

## E-ALERT | Food & Drug

February 1, 2013

### CLINICAL TRIAL DEVELOPMENTS IN 2012

This e-alert is the first in a planned series of alerts summarizing recent developments related to the regulation of clinical trials of drugs, biologics, and medical devices by the U.S. Food and Drug Administration (FDA) and other U.S. government agencies.<sup>1</sup> It covers guidances issued by FDA, pending and final rules by FDA and the National Institutes of Health (NIH), FDA enforcement related to clinical trials, and other developments that may be of interest to companies that sponsor clinical trials. It concludes with a section discussing developments that are expected in 2013.

#### FINAL FDA GUIDANCES

In 2012, FDA issued five new guidances on the conduct of clinical trials. The most recent, a final guidance issued in December 2012, is entitled “Safety Reporting Requirements for INDs and BA/BE Studies.” It is designed “to help sponsors and investigators comply with the requirements for investigational new drug (IND) safety reporting and safety reporting for bioavailability (BA) and bioequivalence (BE) studies.”<sup>2</sup> The guidance was issued as a result of the agency’s rule changes in September 2010, which revised the IND safety reporting requirements for human drug and biological products under 21 C.F.R. Part 312, and added safety reporting requirements for BA and BE studies under 21 C.F.R. Part 320.<sup>3</sup> Applicable to both drugs and biologics, the guidance provides additional background on the terms used in FDA’s adverse event reporting regulations (e.g., suspected adverse reaction) and the circumstances in which adverse events should be reported. The guidance also covers topics such as investigations of marketed drugs, updates of investigator brochures, unblinding in order to report an adverse event, and how to report deaths in a trial that is designed to evaluate the effect of a drug on disease-related mortality or major morbidity.

FDA also issued a small entity compliance guide to complement the guidance.<sup>4</sup> It uses a question and answer format and includes a recommendation by FDA that companies “that provide drug to or receive drug from other entities share safety information with each other” in order to protect human subjects.

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<sup>1</sup> This alert focuses on the legal aspects of the conduct of clinical trials and does not include discussions of the scientific aspects of clinical trial design and conduct.

<sup>2</sup> Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies (December 2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf>.

<sup>3</sup> See 75 Fed. Reg. 59,935 (Sept. 29, 2010).

<sup>4</sup> Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies- Small Entity Compliance Guide (December 2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf>.

In February 2012, FDA issued a guidance on the obligation of Institutional Review Boards (IRBs) to engage in continuing review after a clinical trial is approved by FDA.<sup>5</sup> This guidance was developed as a result of efforts by FDA and the Office for Human Research Protections (OHRP) within the Department of Health and Human Services (HHS) to harmonize the agencies' guidance for human subject research. It is applicable to clinical trials for drugs, biologics, and medical devices and discusses the key topics that IRBs should consider during continuing review, including the adequacy of informed consent and the trial's progress toward, among other things, enrollment goals. The guidance notes that "IRBs involved in multi-site studies may find it difficult to conduct a thorough review with data solely from the site(s) under their purview." Accordingly, FDA recommends that investigators and sponsors ensure that IRBs receive study-wide information, whether through a centralized IRB review process or other means.

Also in February 2012, FDA issued a small entity compliance guidance discussing the requirements of 21 C.F.R. § 50.25(c), which was promulgated in January 2011 and requires informed consent documents to include a standard statement informing subjects that the trial will be included on the clinicaltrials.gov database. This applies to "applicable clinical trials" initiated on or after March 7, 2012.<sup>6</sup> The definition of "applicable clinical trials" is found in 42 U.S.C. § 282(j)(1)(A) and covers many clinical trials for drugs, biologics, and medical devices.

Finally, in March 2012, FDA issued a frequently asked questions guidance discussing how clinical trial sponsors can comply with 21 C.F.R. § 312.120, which sets forth the conditions under which the agency will accept data for an IND, new drug application (NDA), or biologic license application (BLA) from a foreign clinical study not conducted under an IND.<sup>7</sup> Released as part of FDA's efforts to strengthen oversight of foreign clinical trials, the guidance describes the information that should be submitted in order to establish that the foreign research conformed to good clinical practices (GCPs).

## DRAFT FDA GUIDANCES

FDA issued two draft guidances in 2012 related to the conduct of clinical trials. In November 2012, FDA published a draft guidance entitled "IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed."<sup>8</sup> This draft guidance was also the result of cooperation between FDA and OHRP. Among other things, it provides recommendations on how IRBs should review a proposed investigator's qualifications and the adequacy of a proposed research site. The guidance also states that IRBs should review a clinical investigator's determination that an IND or investigational device exemption (IDE) is or is not required.

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<sup>5</sup> Guidance for IRBs, Clinical Investigators, and Sponsors IRB Continuing Review after Clinical Investigation Approval (February 2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf>. This guidance supersedes the Information Sheet entitled "Continuing Review After Study Approval," which was released by FDA in September 1998.

<sup>6</sup> Guidance for Sponsors, Investigators, and Institutional Review Boards Questions and Answers on Informed Consent Elements, 21 CFR § 50.25(c) (Small Entity Compliance Guide) (February 2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM291085.pdf>.

