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Surviving the Aftermath of an FDA Clinical Trial Inspection (Part 1)

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The U.S. Food and Drug Administration (FDA) has the authority to conduct inspections of clinical trials conducted by study sponsors and investigators under 21 CFR Part 312 (Investigational New Drugs) and 21 CFR Part 812 (Investigational Device Exemptions) regulations. Negative findings during inspections can result in citations. Citations based on inspection findings require a response by the party receiving the citation.

If an individual or company is cited and the FDA deems the response to that citation inadequate or the infraction so severe that it potentially or actually places a subject (or subjects) in harm's way, the eventual result can be debarment or disqualification of an individual researcher, a consent decree with the sponsoring company, or even criminal prosecution.

Form FDA 483: Inspectional Report of Observations

At the conclusion of an inspection, the FDA Investigator can issue a Form FDA 483: Inspectional Report of Observations ("483") to document any violations of the drug and device regulations. Ideally, the Investigator will find no violations or none serious enough to require issuing a 483.

Responding to a 483

Upon receipt of a 483, form a response team. Inform the IRB, CRO and/or Sponsor, as appropriate, of the 483. Formally respond in writing to the FDA. The response must be prompt, generally within two weeks from inspection closeout.

If you have made any corrections to address a citation, e.g., you have implemented a new standard operating procedure (SOP), submit proof of the correction. In this example, submit a copy of the SOP, documentation showing that all responsible persons involved with executing the SOP have been properly trained, and a description of how you will ensure that future staff with similar responsibilities will also be trained properly prior to taking on responsibilities covered by the SOP.

If the correction cannot adequately be put in place prior to sending the response, provide a firm date whenever possible, or at the very least, an estimated date for when the correction will be put in place. If you made any commitments during the inspection, try to meet them as well.

Corrections should be timely but not unrealistically swift. For example, if you are with a large organization, the FDA may consider it unlikely that you could get a new, well-written SOP approved and trained within one week. Be sure to meet the timeline and, unless the inspection has been formally closed out by the FDA, provide proof of correction once accomplished. If the citation is minor and the FDA has closed out the inspection, still conduct the steps you committed to and retain documentation for a potential future inspection. The FDA can come back at any time to ensure the corrections you put in place were adequate. Statements to the following effect are often found in FDA Untitled Letters:

> FDA has reviewed your response and it appears to be adequate. The adequacy of your response and implementation of corrective actions may be assessed in a future inspection.

Demonstrate that you take the Investigator's finding(s) seriously. Your 483 response reflects your organization's compliance attitude and corporate culture. If your response is inadequate, defensive, disrespectful or argumentative, the FDA may conclude that you have a poor compliance attitude and that your organization's culture does not support conducting studies in a manner that meets regulatory requirements, even if you have followed "the letter of the law."

Send your response to both the FDA District Office that assigned the Investigator and the FDA Center contact person for your inspection. (The FDA operates three centers: Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) and Center for Devices and Radiological Health (CDRH).) If the contact information is not provided on the 483, ask the FDA Investigator before he or she leaves your facility.

If asked, some FDA Investigators will include your response in their Establishment Inspection Report (EIR), provided you can get it in before the report is sent to the center (usually within two weeks from the end of the inspection). However, do not rush to submit a response that is incomplete, poorly prepared, or subject to change.

After Responding to a 483

Now that you have responded, it's time for a well-earned vacation while you wait to hear from the FDA, right? Wrong!

While waiting to hear from the FDA, do the following:

- Provide feedback to your workforce (both positive and negative).
- Start implementing corrections, including those for FDA observations that were not included in the 483 but might come up in a future inspection.
- Adjust your internal audit program, as necessary.
- Re-audit problem areas, as necessary, especially for studies not inspected by the FDA.

Post-Inspection Activities at the FDA

The FDA is also moving forward. Decision-makers are reading the EIR, any issued 483, and, if available, your response to the 483. They will assign your inspection to one of the following classifications:

- **No Action Indicated (NAI).** The FDA found no objectionable conditions or practices or their significance does not justify further FDA action.
- **Voluntary Action Indicated (VAI).** The FDA found objectionable conditions but will not take any further action because they did not meet the regulatory threshold. The district office may use an Untitled Letter, Regulatory Meeting, or other communication to inform the organization of findings that should be corrected. A written response by the organization is optional and any corrective action is voluntary.
- **Official Action Indicated (OAI).** The FDA found significant objectionable conditions and requires that corrections be made, to be set forth in a Warning Letter.

Warning Letters

The FDA issues a Warning Letter when it has identified violations of regulatory significance observed during the inspection and have determined that OAI applies. Their primary purposes are to obtain voluntary compliance and establish notice prior to enforcement actions being taken, such as disbarment or other legal action.

If you receive a Warning Letter, inform the IRB, CRO and/or Sponsor, as appropriate, of the Warning Letter. Review the issues with your staff, and, if you have not already done so, start taking actions to correct the deficiencies.

When responding to a Warning Letter, follow the same basic principles as with a 483. Review your 483 response and adapt activities and text, as appropriate. Be responsive and consistent in your communications. If your response team does not already include an attorney, regulatory specialist, or sponsor expert, obtain one now. The FDA takes Warning Letters very seriously and you should too.

A response is required within 15 business days. If absolutely necessary, you can request an extension, but try to meet the 15-day deadline. Make sure you can meet any commitments you make to the FDA.

Confer with your legal counsel to determine whether to release a public statement for the trade press.

In Part 2 of this article, we will discuss some of the FDA's criticisms of 483 and Warning Letter responses, along with additional enforcement actions the FDA can take.

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