ADDRESSING AN FDA FORM 483

CLARKSTON CONSULTING

You are in the middle of an FDA inspection and a significant issue just surfaced.

How you handle the situation may determine whether the agency issues an FDA Form 483. Even if you do receive an FDA Form 483 at the end of your inspection, all is not lost; you just have a lot more work to do, quickly. This paper provides guidance to help you optimize the possible outcomes. Let's start with some basic information about FDA Inspectional Observations.

The observation process is required per the Federal Food, Drug, and Cosmetic Act (FDCA) [21 USC 374(b)]. In 1953, section 704(b) was added to the FDCA to provide a process to prevent FDA enforcement action without prior notice being provided to firms. This resulted in the creation of the FDA Form 482 "Notice of Inspection" and FDA Form 483 "Inspectional Observations". The FDA Form 482 provides firms assurance that the inspection is authentic. The FDA Form 483 documents the Investigators' finding of significant objectionable conditions or practices. The cited Inspectional Observations may or may not constitute FDCA violations. The concern is based upon risk that the product is adulterated, may become adulterated, or there are suspected specification non-conformances that may indicate the product is unfit or unsafe for use. The FDA Inspectors are instructed to list the observations in the perceived order of significance.

The FDA and industry have related but differing views on Inspectional Observations. From the FDA's perspective, the observations provide the agency with the opportunity to give firms feedback for voluntary compliance. The observations also comply with FDCA § 704(b) and provide warning prior to enforcement actions. From industry's perspective, the observations are a public scorecard and many firms request confidentiality of the information since the data is available via the Freedom of Information Act (FOIA) [21 CFR 20.101(a)]. The investigators' concerns help industry maintain and advance current Good Manufacturing Practices (cGMPs) in the absence of "best practice" sharing.

Our goal is to ensure the FDA Form 483 does not escalate into a more serious Warning Letter or enforcement action. At the conclusion of the inspection, the inspector can only issue a Form 483; a warning letter could be issued later. The FDA views a warning letter as an "advisory" action rather than an enforcement action. Warning letters are available on the FDA's public website and explain areas of non-compliance that could lead to legal liability and might result in shareholder or consumer litigation actions; not to mention your damaged reputation and competitive disadvantage the public disclosure may bring. If you fail to address the warning letter appropriately, you may be subject to enforcement actions such as an untitled letter, product recall, product seizure, injunction, fine, debarment, disqualification, license suspension or revocation, prosecution, consent decree, withheld approval of New Drug Applications (NDA), denied Certificate to Foreign Government (CFG) for Export, or Import alert.

In view of these implications, it is important to meet the FDA Form 483 response deadline and to provide enough information to the FDA to ensure no further escalation is warranted. The FDA requires a focused response within 15 working days. Best practice for response preparation is to involve all stakeholders in the investigation, solution development, and any required mitigation of root causes that resulted in the observation. It is imperative to have commitment from all stakeholders regarding the root causes and actions to take since the outcome is so critical. In complex cases, the development of the full corrective action plan or complete implementation of the actions may take longer than the 15 working days allowed for the response. In this case you must share your detailed plans and completed actions with the FDA during the regular updates.

WE RECOMMEND A FIVE-STEP PROCESS TO PREVENT OR DEAL WITH THE FDA FORM 483:

1. Understand
2. Study
3. Respond
4. Continuing Investigation
5. Follow Up

understand.

The first step is to fully understand the inspectors' concern. You will have at least three opportunities to discern the inspectors' understanding of the situation: During the inspection; at the daily wrap-up; and at the close-out meeting.

During the inspection it is important to listen to and clarify the discussion between the investigator and the site Subject Matter Expert (SME). Ensure the investigator has an accurate understanding of the situation. If necessary, pause the discussion and convene knowledgeable SMEs to gather additional evidence that demonstrates compliance to your system and applicable regulations. Do not argue with the inspector or imply the inspector does not understand.

Your next opportunity is at the daily wrap-up. If the investigator presents a concern, it is important to clarify the situation to ensure you fully understand the identified gap. Provide objective evidence to the investigator of any deficiencies that were corrected during the inspection. Be very careful when doing this – actions need to be fully thought out and the change process must be followed. This includes the process to update the related documentation, and all training must be completed before any changes are implemented. Hastiness may create bigger issues if process shortcuts are taken.

The final opportunity for clarification is at the inspection close-out meeting. The investigator is unlikely to consider new information at this time – they will ask you to include the information in the response to the FDA Form 483. However, if an observation has already been closed out during the inspection and evidence can be provided at the close-out meeting, you should present it, as it may be accepted by the inspector at that time.