<sup>7</sup> Guidance for Industry and FDA Staff FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions (March 2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf>.

<sup>8</sup> Draft Guidance for IRBs, Clinical Investigators and Sponsors IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed (November 2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM328855.pdf>.

In June 2012, FDA published a draft guidance entitled “Considerations When Transferring Clinical Investigation Oversight to Another IRB.”<sup>9</sup> It covers topics such as how to transfer records across IRBs, how to notify key parties of the change, and how to determine whether a consent form should be revised. The guidance generally advises that the “[t]ransfer of review responsibility for a clinical investigation from one IRB to another should be accomplished in a way that assures continuous IRB oversight with no lapse in either IRB approval or the protection of human subjects, and with minimal disruption of research activities.” Although the guidance does not require an incoming IRB to conduct a review before it accepts responsibility for the study, it does state that “[i]n practice, however, IRBs often choose to perform some type of review before accepting responsibility for a study, as part of their own due diligence efforts.”

## FINAL FDA RULES

**Disqualification of Clinical Investigators.** FDA finalized amended regulations for the disqualification of clinical investigators in April 2012.<sup>10</sup> The changes were primarily intended to expand FDA’s disqualification authority. Previously, if a clinical investigator had been disqualified to conduct trials on a certain type of product (e.g., investigational drugs), that disqualification would not extend to conducting clinical trials on other FDA-regulated products. The final rule addresses this issue by extending the disqualification to all FDA-regulated products, “including drugs, biologics, devices, new animal drugs, foods, . . . and tobacco products.”<sup>11</sup>

## FDA ENFORCEMENT

**Warning Letters.** Across the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), FDA issued 17 warning letters related to the conduct of clinical trials. This included six letters to clinical investigators, with observations such as failing to maintain accurate records, failing to conduct the study according to the protocol, and submitting false information to FDA. Eight warning letters were issued to IRBs, which contained allegations such as failing to ensure that no IRB member had a conflict of interest, failing to fulfill IRB membership requirements, and failing to maintain adequate documentation of IRB activities. Finally, CDRH issued five warning letters to sponsors (or, in one case, a sponsor/investigator). These letters cited issues such as failing to provide investigators with the information they need to conduct the investigation properly, failing to maintain accurate records, failing to ensure that informed consent was properly obtained, and failing to ensure proper monitoring of the investigation. CDER and CBER did not issue any warning letters to clinical trial sponsors.

## OTHER DEVELOPMENTS

**Remote Monitoring of Clinical Trials.** In December 2012, Transparency Life Sciences, LLC (TLS) announced that its investigational new drug application for lisinopril for the treatment of multiple sclerosis had been cleared by FDA. Trade press reported that this is the first FDA-approved clinical trial that will use remote monitoring to collect data from trial participants.<sup>12</sup> Patients will wear vital

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<sup>9</sup> Draft Guidance for IRBs, Clinical Investigators, and Sponsors Considerations When Transferring Clinical Investigation Oversight to Another IRB (June 2012), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM307779.pdf>

<sup>10</sup> 77 Fed. Reg. 25,353 (Apr. 30, 2012).

<sup>11</sup> *Id.* at 25,354.

<sup>12</sup> See, e.g., Slabodkin, Greg, “FDA approves first remote monitoring drug trial,” FierceMobile Healthcare (Jan. 1, 2013), *available at* <http://www.fiercemobilehealthcare.com/story/fda-approves-first-remote-monitoring-drug-trial/2013-01-01>.

sign monitors that transmit data to investigators and will participate in video conferences with investigators. The remote monitoring is designed to significantly reduce the cost of the study and reduce the number of in-person visits by participants, who will visit an investigator only twice throughout the 12-month study. The trial is also notable because of its use of “crowdsourcing” to design the trial. TLS used an online tool to elicit input from patients, physicians, and researchers to help design the trial, including to help select endpoints and inclusion/exclusion criteria.<sup>13</sup>

**FDA Authority Related to ClinicalTrials.gov.** On September 5, 2012, the Secretary of HHS formally transferred authority to FDA to oversee certain aspects of the clinicaltrials.gov database. In particular, FDA now has the express authority “[t]o determine that any clinical trial information was not submitted as required under 42 U.S.C. 282(j) or was submitted but is false or misleading in any particular and to notify the responsible party and give such party an opportunity to remedy non-compliance by submitting required revised clinical trial information not later than 30 days after such notification.”<sup>14</sup>

**Center for Drug Evaluation and Research Small Business Webinar.** On May 14, 2012, CDER hosted a webinar entitled “Building Quality into Clinical Trials – an FDA Perspective.”<sup>15</sup> According to the agency, ensuring the quality of clinical trials is an issue of increasing importance given the increasing complexity of medical products and studies, as well as the use of multisite, international studies, the increasing cost of trial monitoring, and the inability to “monitor or inspect in” quality. The agency recommended that sponsors take several steps to design a quality study, including selecting qualified investigators, ensuring that the protocol is optimized, providing adequate training (including an emphasis on the importance of the informed consent process), ensuring adequate monitoring and investigator compliance, and ensuring that all third parties with whom a sponsor or investigator contracts comply with all applicable regulations.

