REGULATORY

How to respond to **FDA Form 483s and warning letters**

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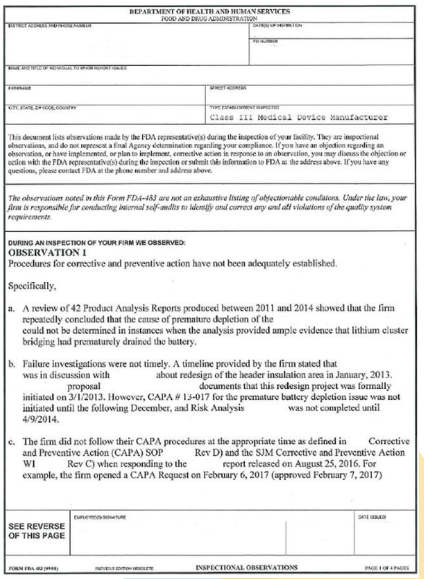
FDA issues hundreds of Form 483s and dozens of warning letters annually. What should you do if one shows up on your desk?

There are many reasons medical device manufacturers receive FDA warning letters, but the root cause often boils down to one thing: Manufacturers weren't prepared to respond to observations cited on the FDA's Form 483.

In 2015, the FDA conducted 1,484 U.S. medical device inspections, with about half resulting in a dreaded 483. Manufacturers have just 15 business days to fully address the inspection findings, evaluate the root causes and identify short- and long-term corrective actions with realistic milestones and timelines. It's a challenging demand and an area in which many manufacturers fall short.

The FDA issued 121 quality system warning letters to medical device manufacturers in 2015. The most-often-cited violations included deficiencies in CAPA and production & process controls (P&PC); the letters often find that a 483 response was deficient. Do you know what to do if an FDA inspection of your facility results in a 483?



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Class III Medical Device Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

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 any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:
OBSERVATION 1
Procedures for corrective and preventive action have not been adequately established.

Specifically,

a. A review of 42 Product Analysis Reports produced between 2011 and 2014 showed that the firm repeatedly concluded that the cause of premature depletion of the could not be determined in instances when the analysis provided ample evidence that lithium cluster bridging had prematurely drained the battery.

b. Failure investigations were not timely. A timeline provided by the firm stated that was in discussion with about redesign of the header insulation area in January, 2013. proposal documents that this redesign project was formally initiated on 3/1/2013. However, CAPA # 13-017 for the premature battery depletion issue was not initiated until the following December, and Risk Analysis was not completed until 4/9/2014.

c. The firm did not follow their CAPA procedures at the appropriate time as defined in Corrective and Preventive Action (CAPA) SOP Rev D) and the SJM Corrective and Preventive Action WI Rev C) when responding to the report released on August 25, 2016. For example, the firm opened a CAPA Request on February 6, 2017 (approved February 7, 2017)

SEE REVERSE OF THIS PAGE

INSPECTIONAL OBSERVATIONS

1: Minimize the damage

The close-out meeting at the end of the inspection can be crucial to minimizing the damage from a poor showing during the inspection. If the investigator observed objectionable conditions at your facility, he or she will present the findings at the close-out.

Take the time to listen. Use the meeting to fully understand the intent and scope of the observations. Ask for clarification when needed, but remember that everything you say is likely to be included in the Establishment Inspection Report (EIR). Correct any misperceptions or inaccuracies and be prepared to provide evidence to support your claims. Only observations you can demonstrate as factually incorrect are likely to be modified or removed from the 483.

2: Take the inspection process seriously

When the FDA sends an investigator to your facility – sometimes for days, weeks or even months at a time – it's a significant investment. Be sure to take the inspection process seriously and give it the preparation and attention it deserves.

Identify the internal and external resources you'll need to prepare for and manage the inspection. Make sure you're ready by assigning front-room roles and responsibilities at your facility, including hosts, runners, subject-matter experts and scribes. Demonstrate professional respect and engagement by including senior leaders in the inspection's opening and close-out meetings. Set up a back room for quick responses to document requests. Any employee can be called on during an inspection, so train them all on inspection behaviors and protocol. If needed, hire a consultant with experience in medical device quality system improvement and remediation to help prepare for an inspection or respond to a 483. Remember, your organization will have just 15 days to fully address the inspectional observations.

3: Cooperate with FDA investigators

Arguing with the FDA is never a good idea – not during the inspection, the close-out meeting or in your written response. Listen carefully and review the 483 observations thoroughly before you try to defend your position. Ask questions if you need more information. FDA investigators often have a broader perspective and it may take some time to fully understand their concerns.

After that, if you disagree with the findings, respectfully explain your concerns and provide objective evidence to support your position. If necessary, request a separate meeting with the FDA district office to further

discuss the issue. If you're unsuccessful explaining your position during the inspection or follow-up, don't use the same rationale in your written response.

Correct as much as possible in the first 15 business days and provide realistic completion timelines for longer-term corrective actions. The FDA understands that it's not always possible to complete corrective actions in just 15 days, but a detailed response with reasonable milestones and completion timeframes will show that you're cooperating and are committed to addressing the issues.

4: Provide evidence of your actions

Failing to provide objective evidence may be the most common inadequacy in unsuccessful 483 responses. You may have revised the appropriate procedures, conducted training and performed retrospective reviews, but the FDA will not take your word for any of it. If you don't document your actions, the FDA may conclude you didn't do it.

Provide evidence of completed corrections and corrective actions in your response, including updated procedures, training records, CAPA plans and reports. The same holds true if you must argue an FDA observation. You will need to provide objective evidence that an inspection finding is factually incorrect for the FDA to reconsider an observation.

5: Focus on the details

Your response to a 483 or a warning letter should be comprehensive and address all observations or violations. Be sure to address specific examples. Many manufacturers focus so much on addressing the root cause of the issue that specifics are overlooked.

When revising or creating procedures, it's important to fully understand the FDA's definition of "establish:" To "define, document (in writing or electronically) and implement." New procedures are not "implemented" until SOPs are in place and training is complete. FDA expects you to include evidence of training in your response package.

6: Look beyond the details

Although it's important to address specific examples of non-compliance, don't overlook the larger quality system glitches that allowed the non-compliance in the first place. The "Band-Aid approach" doesn't work. Look beyond the immediate issue to anticipate similar non-compliance issues and take systemic corrective action. You need to understand the root cause to truly understand its impact on all products. Manufacturers commonly underestimate the breadth or impact of a cited non-compliance.

Just as it's important to look beyond the immediate issue and take systemic corrective actions, we must also look back and evaluate the impact of long-standing deficiencies on past practices, decisions and records. Consider conducting a retrospective review to identify and remedy past deficiencies. When new or revised procedures result in significant changes to processes or decision-making criteria, a retrospective review may be needed. Two years is generally considered an adequate timeframe for a retrospective review, but a longer duration may be necessary for long-standing or high-risk issues. Be prepared to defend the duration of the retrospective review as well as any sampling plans that are used to analyze the data as part of the response.

Keep all these steps in mind when the FDA comes calling. They may help in your response to 483s and warning letters. The FDA will focus on what's wrong with your medical device quality system. It's up to you to determine the best way to fix it.

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