The FDA Form 483 will be presented at the inspection close-out to the most senior manager present; usually this is the site leader. The investigator will present the Inspectional Observations one by one. This is your final opportunity for clarification from the inspector. Ensure you fully understand the issue and the intent of the wording used in the observation. Correct any misperceptions or inaccuracies that may be included. Only observations shown to be factually incorrect and supported by objective evidence are likely to be modified or removed. Be careful since everything you say will be part of the official record of the audit and will likely be included in the Establishment Inspection Report (EIR). Ask for the inspectors' view of the significance of the Inspectional Observations. The FDA will not classify the observations as Critical, Major, or Minor but the inspector may share an opinion on whether the EIR will be classified "Voluntary Action Indicated (VAI)" or "Official Action Indicated (OAI)."

At the conclusion of the close out meeting, thank the investigators for helping you improve your quality systems and promise that you will provide a written response within 15 working days.

Note: The Medical Device FDA Form 483 has an optional annotation section where information on each observation can be entered during the inspection close out meeting:

- Reported corrected, not verified
- Corrected and verified
- Promised to correct [by xxx date] or [within xxx days or months]
- Under consideration

study.

Now that the inspectors have left, it's time to study the report. It's important to take the observations seriously – if it was critical enough for the FDA to document, it needs to be addressed. It may take some additional research to fully understand the observation.

Assemble a team to address the findings; include Quality Assurance, Operations, Compliance, Regulatory Affairs, and applicable SMEs. Identify a team leader to oversee preparation of the response. Evaluate the need for additional organizational or external experts to fill knowledge gaps and assist with the effort.

It is important to clearly formulate the problem statement in order to address the concerns. The FDA Form 483 uses best-match phraseology from their database and this "boiler plate" wording may not best describe the true concerns. Use your understanding from discussions with the investigator to clearly identify the concerns that have been raised. Evaluate the examples the FDA provided as evidence. Review all related documentation from the inspection and any additional documents that may not have been presented to the FDA. Reread the applicable regulations and find the preamble from when the regulation was published. Sometimes the preamble will clarify the FDA's intent. You may want to contact the FDA directly to develop an appropriate understanding of their concerns, verify adequacy of proposals, and achieve agreement on approach. Involve your regulatory team and legal counsel prior to making contact to ensure their agreement.

After your problem statement is formulated you can start the investigation. Be sure to document the scope of the investigation and the investigation methodology used. The goal of the investigation is to determine the true root causes that led to the situation cited by the FDA. Document the root cause analysis tools used in the investigation. For each cited example clearly articulate the root cause and the actions needed. This may involve immediate corrections to address the cited situation as well as corrective actions to prevent recurrence. Preventive actions are also needed to ensure similar risk areas are addressed. Expand the investigation outside the immediate focus to look for systemic issues that could be contributing causal factors. If systemic factors are identified, additional actions are needed to address these root causes.

The FDA will be concerned with the patient safety implications of the observations. Analysis and documentation of product impact is critical. Evaluate the safety, identification, strength, purity, and quality (SISPQ) of the product. If there is product impact, document actions taken concerning this product. If there is no product impact, describe how this was determined and provide supporting evidence. This documentation should be in your Quality System.

Best practice is to develop a parent Corrective Action/Preventive Action (CAPA) Plan in your Quality System for each observation. With a unique CAPA Plan for each observation you can document your plans and demonstrate progress, as well as report closure when the individual actions have been completed. However, related observations that are very simple and straightforward may be combined into one CAPA Plan. Each CAPA Plan should drive for identification and implementation of true solutions that are achievable in a realistic time frame. Ensure focus on both the cited issues as well as any related systemic issues. For the cited examples, provide specific corrective actions to address and correct each separate issue. Provide a detailed explanation and a mitigation plan for any issue that cannot be immediately corrected.

For any systemic issues, the CAPA Plan needs to extend beyond the specific cited issues. It may be necessary to invoke change control to revise SOPs, develop new SOPs,

and validate or revalidate test methods, processes and systems. Ensure any required training is completed before implementation of the changes.With a preventive action mindset, review for similar gaps in other systems. Look at a longer time span, other products using the same systems, and any similar processes in other quality systems.

Evaluate the need for product actions on impacted products and impacted lots. If product actions are necessary, implement by putting quality holds on current inventory both on-site and in distribution. If product is not under your control, evaluate the need for a recall. An FDA Field Alert Report may be required.

For actions that may take significant time to fully implement, a mitigation plan is necessary to assure compliance until permanent solutions are in place. This plan should address interim controls such as additional manufacturing controls, process monitoring, in-process testing, or release testing.

Focused and measurable effectiveness checks should be planned to verify resolution within a reasonable time frame to ensure the action had the intended impact. Consider utilizing experts from outside the process to conduct the effectiveness checks for an objective perspective. Attach documented evidence to prove effectivity.

respond.