**Good Clinical Practice for Medical Devices.** On March 16, 2012, the Center for Devices and Radiological Health announced that it was formally recognizing the following consensus standard: ANSI/AAMI/ISO 14155: 2011 Clinical investigation of medical devices for human subjects – Good clinical practice. According to the agency, this standard “describes and defines the duties of the study sponsor, clinical investigator and monitor, includes a detailed section on the ethical conduct and protection of human subjects, and provides detailed annexes specifying the content and format of essential clinical trial documents.”<sup>16</sup> CDRH served on a committee to assist in updating this standard.

**Modernizing the Regulation of Clinical Trials and Approaches to Good Clinical Practice.** On April 23, 2012, FDA held a public hearing to solicit input on the ways in which the agency can modernize the regulation of clinical trials and GCPs. The agency “is aware of concerns within the clinical trial community that certain regulations and policies applicable to the conduct of clinical trials may result in inefficiencies or increased cost and may not facilitate the use of innovative methods and technological advances to improve clinical trial quality.”<sup>17</sup> FDA also solicited written comments,

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<sup>13</sup> See FDA Clears IND For First Clinical Trial Protocol Developed Using Crowdsourcing, PR Newsire (Dec. 18, 2012), available at <http://www.prnewswire.com/news-releases/fda-clears-ind-for-first-clinical-trial-protocol-developed-using-crowdsourcing-183922651.html>.

<sup>14</sup> 77 Fed. Reg. 59,196 (Sept. 26, 2012).

<sup>15</sup> The webinar slides can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm303135.htm>.

<sup>16</sup> See FDA's HSP/BIMO Initiative Accomplishments: Update May 2012, available at <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm305275.htm>; see also FDA, CDRH Recognized Consensus Standards (Recognition List Number: 028), available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/detail.cfm?id=29517>.

<sup>17</sup> 77 Fed. Reg. 13,513 (Mar. 7, 2012).

which included suggestions that FDA expand, update, or finalize existing guidances on clinical trials, that FDA create a “Chief Innovation Officer,” that FDA seek greater global harmonization of clinical trial requirements, and that the agency ensure that any limitations in its own information technology infrastructure do not discourage sponsors from using electronic health records.

**Revision of the Declaration of Helsinki.** On December 5-7, 2012, the World Medical Association (WMA) held a meeting in Cape Town, South Africa to discuss proposed revisions to the Declaration of Helsinki (DOH), which sets forth basic ethical principles for medical research involving human subjects. A representative from HHS spoke at the meeting and urged the WMA to avoid adding specific procedural requirements in the DOH because doing so would conflict with the mandatory procedures already required by existing country-specific laws. No revisions have yet been adopted.

## LOOKING FORWARD

**NIH Final Rules.** The FDA Amendments Act of 2007, which was enacted in September 2007, required NIH to create a set of rules that would allow for the expanded use of [clinicaltrials.gov](http://clinicaltrials.gov) by requiring the submission of more complete results information and enhancing patient access to and understanding of the results of clinical trials. These rules were due by September 2010. In the fall of 2012, NIH stated that the proposed rules would be published by January 1, 2013,<sup>18</sup> but the rules are still pending.

**Sunshine Act Final Rules.** The Physician Payment Sunshine Act (which was added by section 6002 of the Affordable Care Act) requires manufacturers of certain drugs, biologics, and devices to report payments or other transfers of value made to a physician or teaching hospital. The reports must categorize the payments by type, and the statute includes a payment category for “research.” In addition, the statute provides that information related to payments for clinical investigations may be temporarily withheld from public release. In 2011, the Centers for Medicare & Medicaid Services published draft rules implementing the Act, including a proposal to separate the classification of research payments based on whether the payment or other transfer of value went indirectly to a physician (*i.e.*, a payment made through a hospital) or directly to the covered recipient.<sup>19</sup> The final regulations are expected to be issued in 2013.

**Pending Draft Guidances.** In May 2012, FDA’s Human Subject Protection (HSP)/Bioresearch Monitoring (BIMO) Initiative noted that the following draft guidances were currently under development at FDA: (1) guidance on informed consent, including topics such as review of patient records, enrolling children as subjects, and subject participation in more than one study, (2) guidance on protections for children enrolled in research, and (3) guidance on the “core” responsibilities of IRBs (which will be developed jointly with OHRP).

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If you have any questions concerning the material discussed in this client alert, please contact the following members of our Food & Drug Practice Group

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<sup>18</sup> See HHS/NIH Regulation Identifier Number 0925-AA55, Expanded Registration and Results Reporting at [ClinicalTrials.gov](http://ClinicalTrials.gov), available at

<http://www.reginfo.gov/public/do/eAgendaViewRule?pubId=201210&RIN=0925-AA55>.

<sup>19</sup> 76 Fed. Reg. 78,742, 78,749 (Dec. 19, 2011).

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