"In order to realize the promise of cost savings and recruitment efficiencies in conducting... foreign clinical trials, sponsors must consider the impact of the amended regulatory requirements on their ultimate goal."

New FDA Regulation Alters Standards for Foreign Clinical Trials

The US Food and Drug Administration (FDA) issued new regulations on April 28, 2008, revising the standards under which the agency will accept data from foreign clinical trials in support of domestic applications and submissions. Sponsors currently conducting, or contemplating, studies outside of the Investigational New Drug (IND) process should be aware of these new requirements as they may impact FDA's acceptance of the data that is generated in support of ultimate approval of the sponsor's product. The revised regulations require that foreign clinical trials to be used as support for an IND, a new drug approval (NDA) or an abbreviated new drug approval (ANDA) application be conducted pursuant to the oversight of an independent ethical committee (IEC) and in compliance with FDA's Good Clinical Practice (GCP) regulations.

Before promulgating the new foreign clinical trial regulations, FDA accepted data from non-IND foreign clinical studies, provided such trials were well-designed, performed by qualified clinical investigators and conducted in accordance with ethical principles acceptable to the world community. To support the use of such a foreign clinical trial, sponsors had to submit data describing investigator qualifications, research facilities, study protocol and results, drug products used in the study, and information showing that the study was adequate and well-controlled. FDA also required sponsors to demonstrate that the foreign study was conducted in accordance with the Declaration of Helsinki (Declaration) or the laws of the local host country, whichever afforded greater protection to human subjects.

Rationale for the New Requirements

FDA has grown increasingly wary of relying on data collected from foreign studies due to the difficulty in verifying the data and the concern that sponsors are conducting trials overseas to escape the rigorous regulations that control domestic research. These concerns are fueled by the fact that, increasingly, countries with less experience in clinical drug research are emerging as desirable locations to site foreign clinical studies. FDA expressed four rationales for promulgating regulations that replace the international standards with GCP standards and for requiring oversight of the trial by an IEC. The agency indicated that its primary goal is to better ensure the protection of human subjects. In the preamble to the new regulations, FDA noted that: "Although the Declaration states that it is unethical to enroll human subjects in poorly designed or conducted clinical trials, it does not provide guidance on how to ensure proper conduct of trials."
contrast, FDA’s GCP regulations impose a "standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected." 4 FDA believes that the GCP standards will ensure adequate protection of human subjects while providing the flexibility necessary to accommodate differences in how countries regulate clinical research and obtain informed consent. 5

The revised regulations are also intended to ensure the quality and integrity of data obtained from foreign clinical trials. High-quality clinical data is critical to FDA’s review of marketing applications and product labeling. The GCP provisions impose explicit requirements for study monitoring and conformance with protocols. Submission of information demonstrating compliance with these requirements is intended to assure the FDA that the data is credible and accurate. 6

FDA further noted that it decided to supplant compliance with the Declaration with adherence to GCP in order to provide clarity and consistency in the context of ever-evolving international standards. The Declaration itself has undergone several revisions’ and host countries vary in their regulation of clinical research. FDA concluded that it was necessary to delete reference to international law to eliminate potential confusion about the requirements for non-IND foreign clinical studies that may result from further revisions to the Declaration and differing national standards. 7 Finally, FDA concluded that the amendments to the foreign clinical trial regulations would ensure logical symmetry between FDA regulation of foreign studies and its regulation of domestic studies, and provide a more coherent approach to the complex issues that arise in overseas trials.

FDA expects that compliance with the GCP standards will provide greater assurance of protection of human subjects, improve the quality and integrity of data, and clarify sponsor obligations by more directly regulating foreign clinical trials in a manner that is consistent with the regulations of comparable studies conducted in the US under an IND.

Summary of Requirements

The revisions to the regulations for foreign, non-IND clinical trials’ require sponsors to demonstrate that the studies are conducted in accordance with GCP and to permit FDA to validate the data through onsite inspection. Compliance with GCP requires, among other things, patient informed consent, investigator statements, and adverse event and periodic reporting to FDA. 8 The GCP regulations also require that the study be conducted under the oversight of an IEC—“a review panel that is responsible for ensuring the protection of the rights, safety, and well-being of human subjects involved in a clinical investigation and is adequately constituted to provide assurance of that protection.” 9 11 The GCP standards require that the study protocol be reviewed and approved by an IEC before initiating the study, continuing IEC review of an ongoing study, and IEC approval for obtaining and documenting informed consent.

