous history with that investigator and/or sponsor; 6) the projected rate of enrollment; and 7) whether the study involves novel therapies.

[17] *Id.* at 13.

[18] Expedited review is provided as set forth at 21 C.F.R. §56.110(b) and the current list of criteria for expedited review published in the Federal register. 63 F.R. 60353 (Nov. 9, 1998).

[19] *Id.*