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How to Respond to FDA Inspection Observations, Including Those You Dispute

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Although FDA is strapped with limited resources and competing priorities, the Agency continues to hammer regulated companies with FDA 483 inspection observations and Warning Letters.

In 2014 alone, FDA conducted more than 38,000 inspections and issued 8,457 Form 483s -- inspection observations that, in the inspector's judgment, indicated an operation or product violated FDA requirements.

To maintain this enforcement pace while replacing an aging workforce, FDA has hired a number of new inspectors. Although some "veterans" remain, it's highly possible your next inspection will be conducted by one of the Agency's less experienced investigators.

Lacking industry-specific knowledge, new inspectors are less likely to understand and accept your explanation of unfamiliar products or processes. So if you find yourself in a situation where you disagree with a 483 observation, you need to know how to respond effectively and responsibly to keep a minor dispute from escalating to a major legal battle.

A Glimpse Into the Post-Inspection Process

Your response to a 483 observation is your last and best opportunity to tell your side of the story before higher-ups in the Agency (including enforcement officials in Washington) become involved.

You may be surprised to learn that FDA believes it's your responsibility to work with its investigators before they leave your facility to remove -- or at least address -- what you believe are incorrect points on the Form 483.

In their wrap-up meeting with you after an inspection, FDA investigators should go over each 483 observation, one by one, annotating them with your responses and any corrective actions you've made during the inspection.

When you can verbally respond with 100% confidence to an observation -- disputed or not – do it. But if you are uncertain how to respond, it's better to tell the investigator you will send FDA a written response about the observation.

Even if you respond verbally to each point, it's still imperative for you to provide FDA a follow-up, written response immediately. Here's why:

After they complete the inspection of your facility, FDA inspectors have a maximum of 10 working days to submit to their supervisor the Establishment Inspection Report (EIR), which summarizes their findings. FDA's chain of decisions regarding whether to issue a Warning Letter or take other enforcement actions begins when the EIR is submitted.

FDA suggests you respond to a 483 observation within 15 days, but I recommend you respond ***within 10 days*** to match the time allowed for the inspector to finalize the inspection report. ***A quick response gives you the maximum opportunity to have your input heard at the next levels of FDA.***

Your response then will be seen by all interested parties, including the investigator's supervisor (usually a district compliance officer) and other Agency enforcement officials who decide whether or not the inspector's 483 observations warrant a Warning Letter.

If your response is considered adequate by the Agency, you will receive a letter accepting your proposed corrective actions and indicating a Warning Letter won't be coming. Don't think you're totally off the hook, however. If a future re-inspection of your facility finds your corrective actions weren't taken or weren't effective, the re-inspection likely will be conducted as if a Warning Letter had been issued after the initial inspection.

What Your Response Should Include

Your response -- especially the written one -- should contain:

- A re-statement of the investigator's observations (from your perspective) to show you understand the issue
- The possible reason for the observation
- What you have done to ensure the observed situation did not (and will not) affect product specifications, and
- How and when you will address the observation.

Your response will be read by FDA officials who likely won't be familiar with your operations, so include a short overview of your company and its history, products, and operations.

If you disagree with an observation, your response should offer background information on the point, indicate why you think the investigator made the observation, and explain why you believe it's not valid.

Use sound, scientific reasoning. Discuss your experience with the process or product. But don't demean the investigators' experience or the inspection process; that won't win you any friends at the Agency.

In any written or verbal response, ***it's critical to show FDA you are in control of the situation*** and are attempting to comply voluntarily by doing everything possible and reasonable to ensure your products meet their specifications.

And here's what *not* to do in your response:

- Don't argue over an interpretation of the regulation. Odds are the FDA investigators -- even the less experienced ones -- know the finer points of the regulations better than you do. You usually won't win a regulatory interpretation clash with the Agency.
- Don't simply acknowledge you received the 483 without outlining specific corrective actions you plan to take. Not offering corrective actions makes the Agency think you don't understand the problem or appreciate its significance.