The revised regulations describe the information that must be provided when a clinical trial sponsor submits foreign clinical data to FDA in support of an IND, NDA or ANDA. 11 These data submission requirements include a description of investigator qualifications, research facilities, drug product, study protocols and results. In order to enhance FDA oversight and to facilitate FDA review, sponsors must also document compliance with GCP and IEC procedures. Specifically, when submitting foreign clinical data to FDA, sponsors must identify the IEC,
document the IEC decision to approve or modify the study, describe the methods for obtaining informed consent and any incentives provided to subjects, describe study monitoring procedures, and describe the training provided to ensure compliance with GCP and the approved protocol. FDA has also added a record retention requirement which lasts for two years after the agency’s decision on an application for marketing approval or, if a study is submitted in support of an IND but not an application for marketing approval, for two years after the submission of the IND. The purpose of this record retention requirement is to enable FDA onsite inspection, if necessary.

Implementation

The new regulation becomes effective October 27, 2008, and it will be applicable to all foreign clinical studies regardless of the status of subject enrollment, whether ongoing, completed or not yet initiated. The new regulations do not grandfather trials already in progress, in order to decrease the potential for confusion about which version of the regulations governs a particular foreign trial. The new requirements for the design, conduct and reporting of foreign clinical trials will apply equally to studies that result in NDA and ANDA applications for domestic marketing approval.

Sponsors interested in lowering costs and shortening the timelines of their clinical trial programs are increasingly looking overseas to conduct clinical trials. FDA estimates that, annually, 115 firms are conducting 575 non-IND foreign trials for eventual submission to FDA as part of an IND, NDA or ANDA application. This avenue to new drug development offers sponsors a number of advantages, including avoiding the formal IND requirements, recruiting patients more quickly from an expanded subject pool, lowering overall costs, increasing the availability of investigators, and enrolling subjects who are not exposed to confounding medications or who lack access to approved alternative treatments. By enhancing FDA oversight and more closely aligning non-IND foreign clinical trial requirements with those applicable to domestic programs, the new regulation may restrict the scope of these advantages. In order to realize the promise of cost savings and recruitment efficiencies in conducting...foreign clinical trials, sponsors must consider the impact of the amended regulatory requirements on their ultimate goal: FDA approval to market their product in the US.

Endnotes

1 21 C.F.R. § 312.120 (2008).
5 Id.
6 Id.
9 21 C.F.R. § 312.120(a).
10 21 C.F.R. pt. 312, see subpt. D.
12 21 C.F.R. § 312.120(b).
13 C.F.R. § 312.120(d).
14 73 Fed. Reg. at 22812.
If you have any questions about this Client Alert, please contact one of the authors listed below:

**Carolyne R. Hathaway**
Washington, D.C.

**John R. Manthei**
Washington, D.C.

**Cassie A. Scherer**
Washington, D.C.

or any of the following attorneys listed to the right.

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**Barcelona/Madrid**
José Luis Blanco
+34.93.545.5000

**Brussels**
Andreas Weitbrecht
+32 (0)2 788 60 00

**Chicago**
Stephen S. Bowen
+1-312-876-7700

**Dubai**
Rindala Beydoun
+971.4.704.6300

**Frankfurt/Hamburg/ Munich**
Ulrich Börger
Henning C. Schneider
+49-40 41 40 30

**Hong Kong**
Joseph A. Bevash
+852-2522-7886

**London**
Andrew C. Moyle
+44-20-710-1000

**Los Angeles**
Daniel K. Settelmayer
+1-213-485-1234

**Milan**
Michael S. Immordino
+39 02-3046-2000

**Moscow**
Mark M. Banovich
+7-501-785-1234

**New Jersey**
David J. McLean
+1-973-639-1234

**New York**
David A. Gordon
+1-212-906-1200

**Northern Virginia**
Eric L. Bernthal
+1.703.456.1000

**Orange County**
Perry J. Viscounty
+1-714-540-1235

**Paris**
Jean-Christophe Tristant
+33 (0)1 40 62 20 00

**Rome**
Fabio Coppola
+39.02.3046.2000

**San Diego**
Katherine A. Lauer
+1-619-236-1234

**San Francisco**
James R. Dutro
Paul R. DeMuro
Jerry Peters
+1-415-391-0600

**Shanghai**
Rowland Cheng
+86.21.6101.6000

**Silicon Valley**
Alan C. Mendelson
+1-650-328-4600

**Singapore**
Mark A. Nelson
+65-6536-1161

**Tokyo**
Bernard E. Nelson
+81-3-6212-7800

**Washington, D.C.**
Carolyne R. Hathaway
John R. Manthei
+1-202-637-2200