

FDA Inspection Trends

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The landscape of today's clinical trials is ever changing, posing greater challenges for sponsors, investigators and FDA alike. Challenges include increased complexity, novel therapies, large multi-site trials, inclusion of vulnerable patients, trials conducted outside of the United States, and outsourcing of various trial related responsibilities. In response to these complexities, FDA is implementing several new initiatives to maintain better oversight, and sponsors and investigators will need to be more vigilant throughout all phases of a clinical trial in order to achieve success.

One such initiative recently implemented by FDA is to conduct routine inspections of contract research organizations (CROs). Realizing the integral role CROs play with more sponsors outsourcing critical tasks or the entire trial, FDA is increasing their oversight of CROs. A CRO that assumes any obligation of the sponsor will be held to the same regulatory actions as a sponsor for failure to comply with applicable regulatory requirements.

Another FDA initiative is the Institutional Review Board (IRB) Registration requirement that went into effect 14 July 2009. The final rule required all IRBs that review FDA regulated trials to be registered by the 14 September 2009 compliance date. Registration is completed online at <http://ohrp.cit.nih.gov/efile> or by mail. IRBs designated under FWAs were required to update their

information in the modified system by the compliance date. Changes to information must be updated in the system within 90 days; however, if an update involves a new type of FDA regulated product being reviewed, the discontinuation of the review of FDA regulated trials, or the disbandment of the IRB, updates must be made within 30 days. At a minimum, information must be updated every 3 years. If a FDA regulated trial is reviewed by an IRB that is not appropriately registered, the Investigator and Sponsor will be considered noncompliant with FDA regulations.

In order to further ensure the protection of human subjects and the validity of data used to make critical approval decisions, FDA has released a new proposed rule (FR 2/19/10) on the reporting of information regarding the falsification (or suspected falsification) of data in proposing, designing, performing, recording, supervising, reviewing or reporting of results for clinical trials. The proposed rule covers all parties involved with the clinical trial, and includes both human and animal trials. A sponsor would need to report such information no later than 45 days following the date in which the sponsor becomes aware. In addition, FDA has developed several new guidance documents such as Adverse Event Reporting to IRBs (issued Jan 2009), Supervisory Responsibilities of Clinical Investigators (issued October 2009), and IRB Continuing Review after Clinical Investigation

Approval (draft January 2010). Clinical trial inspections of both investigators and sponsors continue to serve as an important tool for FDA in ensuring the protection of subjects and validity of data. In FY2009, over 1100 BIMO audits were conducted, with 305 conducted by the Center for Devices and Radiologic Health (CDRH). The CDRH audits were comprised of 163 Clinical Investigators, 79 IRBs, 59 Sponsors and 4 GLP laboratories.

The most common findings reported by all FDA centers in 2009 were: 1) failure to follow the investigational plan, 2) inadequate or unavailable records, 3) inadequate informed consent / documentation, 4) inadequate test article accountability, 5) IRB notification / approval issues, 6) lack of appropriate delegation / investigator oversight, and 7) adverse event reporting issues.

Additional issues of interest cited in recent FDA Warning Letters include:

1) Subject case records were found to be unbound and appeared to lack system controls, with entries posted to the wrong visit form, multiple versions completed for the same visit, missing pages, numerous unexplained corrections and conflicting information.

2) Investigational plan required randomization and dosing on the same day; however, dosing

was conducted 11 days later for one patient. A monitoring report indicated that the delay was due to personal problems of the patient but the incidence was not mentioned to the investigator in the post-visit letter and no corrective action plan was conducted.

3) Investigators may have been unblinded as nursing notes contained the name of the medication. A black marker was later used to prevent further potential unblinding; however, GCP guidelines indicate original entries should not be obscured. Thus the site failed to make corrections to source documents appropriately.

4) No documentation was found to support protocol versions 2, 3 or 4 were approved by the IRB prior to the retroactive letter issued by the IRB indicating the respective approval dates.

5) No documentation was found to support that the IRB specifically approved the investigator and his clinical study site.

6) The informed consent used to enroll subjects did not adequately describe the purpose of the study. Even though subjects were re-consented with a revised form, this is considered insufficient as this did not occur until 3 months after the IRB had approved the form.

7) The site distributed tote bags, diary cards, and subject calendars that had not been approved by the IRB.

8) "Memos to file" were generated noting deficiencies; however, the sponsor failed to take appropriate corrective actions.

9) The sponsor was repeatedly notified in monitoring reports of problems, yet compliance was not secured nor was the trial terminated at the site.

Table 1: Most Common BiMo Inspection Deficiencies Reported by CDRH (2007)

Deficiency	Frequency (% of Inspections*)
Inadequate Monitoring	39
Failure to Submit Progress Reports	36
Failure to Secure Investigator Compliance	27
Inadequate UADE Analysis and Reporting	27
Failure to Inform Investigators	21
Inadequate Device Accountability	15
Failure to Obtain Signed Investigator Agreement	15

**More than one type of deficiency may be reported per investigation.*

Data available regarding the most common findings noted by CDRH in 2007 included inadequate monitoring, failure to submit progress reports, failure to secure investigator compliance, and failure to inform investigators (see Table 1 below for additional information).

FDA continues to conduct inspections while trials are ongoing as well as prior to product approval and uses a risk-based model for determining the trials to be inspected. Generally, studies involving pediatric or vulnerable subjects, a novel and/or high-risk product, and sites / sponsors with no prior clinical trial experience / inspection history are more likely to be inspected. Areas receiving increased scrutiny by FDA during inspections include the reporting of financial interests by investigators, transfer of responsibilities to a CRO, delegation of responsibilities by the investigator, investigator oversight, IRB registration and oversight, and actions taken in regards compliance issues.

Should violations be observed during an FDA inspection involving the issuance of a Warning

Letter, the FDA is now offering a Warning Letter close-out program. Warning Letters issued after 1 September 2009 may receive a close-out letter from FDA following verification that the corrective actions implemented adequately addressed the violations. Verification is generally completed during a follow-up inspection, and close-out letters are issued by the same FDA office that issued the Warning Letter. If a violation is not correctable, no close-out letter will be issued.

With the changing environment of clinical trials and FDA's initiatives to increase oversight, many sponsors are seeking third party audits of ongoing trials as a routine measure or in preparation for an anticipated FDA inspection. Third party audits provide objectivity and can help ensure a successful trial. RCRI has several staff members with extensive experience in conducting clinical trial audits and can fulfill any auditing needs.

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