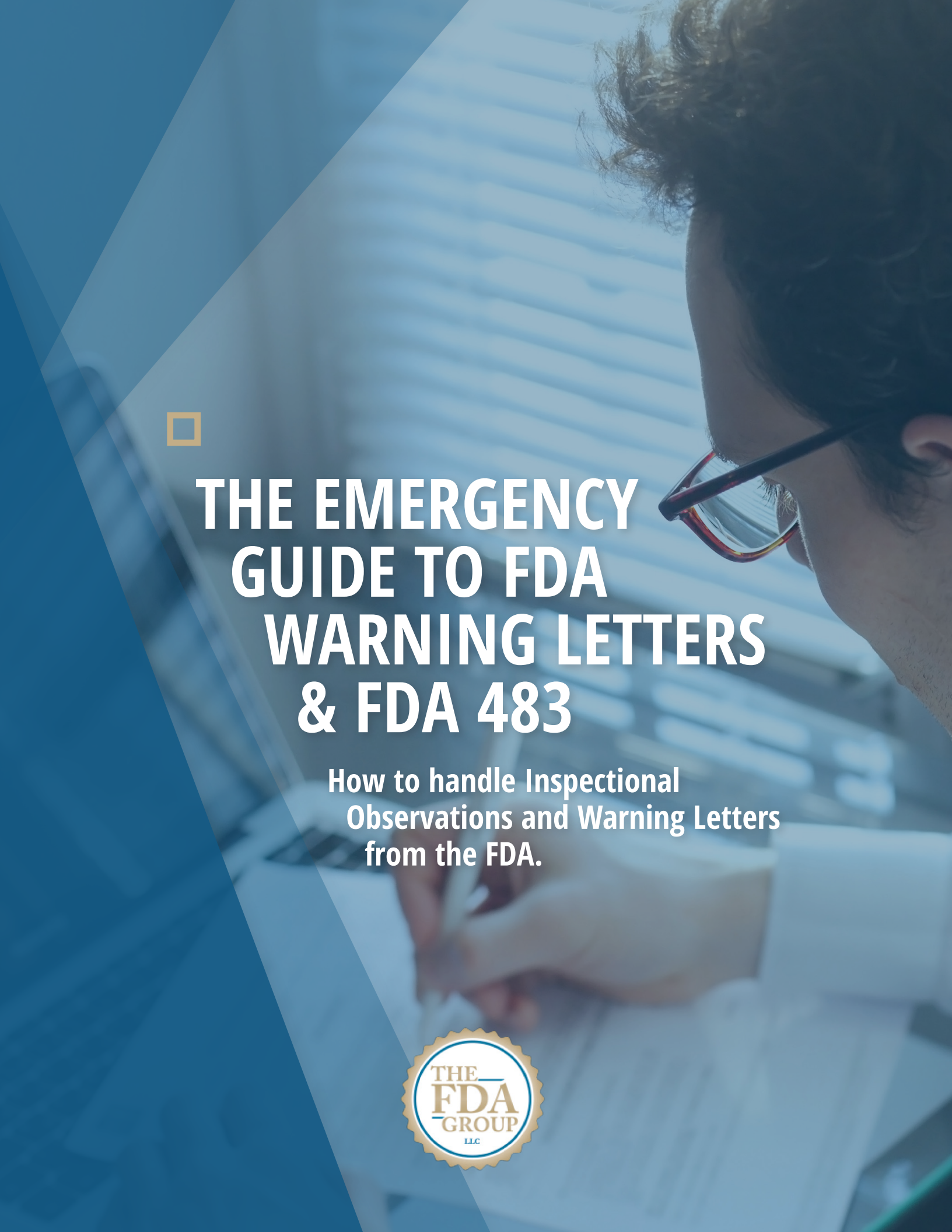

THE EMERGENCY GUIDE TO FDA WARNING LETTERS & FDA 483

How to handle Inspectional Observations and Warning Letters from the FDA.

THE FDA GROUP LLC

STOP.

Before you go any further, understand that a Warning Letter or FDA 483 does not signal the end of your product, your job, or your company. There are clear procedures to follow to overcome this hurdle. We've helped pharmaceutical, diagnostic and medical device companies of all sizes resolve serious regulatory compliance problems. This guide is intended to help you solve these issues, too.

