Post Pandemic FDA Inspections: FDA 483 and Warning Letters

Post Covid-19 Pandemic FDA Inspections

Now that Covid-19 Vaccinations are rolling out, OPTIM Associates expects to see more Foreign and Domestic Inspections on the horizon. Quite simply: more inspections lead to more 483's and more OAI Classified 483's leads to more Warning Letters.

In preparation for this expected trend, preparation is key. This White Paper discusses how to respond if your organization receives a 483 or a Warning Letter from the FDA. These recommendations are based on years of experience, including successfully guiding clients through the journey from citation to successful closure. A sample Warning Letter Response is included at the end of this White Paper.

Recent FDA Decisions

March 2020 FDA has protected their investigators from Covid-19 Pandemic and suspended Foreign Inspections (FDA Notice) and Domestic Inspections (FDA Notice) of Medical Device companies.

July 2020. The FDA published a goal of resuming domestic on-site inspections the week of July 20. (FDA Notice)

As of as of June 30, 2020, the FDA completed only 2 inspections of Medical Device Companies in FY 2020. (FDA Published Data).

Reasons for 483 / WL

There are many reasons medical device manufacturers receive 483's from the FDA – failing to maintain proper documentation, overlooking or not completely investigating customer complaints, incomplete corrective and preventive action (CAPA) files, poor design controls to name just a few.

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If 483's are not properly addressed, they can lead to OAI Classification. (i.e., Official Action Indicated, meaning objectionable conditions were found and regulatory action should be recommended) and a Warning Letter.

If Warning Letter responses are not properly constructed, the FDA could escalate to a Consent Decree, impose significant penalties, injunctions and import bans. Additionally, they can suspend pre-market clearance activities. It all leads to major business disruptions, increased expenses and decreased revenue.

Like any business challenge, an effective response requires experience, dedication, short and long-term focus on the entire company's resources to resolve the problem(s) as well as continue to run the business. The end goal is to repair whatever issues were found—as well as those that weren't found—to ultimately leave your company with a greater competitive advantage.

Before we get into the nuts and bolts how to respond, let's set the context for exactly "What is a 483 and what is a Warning Letter".

Context: What is an FDA 483?

An FDA 483 actually is short-hand reference an actual FDA Form #483. The form contains the investigator observations that document any conditions that may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts or regulations.

At the conclusion of an inspection, the FDA Form 483 is presented and each observations are read and discussed with the company's senior management to ensure full understanding of what the observations are and what they mean.

The observations are listed in descending order of importance and the investigator makes sure that senior management understands that the specific observations is not an all-inclusive list, but more of a snapshot of issues noted at the site.

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It is vital to understand that the FDA Form 483 does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations. Rather, the FDA Form 483 is considered—along with an Establishment Inspection Report, all evidence or documentation collected on-site, and any company responses—and then determines what further action is necessary to protect public health.

***NOTE**: While you are not required to submit a written response to a Form 483, it's considered best practice to respond to the FDA Form 483 in writing within 15 calendar days. If you do not respond within 15 days the agency does not have to consider your response in their decisions for further possible escalation.*

Context: What is an FDA Warning Letter?

After a Form 483 is issued and the inspector completes the Establishment Inspection Report, the agency may issue an FDA Warning Letter.

A warning letter indicates that FDA officials have reviewed the 483 Observations—as well as any company responses—and documents their determination that the company has significantly violated FDA regulations.

The Warning Letter identifies the violation(s), such as inadequate design practices, manufacturing practices, problems with claims for what a product can do, or incorrect directions for use. Some specific examples are listed below.

- *Failure to establish and maintain corrective and preventive action procedures, as required by 21 CFR 820.100.*
- *Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure, as required in 21 CFR 820.75(a).*
- *Failure to establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit, as required by 21 CFR 820.198(a).*
- *Failure to establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements, as required by 21 CFR 820.50.*
- *Failure to establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met, as required by 21 CFR 820.30.*

The Warning Letter also makes clear that the company must correct the specific problems and provides directions and a timeframe for the company to inform FDA of its plans for correction. Additionally, the agency states that the documented violations do not represent an "all-inclusive list of violations" and that it is the company's responsibility to make sure the entire QMS is in compliance with the regulations.

***NOTE**: You should take immediate action to correct the violations cited in this letter. This letter is not meant to be an all-inclusive list of violations that exist in connection with your product(s) or operations. It is your responsibility to ensure that your actions and the products you sell are in compliance with applicable legal requirements.*

The Warning Letter specifies the required response time frame—usually 15 calendar days—and their expectations of what should be included (i.e., the specific steps to correct the violations, including how your company plans to prevent the violation(s) or similar violation(s) from occurring again.)

***NOTE**: If your firm's planned corrections and/or corrective actions will occur over time, please include a timetable for implementation of those activities in your initial response. If corrections and/or corrective actions cannot be completed within fifteen calendar days, please state the reason for the delay and the time within which these activities will be completed.*

How to Respond?

Although every situation is different, the following steps are almost always effective when facing FDA scrutiny and potential regulatory action.

OPTIM Associates recommends both a 483 and a Warning Letter response to include a Cover Letter and a Phased Program Plan to address the specific issues and any latent quality systems challenges. We have also listed some general guidance and a sample WL Response at the end of this article.

A. Develop an Effective Cover Letter

Issuing the initial response to a 483 and/or Warning Letter is one of the most critical regulatory responses you will ever have to provide to FDA. A thorough, thoughtful and meaningful response can change the tenor of the interaction with FDA and establish your company's commitment to quality.

Conversely, a misguided or antagonistic response can be a key reason for escalation to further enforcement action.