Once you have evaluated the causal factors, determined the true root cause(s), and developed the appropriate CAPA Plans, you are ready to write your response to the FDA Form 483 Inspectional Observations.

The initial response can be preliminary but the CAPA Plan should be well defined. Your planned path forward must be clearly communicated to the FDA. Warning Letters often result from inadequate response to the FDA Form 483. There are two objectives for the response: 1) Explain the process to correct and prevent compliance problems (CAPA Plan), and 2) Provide understanding of whether issues underlying the observations have any adverse impact on the safety or effectiveness (SISPQ) of products. This includes providing objective evidence that products are safe and effective in order to remain on the market. If they are not safe or effective, take voluntary action through field corrections, product withdrawal, or recall.

The FDA is your only audience for the FDA Form 483 response but there are several groups within the agency that may be reviewing your response: Investigators, District Office Director or Compliance Officer, and applicable FDA Center offices such as Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER). You must convince these readers that you take the observations seriously and are committed to eliminating the root causes at an organizational level. Write your response with these concepts in mind.

Your language should be clear and compelling - leave no doubt about what you intend to do to correct the situation. Provide a factual specific response to each observation in a chronological narrative format. You want the response to be easy to follow with well-supported descriptions of events, systems, procedures, and other information relevant to the situation. Anticipate potential questions the readers may have and put the company in the best light possible.

We recommend using a three-part structure:

i. Cover letter
ii. Body
iii. List of attachments

1. Cover Letter

The cover letter should begin by respectfully thanking the FDA for identifying opportunities for continuous improvement. Acknowledge the firm's obligation to comply with the law through commitment to action without being self-incriminating. Provide a high-level background or context for the response as a whole. If the actions have not yet been fully implemented, communicate the frequency of periodic updates with supporting rationale. Updates are typically provided monthly. The cover letter should be written and signed by senior management.

2. Body

In the body of the response, provide a separate section for each observation. Start with a verbatim re-statement of the observation cited by the FDA. Acknowledge the issue cited while providing contextual background for the situation. Include any necessary clarifications or new evidence not seen during the inspection.

In the discussion of each observation, address both the specific examples cited as well as any systemic issues that contributed to the situation. Include an explanation of the root cause assessment of the problem. If additional time is needed for further investigation, provide a target date for completion. Explain and justify the significance of the observation to assure the quality of distributed product.

Elaborate on the CAPA Plans by including a description of actions. Explain all actions taken to immediately correct issues. Explain corrective actions to address the cited issues. Include explanations for preventive actions taken to address any systemic issues found.

For completed actions, provide completion dates and objective evidence with referenced attachments. Be sure to address the specific examples related to the cited deficiencies. Objective evidence should be referenced and attached as proof of action. Direct the reader to the pertinent portion of the referenced attachment. Be sure to include all related training records to demonstrate full implementation. These also need to be clearly referenced and attached

For ongoing actions, provide description of work completed to date and realistic expected completion date of remaining work.

Provide plans for any identified future actions. These can be applicable to the specific examples related to the cited deficiencies or global or systemic issues that go beyond the cited deficiencies. Ensure the projected completion dates for each are reasonable, responsive, and have a realistic timeline.

3. List of attachments

As stated in the previous section, all attachments should be referenced within the body of the response. Do not include un-referenced attachments. Clearly describe and identify each attachment. The attachment number and name should exactly match between body and the list. Reference the specific section of the attachment that addresses the topic discussed in the body of the response. The goal is to make the referenced material easy to find, read, and understand.

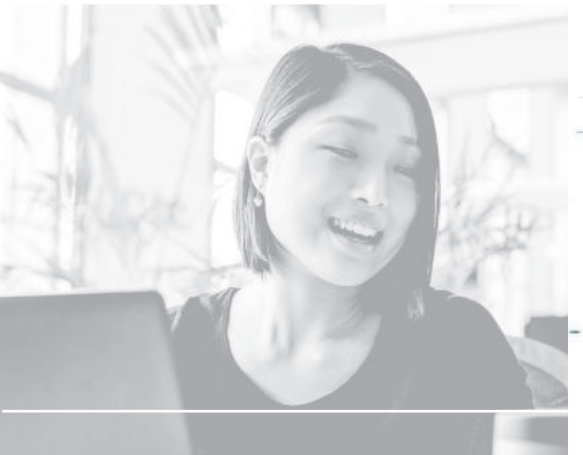
Before you submit your response, be sure to assess it for quality and thoroughness. Proofread, edit, and rework to assure there are no inaccurate statements or typographical errors. Be as complete and compelling as possible. Double check to ensure all citations have been explicitly addressed and any related systemic issues are resolved. Seek the help of independent qualified reviewers for assessment of the response prior to submission.

Send the response letter to the appropriate FDA office via certified mail, FedEx, or electronic submission as instructed.

continuing investigation.

