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What Should You Do After An FDA Inspection?

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The FDA just completed an inspection of your firm, and one or more FDA Form 483 inspectional observations were noted by the inspection team. How and when your firm reacts to these observations is a significant decision. This article will provide guidance on what actions to take to minimize or avoid additional enforcement actions.

How The FDA Can Respond To Inspections

When the FDA begins an inspection, a **Form 482** (notice of inspection) will be presented as well as contact information in the event a 483 response is issued. The 482 explains the Agency's inspectional authority and provides expectations for the Inspector and the firm.

The **Form 483** lists observations made by the FDA representative(s) during the inspection. These observations do not represent a final agency determination regarding compliance. The 483 formally notifies the organization's top management of objectionable conditions or practices relating to violations of the Federal Food, Drug, and Cosmetic (FD&C) Act that were observed during the inspection.

If the inspection does not yield any objectionable conditions or practices, a 483 will not be issued. However, if the FDA representative(s) does observe objectionable conditions, one or more 483 will be issued during the closing meeting. If the agency does issue one or more 483s at the conclusion of the inspection, it is always better to select “promise to correct” rather than “under consideration” in response to each 483 observation.

Depending the nature of the violation(s), the FDA may give the firm an opportunity to take voluntary and prompt action to correct the violation(s) before the agency initiates an enforcement action. However, the FDA generally is under no legal obligation to warn individuals or firms about violations before taking additional enforcement actions, as further described below.

The FDA uses **untitled letters** for violations that are not as significant as those that prompt warning letters. An untitled letter does not include a statement warning that failure to promptly correct a violation may result in an enforcement action.

Warning letters, on the other hand, are issued to manufacturers or other organizations that have violated some rule in a federally regulated activity, i.e., violations of regulatory significance. A warning letter is one of the agency's primary means of achieving prompt voluntary compliance with the FD&C Act.

Injunctions may also be ordered to halt the flow of violative products and to correct the conditions that caused a violation to occur. An injunction is a type of judicial action that is considered for any significant out-of-compliance circumstance, but particularly when a health hazard has been identified. When an injunction is granted by a court, the FDA has a duty to monitor the injunction and to advise the court if the firm fails to follow through on its obligations. The three most common types of injunctions are the temporary restraining order, the preliminary injunction, and the permanent injunction.

The FDA may recommend a ***temporary restraining order*** when it believes that a serious violation has occurred, and the situation must be controlled, or the flow of product stopped immediately. A motion for ***preliminary injunction*** is subject to a full hearing before a court. Once the motion is granted, the preliminary injunction is in effect and may stand indefinitely until the case is settled or a permanent injunction has been entered, after trial.

A decree of ***permanent injunction*** may be entered at any time after the complaint is filed, either after a hearing or as a result of a negotiated settlement between the government and the defendant. A consent decree is a court-ordered agreement between the FDA and a firm that outlines the steps the firm needs to take to resume normal

operations. Although each situation is unique, consent decrees often indicate necessary changes within the organization — and may even require the firm to involve outside consultants to oversee the changes and ensure ongoing compliance

A **product seizure** is a judicial (court-approved) action for removing violative products from the marketplace. Product seizures typically are initiated when the firm has not voluntarily recalled product that the regulatory agency believes is in violation of the law and where there is a perceived or known health risk to the public.

After the inspection, and dependent upon the firm's response to any 483 findings that are issued, the agency classifies the inspection with one of three statuses in the **establishment inspection report (EIR)**:

- ***No action indicated (NAI)*** means no objectionable conditions or practices were found during the inspection (or the objectionable conditions found do not justify further regulatory action).
- ***Voluntary action indicated (VAI)*** means objectionable conditions or practices were found, and the firm's response was satisfactory, so the agency is not prepared to take or recommend any administrative or regulatory action.
- ***Official action indicated (OAI)*** means objectionable conditions or practices were found, and/or the firm's response was not satisfactory, so regulatory and/or administrative actions will be recommended.