While this resource is a great place to start, real help means working with expert professionals who have been through this before and know precisely how to best address the situation, or better yet, help you prepare for your next FDA inspection. If you're in need of help, contact our team of experts today:

TALK TO AN EXPERT»

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FDA 483

RESOLVING FDA 483 OBSERVATIONS

After an FDA inspection, you may be issued an FDA 483, a form listing Inspectional Observations. First and foremost, it's important to take these observations seriously. Issues observed by investigators that are of questionable or negligible significance will not be listed here. While these Inspectional Observations do not represent the FDA's final determination regarding your compliance, not responding will almost certainly result in a subsequent Warning Letter or further enforcement action.

What are Form FDA 483 Observations?

FDA 483 observations are listed on FDA's Inspectional Observations form when in the investigator's judgment, conditions or practices observed would indicate that any food, drug, device or cosmetic has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health.

FDA law is unique in that the Agency does not have to prove a product is injurious to public health, but only that there are *conditions in which this may occur* (e.g. not following the law and its implemented regulations).

Remember, both you and the FDA share the same goal: **protecting public health by ensuring only safe and effective products are available on the market.** We want our products to make people better, not worse.

It's worth noting that documentation should be considered "products" because as far as the FDA is concerned "if you didn't document it, it didn't happen." Good documentation proves to FDA you did what you said you were going to do: **meet the requirements of the Food, Drug, and Cosmetic (FD&C) Act and its implementing regulations**. It provides proof and confidence that you take your charge to protect the public seriously.

If you have received an FDA 483, take the following steps:

1. Discuss the observations with the investigator to ensure both parties have a correct understanding of the situation.

Ideally, this first step is taken before the investigator leaves your facility. Discuss the observations in person to make sure of two key things:

A. The investigator has an accurate understanding of the situation.

This should be done throughout the inspection, during regular discussions and at daily wrap-ups. If the inspection lasts longer than one day, use the evenings with your team to evaluate any potential FDA 483 issues and prepare any additional objective evidence to support your case on the next day of inspection whenever possible.

B. You agree the observations are stated correctly as written.

In most cases, investigators will not change FDA 483 observations unless factual errors are brought to their attention. Remember that all observations are in the judgment of the investigator and any questionable findings have likely been discussed with others at the Agency. Most comments made by investigators are meant to improve your operations and products. Consider this carefully before disputing their findings.

Once you're confident you understand the investigator's point of view, fix any observations that can immediately be addressed and provide objective evidence of those fixes to the investigator.

Resist the urge to try to resolve everything before the investigator leaves. While it may demonstrate initiative, hastiness also shows a lack of investment to fully investigate the issues as well all any potential systematic problems—not to mention the fact that significant compliance issues cannot always be resolved quickly.

For all observations, a Corrective and Preventative Action (CAPA) Plan will be needed to identify root cause and the actions necessary to resolve the compliance problems at hand. In addition to the immediate issues cited in the observations, it's important to identify and resolve any related issues that may be affecting other facilities and production lines as well. If the issues observed by investigators may be present elsewhere, be proactive by fixing them now.

2. Craft a CAPA Plan.

While you may be eager to begin writing your response as quickly as possible, it's important to step back and form a plan of action first.

CAPA Plans collect and analyze information, investigate and identify the root cause of the product and quality problems (both specifically and systematically) and take appropriate actions to correct existing issues while preventing them from reoccurring.

Although it's possible to create CAPA Plans internally, you may choose to retain outside experts to gain an objective perspective—especially when serious problems threaten your quality systems. Contact The FDA Group to learn more about planning and executing CAPA Plans.

Note for Medical Device Companies:

Medical Device inspections allow manufactures to annotate the observations to provide context or perspective directly on the Form 483. While this may be helpful, remember that Form 483s eventually become public documents available through the Freedom of Information Act.

List the observations that were made and begin investigating for root cause before taking action to resolve issues. To help you formulate your plan, we've listed a number of typical actions that appear on responses below. Use these to begin thinking about what actions you will need implement to resolve the problems cited in your observations. Keep in mind that an FDA 483 is by no means an exhaustive list of all potential compliance gaps.