Examples of Effective Responses

Here are three actual inspection observations, followed by the company's initial (and inadequate) responses. Contrast them with what I believe are more measured and effective responses.

Observation 1: There were no recording charts on the storage refrigerator, and the products stored required conditions of 4 to 8 degrees Celsius.

Inadequate Response: We will put recording charts on the refrigerators.

Better Response: A check of all products stored in the refrigerator will be made by re-running all finished testing to assure the storage conditions did not affect the product. The sample will be made under a statistical sampling plan that uses an Acceptable Quality Limited (AQL) of 2.5. If any of the products fail, the entire lot will be destroyed or reworked if possible. A copy of the tests will be supplied upon test completion, which should be within two weeks. Recording charts will be installed on all storage refrigerators within 30 days.

Observation 2: The freeze-drier's manual states you should have six-month maintenance to maintain the unit. You presently do not have any routine maintenance on the freeze-drier.

Inadequate response: We will contact the freeze-drier manufacturer and ask for a maintenance contract immediately.

Better response: The freeze-drier is on our break-down maintenance schedule. In 20 years of use, we never have had a problem with a product freeze-dried in this unit. Preventive maintenance is not necessary to assure the correct operations of the unit.

Observation 3: The results recorded for the electrical testing were only qualitative, not quantitative.

Inadequate Response: Quantitative data for these tests was not required in our standard operating procedures (SOPs) and should not have been a point on the FDA 483.

Better Response: The test the investigator thought required quantitative data actually was for determining conductivity only. The process has been evaluated, and recording quantitative data does not supply any information that could be used to determine if a trend was developing. This information was conveyed to the investigator who did not understand why, in this particular test, quantitative data was not needed to ensure the product met specifications.

Note the specificity and proactive tone of the "better" responses. Note how they each demonstrate the company's understanding and control of the issue. They are not argumentative nor do they offer opinion – just facts.

Not Responding is Not a Smart Option

If you receive a 483 inspection observation, your main objective should be to limit any potential financial and legal damage to your company and address the observation as soon as possible.

There is no legal requirement for you to respond to a 483. But always keep in mind that a 483 is just an investigator's opinion. So a timely and thoughtful response is your best -- and perhaps final -- chance to tell your side of the story before the Agency considers additional action.

Admittedly, it's a delicate balance. You must take up for yourself. But if you show contempt for the Agency and its people, you likely will be forced into compliance through further legal procedures that can cost you increased expense, adverse publicity and loss of business.

Instead, demonstrate to FDA that you recognize the Agency's concerns and are working to resolve them without the need for further legal action. Then the Agency may move on to a "bigger problem" company while continuing to monitor your progress.

What's certain is this: no response, a tardy response, or a poor response to a 483 inspection observation can increase the likelihood of a Warning Letter landing on your CEO's desk.

Additional Resources for Your Response

You can find additional information about FDA's approach to issuing Form 483s and Warning Letters at these three Agency links:

- Frequently Asked Questions about FDA Form 483s
- Chapter 4-1 of FDA's Regulatory Procedures Manual
- Field Management Directive No. 120 (guidance for handling unsolicited 483 responses)

In fact, FDA makes its entire inspection "playbook" publicly available: the Investigations Operations Manual (IOM) is the primary policy guide for all of its field investigators and is updated annually. EduQuest offers a full PDF version of the 2015 IOM for free download from its website.

About the Author

Martin Browning *served as an expert field investigator and as the Special Assistant to the Associate Commissioner for Regulatory Affairs during his 22-year career at FDA. He also co-wrote the original 21 CFR Part 11 regulation and contributed to the development of the Quality System Regulation (21 CFR Part 820). In 1995, he co-founded EduQuest, a global team of FDA compliance experts who provide mock FDA audits, regulatory advice, and a series of FDA compliance training classes.*

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