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Surviving the Aftermath of an FDA Clinical Trial Inspection (Part 2)

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In Part 1 of this article, we discussed how to respond to 483s and warning letters. As noted, if an individual or company is cited and FDA deems the response to that citation inadequate or not handled properly, 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, a consent decree, or even criminal prosecution. In Part 2, we will discuss some of the FDA's criticisms of Warning Letter responses, along with additional actions the FDA can take.

FDA Criticism of Responses

The FDA has cited the following inadequacies in responses to 483s:

- Failure to specify timeframes for corrections yet to be put in place
- Timeframe until correction is in place is too long
- Corrections appear to be applied in a piecemeal manner
- Not enough detail on:
    - What the corrective actions are
    - What will be put in place
    - How the organization will follow up to ensure the proposed corrections are adequate and effective
- Provision of corrections that adversely affect or can adversely affect other systems
- Responses are open to more than one interpretation

FDA Still Not Satisfied?

If the FDA finds your 483 response inadequate, it can issue a Warning Letter. The FDA defines a Warning Letter as:

> ...a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency's principal means of achieving prompt voluntary compliance with the Act.

Your response to a Warning Letter Response should include the following components:

- Address each violation — be specific.
- Provide supporting documentation.
- Set achievable, reasonable timeframes.
- Correct FDA inaccuracies — explain areas of disagreement.

The FDA requires your response to its Warning Letter within 15 days. The FDA takes your response into consideration before taking further steps.

Meeting with FDA

After receiving your response to a Warning Letter, FDA can request a meeting. However, it is very rare for the FDA to make the request; usually it would be the Investigator who requests a meeting. Such a meeting is not mandatory, but if requested, should be arranged through the District Director or Compliance Officer. The primary purpose of the meeting would be to provide additional or new information beyond that previously provided in your 483 and Warning Letter responses. Presenting arguments on why the Warning Letter should not have been issued or re-providing information previously provided will not further your cause and may reflect poorly on the Investigator.

NIDPOEs

Following the Warning Letter (and a meeting, if one occurs), the FDA can issue a notice of initiation of disqualification proceedings and opportunity to explain (NIDPOE). The NIDPOE letter informs the Investigator that FDA is initiating an administrative proceeding to determine whether the Investigator should be disqualified from receiving investigational products based on the regulations. FDA issues a NIDPOE letter when it believes it has evidence that the Investigator repeatedly or deliberately violated FDA's regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to the sponsor.

The NIDPOE letter may contain a Consent Decree that the Investigator can choose to sign or not. A Consent Decree is a final, binding judicial decree documenting a voluntary agreement between the Investigator and FDA, e.g., not to conduct further clinical studies that fall under FDA jurisdiction. If you have not yet engaged legal counsel and a regulatory expert, do so at this point.

The Investigator should review the letter and consent decree as to the extent and depth of the problem(s) and sanction. The Investigator should meet with counsel and a regulatory expert to determine whether there are valid responses to all the observations and, if so, to draft a response letter. Your letter must disagree with the observations and not the regulatory requirements cited. Explain why the Investigator should not be denied access to investigational products. If the Investigator cannot respond to FDA’s satisfaction, he or she should consider signing the consent agreement, if one is included with the NIDPOE letter. Consent agreements normally call for the Investigator’s permanent disqualification or less severe sanctions like, in essence, supervised probation.

Debarment and Criminal Prosecution

Unless the response letter persuades FDA that there has not been repeated and deliberate failure to comply with the regulatory requirements, it will begin the process to disqualify the Investigator. The FDA provides notice of its decision to the Investigator and provides an opportunity to explain in an informal hearing and an opportunity for a formal hearing through a Notice of Opportunity for Hearing (NOOH), which is a proposal to disqualify the Investigator. Disqualification may result in ineligibility to receive investigational drugs, devices or biologics, and is published in the Federal Register.

In severe cases, e.g., fraud, the FDA can pursue criminal prosecution and then also debar an Investigator. Debarment bars a person from providing any services to companies with approved or pending drug, device or biological regulatory approval applications. It can be

applied for a specific number of years or permanently. Historically, it has usually been applied to employees of sponsor companies, but it is not limited to them. In the debarment process, the Investigator will receive a NOOH, which provides him or her with the opportunity for a hearing on a regulatory action, including a proposed action (such as debarment), before a presiding officer designated by the FDA Commissioner.

Organizational Sanctions

FDA can also send a separate Warning Letter and Consent Decree to the Investigator's employer, the study sponsor, or other organization that shares responsibility for the noncompliance. In addition, FDA can debar individuals, including executives, within these organizations.

And, of course, FDA can notify the HHS Office of Research Integrity to ensure the FDA Office of Criminal Investigations, the U.S. Department of Justice, and other agencies are aware of possible civil or criminal violations. How do you know you are under investigation for criminal prosecution? You find out that an FDA Criminal Investigator has interviewed or subpoenaed staff, subjects or the IRB, CRO, sponsor or sponsor's vendors. Criminal cases are under federal jurisdiction and, as such, usually start with a Grand Jury.

Knowledge of illegal activities is not required for criminal liability under the Federal Food, Drug, and Cosmetic Act. In the case of United States v. Park, 421 U.S. 658 (1975), the court held that if someone is willingly in charge of a company or organization, then he or she willingly accepts the consequences of any illegal practices with which the company or organization is involved.

Conclusion

The best way to avoid the consequences of negative FDA inspection findings is to conduct your studies according to applicable FDA regulations and guidelines. You might still receive a 483 and even a Warning Letter, but probably not. Investigators who have been through the process can easily relate to the slogan, "Pay me now, or pay me later."

Reference

1. "Surviving the Aftermath of an FDA Clinical Trial Inspection (Part 1)," Lee Truax-Bellows, Journal of Clinical Research Best Practices, March 2013. Available at: http://firstclinical.com/journal/2013/1303_After_Inspection.pdf.

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