- Evaluate the issues' impact on products
- Take voluntary action if there is a clear public safety risk
- Place a hold on current inventory, both on-site and in distribution
- Investigate for Root Cause and any systemic issues
- Identify CAPAs for both identified and systemic issues
- Where improved procedural controls are required, update/generate procedures
- Conduct training as needed for current, updated or new procedures with documentation of competency evidence
- Carry out full internal quality audits and analyze any additional gaps requiring action
- Provide objective evidence for CAPAs
- Ensure test methods, processes, and systems are validated or revalidated

Once you've laid out a CAPA Plan that effectively addresses each of the observations in full, it's time to structure, write and submit your response to the FDA.

3. Write and submit an effective response.

Once you receive an FDA 483, you have 15 business days to respond. We've laid out the basic steps to planning, writing and submitting your response below.

YOU MUST RESPOND TO AN FDA 483 WITHIN 15 BUSINESS DAYS.

A. Know who will be reviewing your response at the FDA.

Before you write your response, it's important to know your audience. The FDA investigator assigned to your facility and the FDA's District Office will be the first people reviewing your response, but these are just the first two links in a much longer chain of review.

Officials at FDA headquarters will ultimately be deciding on which actions to take after reviewing your response. As such, it should be written to persuade these officials that your proposed actions for correcting and preventing problems are adequate.

Language should be compelling. Write clear, factual, well-supported descriptions of events, systems, procedures and other information relevant to the situation at hand.

B. Know what FDA officials expect to see in your response.

To satisfy regulators, your response should accomplish two essential objectives:

- Explain the process by which your company will correct and prevent compliance problems (CAPA Plan).

  Explain what you plan to do to correct the violations listed in the observations and prevent recurrence. Assure the FDA that you take the public's health seriously by thoroughly investigating the issues, providing robust actions, and ensuring timely corrections for continuous improvement.

- Provide a thorough understanding of whether the issues related to the FDA 483 observations have any adverse impact on the safety or effectiveness of your products.

Provide objective evidence that the products are safe and effective enough to remain on the market or voluntarily take action (e.g. field correction, product withdraw, recall) if they are not. The FDA will not seize your product if you have already taken steps to protect the public.

At the very least, your response should provide reliable information regarding the integrity of your products that remain on the market.

To ensure objectivity, seek the help of third party experts to conduct independent assessments and report on findings.

C. Write a thorough response.

When you clearly understand who you're writing to and what they expect to see, it's time to sit down and craft your response. The structure of your response should follow this 3-part outline:

COVER LETTER:

Respectfully thank the FDA for identifying opportunities for continuous improvement and clearly denote obligation to comply with the law through commitment to action; written by senior management.

BODY:

Restate each observation and include the following for each one:

- Background information regarding the observation
- An assessment of the root cause of the problem or commitment for further investigation if additional time is needed, with target dates for completion
- Corrective actions, immediately corrected if possible with completion dates and objective evidence to be included with attachments or attainable target dates for completion
- Preventive actions (particularly for any systemic issues found)
- Reference to objective evidence to be included as attachments for each completed action

- Commitment to provide a follow-up response, per specific date, if all actions cannot be completed prior to the 15-day submission timeline for the initial response

LIST OF ATTACHMENTS:

- As referenced within the body, clearly describe and identify (number and name of the attachments in the body should exactly match the number and name in the list)
- Attachments should be easy to find, read and understand. For example, if an SOP is attached, reference the specific section(s) that address the issue in the body to make it easy for the reviewer. Avoid forcing them to search though reams of documentation to understand your improvements.

Here are some important points to remember when writing your response:

BE CLEAR.

While the details of a response depend upon the particular observations cited, it should specifically respond to each observation, be easy to follow and leave no doubt about what you intend to do to remedy the situation.

BE COMPELLING.

Typically, the most effective way to write your response is in narrative form. State the observation and address it in a clear, chronological format allowing you to put your company in the best light possible.

ANTICIPATE POTENTIAL QUESTIONS.

Your response should first focus on addressing the central issues raised in the observations and provide accurate, objective evidence that anticipates and answers the potential questions your action plan lays out.

CAREFULLY MANAGE DISPUTES.