Responding To The FDA

Once the FDA has issued a 483 or warning letter, it is important for the firm to understand there may be more objectionable conditions or practices that will need to be addressed. For example, the Instructions for the 483 state: "The observations noted in this Form FDA 483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct and all violations of the quality system requirements." The warning letter instructions state: "You should know that this letter is not intended to be an all-inclusive list of the violations at your firm's facility. It is your firm's responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the FDA 483 issued at the close of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality management systems. Your firm should investigate and determine the causes of the violations and take prompt actions to correct the violations and bring the products into compliance."

When a firm receives an official correspondence form the FDA, the generally accepted and expected practice is to provide a thorough response within 15 business days, addressing the objectionable conditions or practices relating to violations of the FD&C Act that were observed during the inspection.

When the FDA receives a response to a 483 within 15 business days of the form being issued, the agency generally conducts a detailed review of the response before determining whether to issue a warning letter. If the FDA decides to issue a warning letter after reviewing a firm's timely response, that letter will acknowledge receipt of the response and address the adequacy of the firm's corrective actions set forth in the response.

When the FDA reviews a response to a 483, it may reply by acknowledging receipt of the letter and indicating that the firm's response to 483 observation "is not adequate." This usually means the FDA is considering a warning letter but has decided to provide the firm with an additional opportunity to discuss current and future actions to resolve objectionable conditions or practices. In such cases, the firm should provide a thorough response within 15 business days, addressing the concerns, unless a meeting has been requested.

The FDA's response letter may indicate a desire to schedule a regulatory meeting with the firm at the district office to discuss significant issues documented during the inspection. This type of letter usually means the FDA is considering a warning letter but has decided to provide an additional opportunity to discuss current and future actions to resolve objectionable conditions or practices. If a meeting is requested, it is best to acknowledge receipt of the letter and schedule the meeting as soon as possible.

Content Of The Response

A response to a 483 should contain the following:

- ***Containment and correction(s)*** – immediate actions taken to resolve the issue. Examples include cease and desist of the objectionable conditions or practices, quarantine of suspected violative products, etc. The individual(s) responsible for containment and corrections and the expected date(s) of completion should be included.
- ***Completed actions*** – actions that were completed at the time the response was submitted. Examples of completed actions may include a corrective and preventive action was initiated (CAPA), suspected violative parts were re-inspected, etc. The individual(s) responsible for the completed actions and the date(s) of completion should be included.

- ***Planned actions*** – actions the firm will take to resolve the objectionable conditions or practices observed during the inspection. Examples of planned actions may include updating procedures and forms, validating/re-validating a process, additional training, remediation of previous records (CAPAs, NCRs, complaints), etc. The individual(s) responsible for the planned actions and the expected date(s) of completion should be included.
- ***Supporting documentation*** – objective evidence to support the response. The supporting documentation should be clearly labeled to facilitate the review by the agency. Supporting documents should be marked "CONFIDENTIAL" to indicate the organization's view that the documents are considered proprietary confidential information and not subject to the Freedom of Information Act (FOIA).

Conclusion

Many firms are unprepared to manage an FDA inspection or to effectively respond to 483 observations. Perform mock FDA inspections annually, and live each day as though the FDA might show up and begin an inspection. The approaches presented in this article should be used and are based upon industry practice, guidance documents, and regulatory requirements.

References:

1. Investigations Operations Manual 2018, https://www.fda.gov/downloads/ICECI/Inspections/IOM/UCM150576.pdf

About the Author

Mark Allen Durivage has worked as a practitioner, educator, consultant, and author. He is Managing Principal Consultant at Quality Systems Compliance LLC, an ASQ Fellow and SRE Fellow. He earned a BAS in computer aided machining from Siena Heights University and an MS in quality management from Eastern Michigan University. He holds several certifications including; CRE, CQE, CQA, CSQP, CSSBB, RAC (Global), and CTBS. He has written several books available through ASQ Quality Press, published articles in Quality Progress, and is a frequent contributor to Life Science Connect. Durivage resides in Lambertville, Michigan. Please feel free to email him at mark.durivage@qscompliance.com with any questions or comments, and connect with him on LinkedIn.