While the response is being prepared and after submission, continue the investigation and implementation of CAPA, if not already completed. Ensure all commitment timelines are met. Confirm root cause identification and resolution through process monitoring.

Carry out internal quality audits and effectiveness checks within a reasonable time frame to identify any additional gaps requiring action. There are many citings in FDA Form 483 and Warning Letters for lack of adequate effectiveness checks. Analyze the results and, if necessary, implement additional solutions.



follow-up.

Track progress of the CAPA Plans very closely and continuously prepare for the next periodic follow-up letter to the FDA until all CAPA are reported closed to the FDA.

All follow-up letters should use the same structure as the original response letter. In the letter review the progress made since the communication and explain any delays on pending actions and what was done to mitigate the impact. Include and explain any new information discovered. In the final letter reporting full closure of all CAPA Plans, identify the recipient of the EIR.

The EIR process is described under directive DIR-000067 "FMD-145 – Release of the Establishment Inspection Report (EIR)." The FDA will release to the inspected firm only the narrative portion of a redacted EIR or abbreviated report. Attachments and exhibits will be excluded. FMD-145 letters will be transmitted within 45 calendar days of the determination that the inspection is closed per the FDA procedures for release of the EIR [21 CFR 20.64(d)(3]). The timeline will be expedited if requested by the Division of Information Disclosure Policy in response to a FOIA request.

common mistakes.

There are several common mistakes that firms make that are easily avoided if recognized. Review the following list to ensure you are not making any of these mistakes:

- Defending non-compliant practices / procedures
- Arguing with or dismissing FDA's concerns
- Response not clear/understandable
- Failure to address the violation
- Failure to address the sited examples
- Failure to properly identify root cause
- Failure to assess all "affected" product
- Failure to "correct the record"
- Failure to perform "systemic corrective action"
- Failure to consider or conduct retrospective reviews
- Failure to provide objective evidence of action implementation
- Failure to provide evidence of training to updated procedures / processes
- Failure to implement commitments
- Failure to optimize the time available for response preparation
- Failure to identify correct action due dates
  - Unreasonably long timelines
  - Unrealistic goals
  - Missed due dates
  - Due dates not defined
- Self-incrimination
- Referencing other firm's or sister site's practices
- Blaming everything on lack of training
- Re-training as the primary solution
- Referring to attachments without explanation
- Lack of careful review / proofreading of all documents

conclusion.

Industry and FDA have a mutual objective in this process: Protecting public health through compliance. Our goal is to avoid escalation or enforcement action. The only proven technique to do this is to establish an effective Quality System that is well defined, documented, and implemented. Commitment to bring in outside help in setting up the Quality System may avoid escalation by the FDA. Effective organizational communication is vital, and accountability must be achieved. Stakeholder commitment for response preparation, issue resolution, quality system enhancements, and resolution of identified concerns in a timely manner is critical. Significant financial investment may be required.

Even the best response may not prevent a Warning Letter. Completion of the CAPA Plan or a promise to correct may not be adequate. Official Action Indicated (OAI) may result when there is a total failure to define, document, or implement a quality system or one of the seven subsystems. FDA's action is influenced by several things:

- Significance of findings
- Company's response
- Inspection report and documentation
- Inspection history

If a Warning Letter is received, repeat this entire remediation process. The Warning Letter is an official notice of a significant violation of the FDCA. It is an opportunity to voluntarily correct violations prior to enforcement action. You need to understand the reason for the escalation and evaluate the need to involve outside help throughout the process. After resolution, the Warning Letter will be followed by Close-Out Letter when compliance issues are confirmed.

Immediately start preparations for your next inspection. Prepare an easy to review package of all actions taken, with objective evidence, for review during next FDA inspection. Monitor the Quality System closely for similar concerns - repeat findings during your next FDA inspection will likely result in a Warning Letter. Review the FDA's top cited observations on the FDA website. The observations are very consistent year-to-year and can easily be avoided. Reinforce the organization's quality culture. Daily work must provide inspection-ready results and associated documentation. Conduct a mock audit to verify the effectiveness of the CAPA Plans and associated remediation projects. Consider if external support is needed to help you to complete all the work required prior to your next inspection.

CLARKSTON CONSULTING CAN HELP

The processes of preparing adequate CAPA plans, responding to an FDA Form 483 or warning letter, monitoring the execution of the CAPA plans, and preparing for the next FDA inspection can be difficult and time-consuming. Clarkston Consulting has the knowledge and experience to support you in these efforts. Utilizing Clarkston Consulting resources as you work through these key areas will minimize the likelihood of escalation and ensure you are ready for your next inspection. Let us work with you to review your situation and demonstrate that we are your best partner to ensure you are always inspection ready.

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