If you decide to dispute an observation, you must be prepared to back it up with enough factual, objective evidence to be convincing. Never ignore an investigator's claims. Even if you believe something may be inaccurate, your response should clearly provide the explanation required to show exactly why you do not concur with the observation.

SUPPORT ALL CLAIMS WITH FACTS AND HARD DATA.

"Just the facts, Madame." Every claim and response you make in your response must be backed up with objective evidence. Unsupported or poorly explained assertions are of no value to the FDA and only raise more doubts about your ability to resolve the problems identified.

ASSESS YOUR RESPONSE FOR QUALITY AND THOROUGHNESS.

Proofread, edit, and re-work your response before submission to ensure it is as complete and compelling as possible. Even one typo or inaccurate statement can hurt the FDA's confidence in your ability to provide high quality products to the market and protect the public—increasing the likelihood that a Warning Letter will be issued and potential escalation to enforcement action.

To ensure perfection and objectivity you may choose to seek the help of third party experts to conduct an independent assessment of the thoroughness and acceptability of the response prior to submission.

CONTACT THE FDA GROUP FOR AN ASSESSMENT »

RESPONSE LETTER CHECKLIST

Use the following checklist to ensure you're submitting a comprehensive response to the FDA.

- ☐ Ensures a commitment for corrective and preventative action from responsible senior quality or management personnel
- ☐ Cites all observations, the organization's response, action plan and evidence of correction
- ☐ Addresses each particular problem—even those explained in longer observations
- ☐ Describes in detail, the underlying root causes and systemic issues specific to the observations and how your organization plans to correct the problems cited
- ☐ Sets realistic timeframes to resolve issues
- ☐ Supplies all the supporting evidence needed to show corrective and preventative action
- ☐ Commits to a follow-up response if all actions cannot be completed prior to the initial response

SUBMISSION

Once you're confident your response is ready for submission, make sure it's sent to the appropriate office within the 15-business day timeframe allotted by the FDA via certified mail. You may be provided instructions to submit your response electronically. Read and follow these instructions and provide a hard-copy via certified mail. You will receive acknowledgment that your response has been received.

After submission, be sure to make good on all commitments, including meeting the dates for all actions and follow-up responses until all actions have been completed (Final Response).

"Do what you say you're going to do when you said you were going to do it."

NEXT STEPS

After the FDA receives your response, one of two outcomes will occur:

1. **Your response satisfies regulators and the matters are deemed resolved. While FDA may send a closeout letter or Establishment Inspection Report (EIR) to acknowledge they've received your response and deem the matters resolved, this confirmation is not guaranteed. If you haven't heard back after 30 days, contact the FDA to follow up on your response.**

   Be prepared to provide an easy-to-review package of all actions taken, with objective evidence at the next FDA inspection. The easier to review, the more confidence the FDA will have in your ability to drive continuous improvement and protect the public. Any uncorrected, repeat or similar findings at a subsequent inspection will most likely lead to a future Warning Letter.

2. **Your response does not satisfy regulators and a Warning Letter or enforcement action will ensue. If you have received a Warning Letter, keep reading to learn what to do next.**

FDA WARNING LETTERS

RESOLVING AN FDA WARNING LETTER

FDA Warning Letters are official notices to inform manufacturers and other companies that they are in violation of the FD&C Act while providing them with an opportunity to voluntarily correct these violations prior to initiating enforcement action. More specifically, a Warning Letter:

"...notifies a company that the FDA considers one or more products, processes, practices or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes."

Warning Letters are only issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected.

They are typically addressed to the company CEO or another management executive in order to get immediate attention. When a Warning Letter is issued, it is immediately posted on the FDA website. It's not long until the news will reach investors, competitors, and customers, which will undoubtedly bring a wave of questions and concerns.

Unlike an FDA 483, Warning Letters can affect product submissions, prevent you from reaching international markets, and a variety of other negative consequences (e.g. product seizure, injunction, criminal prosecution). If you're a foreign manufacturer, a Warning Letter can put you on the import hold list, removing you from the U.S. market entirely.

It's not uncommon for major manufacturers to pay millions of dollars in costs to resolve a Warning Letter.