A well-constructed cover letter that emphasizes your company's (and its executive team's) commitment to quality and compliance sets a positive stage for responding to any FDA findings. Like all good writing, a good cover letter should state up-front what you are going to tell the agency. A message of "we hear you" and "commitment to patient safety is paramount" should be reiterated throughout the response.

In cases where resources are limited, it may be wise to state up front that expert consultant(s) have been engaged to assist in remediation, showing the company's commitment to thorough remediation.

A sample Warning Letter Response is included at the end of this White Paper.

B. Develop a Phased Program Plan

The more comprehensive the response, the more FDA will be assured that your company takes its concerns seriously. Develop and provide as much detail about your company-wide **Quality Systems Improvement Plan (QSIP)** and your intentions to follow it.

The recommended major contents of your QSIP are as follows:

I. Phase 1: Quality Systems Improvement Plan (QSIP) Ownership

The ownership section should outline the following:

- Ownership of the QSIP.
- Roles / Responsibilities of Executive Management within the QSIP.
- Roles / Responsibilities of other Directors, Managers and employees within the QSIP.
- Whether you are going to utilize outside resources and if so, who are they?

II. Phase 2 – Immediate Gap Identification and Analysis.

This should address the need for immediate containment or retrospective record review. Identify if you need to institute any Containment Activities or Retrospective Record Review to address any 483 / WL items and describe how this will be done. Describe to the agency how this will be done.

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III. Phase 3 – System-Wide Gap Identification and Analysis.

This should address an overall Quality Management System assessment of gaps the FDA may not have found during their inspection and/or investigation. Describe to the agency how this will be done.

Since both the 483 and Warning Letter observations are just a "snapshot" in time, it is best to evaluate the entire QMS.

IV. Phase 4- Root Cause Investigation.

This should be an indepth investigation to determine the actionable causes that lead to the 483 / Warning Letter Observations as well as any other system-wide Gaps identified in Phase 3. Describe to the agency how this will be done.

Many techniques are available including, a "Five Whys" Analysis or a "Fishbone" Diagram (a.k.a., Ishikawa Diagram).

V. Phase 5- Development and Implementation of CA/PA Plans.

Under the umbrella of the top-level QSIP, develop individual CA/PA Plans to address the grouped Gaps identified in Phase 3. Major elements of this phase may include process mapping, developing or revising Standard Operating Procedures (SOP's), Work Instructions (WI's) and Forms / Templates. Describe to the agency how this will be done.

Creating new documents and/or records as well as developing new training materials and executing training may also be necessary. During this phase, it is recommended that the closure and effectiveness criteria is pre-specified.

VI. Phase 6- Verification of Effectiveness (VOE).

This phase should address the effectiveness of the CA/PA Plans developed in Phase 5 to close the Gaps identified in Phase 3. Make sure that the effectiveness criteria are met as specified in Phase 5. Describe to the agency how this will be done. In some cases, effectiveness may be determined via a third party audit.

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Guidance and Best Practices

- Respond On Time

  A due date will be noted in a Warning Letter, usually 15 calendar days. An extension can be requested with justification of why more time is needed. Additionally, make sure you respond as promised with your regular agency updates.

- Take Responsibility

  Accept responsibility as top level management. Not passing the buck will demonstrate recognition of seriousness of violations and your commitment to comply with applicable laws and regulations.

- Take the Warning Letter Seriously

  The FDA took considerable time investigating your issue and writing up the 483 / WL. Be sure to take the 483 / WL and subsequent communications seriously and give it the preparation and attention it deserves.

- Assign A Response Team

  The 483 / Warning Letter will most likely be addressed to top level management. Those ultimately responsible (Top Level Management) should assign an owner to write the response and a group to review and finalize the response to the 483 / WL and assign supporting groups and individuals to help the owner drafting, reviewing and finalizing the 483 / WL response(s) and any corrective action plans to be developed.

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Sample Warning Letter Response

Response to <###> Warning Letter dated <MM/DD/YYYY>

Dear <Agency Personnel>,

<Company Name> recognizes the serious nature of the Warning Letter and FDA's concerns resulting from the inspections conducted at <Site Location(s)>.

<Company Name> understands that the list of deficiencies noted during the inspections does not represent an all-inclusive list of the possible violations at their facility. Therefore, as a result of the serious nature of the concerns, <Company Name> has partnered with <Consulting Company> to help us comply with applicable regulations. Reference Attachment 1: Individual Warning Letter Observations and Response.

Additionally, <Company Name> in conjunction with <Consulting Company> has performed an initial assessment to determine potential risk to patient safety and product quality. Reference Attachment 2: Impact Assessment. <Company Name> in conjunction with <Consulting Company> has also developed a Quality Systems Improvement Plan (QSIP) to facilitate the actions required to bring <Company Name> into systemic compliance with the Quality System Regulations in a timely and efficient manner. We believe that this response demonstrates the level of commitment <Company Name> has made to address the deficiencies by implementing and sustaining the quality system approach outlined in the QSIP. Reference Attachment 3: Quality System Improvement Plan (QSIP).

As part of the QSIP, periodic updates showing the progress made and adherence to this plan shall be submitted to FDA. Please see the chart contained in the QSIP that outlines the processes to be established and submitted to FDA.

We sincerely appreciate the cooperative support that has been offered to <Company Name> as we continue to work through this difficult time. If you have any questions or require additional information regarding this response, please do not hesitate to contact the individuals below.

Sincerely,

<Company Top Management Individual>
<Company Top Management Title>
<Company Top Management Contact Information>

<Consultant Company Name>
<Consultant Company Individual>
<Consultant Company Title>
<Consultant Company Contact Information>

Attachment 1: Individual Warning Letter Observations and Response.
Attachment 2: Impact Assessment.
Attachment 3: Quality System Improvement Plan (QSIP).