Now that the consequences are clear, let's talk recovery—step-by-step:

A 5-STEP GUIDE TO FDA WARNING LETTER RECOVERY

1. Acknowledge you've received the Warning Letter.

Through certified mail, inform the FDA that you intend to respond to the Warning Letter within 15 business days.

2. Assemble an action team and/or seek experienced outside help.

Once you've informed the FDA you intend to resolve the issues, assemble a team to address the findings internally and/or seek third party experts that have experience helping companies like yours.

If you're confident you have the right personnel on staff, gather key Quality Assurance, Operations, Compliance and Regulatory Affairs personnel, designating a trusted individual to lead the team. This person must have a comprehensive understanding of the problems cited and a clear idea of how to fix them.

If you have any doubt in your ability to completely solve the problems internally, find an experienced third party firm that has a track record of success. The best firms can supply former FDA experts who can build valuable lines of communication directly within the Agency. If you opt for outside help, the following steps can essentially be managed by consultants who will lead and support you through the process.

If you've received an FDA Warning Letter and need assistance from qualified, experienced professionals, contact The FDA Group today.

CONTACT AN EXPERT NOW »

3. Craft a CAPA Plan.

The same process for creating a CAPA Plan can be followed found on page 5 of this guide. FDA 483s and FDA Warning Letters both require companies to carefully design a Corrective and Preventative Action (CAPA) Plan to address the problems cited by regulators.

In the case of a Warning Letter, however, be aware that the stakes are higher. While failing to satisfy regulators with an FDA 483 response typically risks a Warning Letter, failing to submit an adequate Warning Letter response can bring far more severe enforcement actions which can have extremely detrimental effects on your ability to market products.

4. Provide the FDA with a timeline estimate for a CAPA Plan.

If the issues cited in the Warning Letter require more 15 business days to fully implement, provide the FDA with a detailed timeline actions beyond that timeframe. Remember to follow through on all deadlines you provide. Regulators will likely be monitoring your progress closely.

5. Meet with the FDA to discuss your plan.

The FDA will work relatively closely with you to discuss the corrective and preventative actions being planned. Once they are satisfied your plan is adequate, you will be informed of the date for a follow-up inspection and closeout meeting. Request face-to-face meetings with the FDA only if appropriate.

IMPORTANT CONSIDERATIONS FOR RESPONDING TO FDA 483S AND WARNING LETTER:

- Form FDA 483 and Warning Letter responses should restate issues cited by the FDA verbatim before replying to them.
- Responses should be sent via Certified Mail, FedEx or electronically if the option is provided.
- While most companies assign management representatives for quality as point of contact, it's also acceptable for CEOs to fill this role as well. If upper management does not sign the responses, be sure they are clearly CC'd on any communications.
- Always be prepared to answer questions and justify your actions and timelines.
- Carry out a comprehensive mock audit to test the effectiveness of your CAPA plan/remediation project.

Remember that third party experts will provide fresh, independent unbiased assessments and can accomplish comprehensive remediation projects.

GET EXPERT HELP »

THE ADVANTAGES OF WORKING WITH AN EXPERIENCED COMPLIANCE AND REMEDIATION CONSULTING FIRM:

- Access to former FDA staff
- Strong relationships with the FDA
- Objective, unbiased perspective
- Ability to plan and write effective CAPA Plans
- Ability to identify additional gaps in compliance
- Knowledge of ever-changing regulatory environment

BE PROACTIVE AND PREVENT COMPLIANCE ISSUES.

While we help many companies resolve FDA 483s and Warning Letters, we also help prevent them from being issued in the first place. At The FDA Group, we plan and conduct effective internal quality audits to ensure your Standard Operating Procedures (SOPs) are completely aligned with all documentation and operations—the critical part of any internal audit.

While European regulators monitor this process with SOPs in-hand, FDA in particular relies heavily on documentation to hold companies accountable for their actions. Our team of former FDA and industry experts can evaluate your procedures, personnel, and closely look at all documentation to ensure consistency throughout your organization.

Are you in need of expert assistance with responding to a Form FDA 483, Warning Letter or preventative action? The FDA Group offers world-class regulatory, expert witness, and GxP auditing & remediation services to the pharmaceutical, biotechnology, and medical device/diagnostics industries.

CONTACT THE FDA GROUP FOR EXPERT ASSISTANCE »