The Scilife Success Guide

How to respond to FDA warning letters

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to respond to an FDA warning letter

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What is a warning letter?

In the event that a manufacturer violates FDA regulations, a warning letter is used to notify the manufacturer about the violation. In most cases, notifications appear in the form of warning letters.

The FDA sends warning letters to companies to encourage voluntary compliance before sending them a notice. If these violations are not promptly and adequately corrected, the FDA may take enforcement action. Any warning letter requires you to take voluntary and prompt corrective actions before initiating an enforcement action.

Read more here to learn further what a warning letter is and what types of warning letters there are.

Knowing what a warning letter is and what it contains, let's have a closer look at which steps you need to follow when you receive a warning letter.

02

8 Steps to respond to an FDA warning letter

Each year, tens of hundreds of pharmaceutical manufacturers violate FDA regulations and receive a warning letter. And without a digital quality management system (eQMS) in place, mitigating those quality and compliance issues is challenging and takes a lot of time and effort.

When you get a warning letter, take it very seriously. And respond to it appropriately. A response includes the following

> The letter should be acknowledged immediately
>
> A CAPA Plan
>
> A timeline with the actions that are addressed for each issue. (only if corrective actions will take more than 15 business days)
>
> Implementation plan prior to a follow-up inspection

If you receive a warning letter that claims violation(s) on your process or your products, it's crucial to assure the FDA that your products and production processes are conducted to manufacture safe products for human use. As a manufacturer, you should consider this when you investigate and take all actions, as well as responding to the FDA with all your CAPA and implementation plans.

02.A Step 1
Review the warning letter in detail

Once you receive an FDA Warning Letter, acknowledge you've received the Letter and inform the FDA that you intend to respond within 15 business days.

Then, you should read, read over, and read over again... until you understand every detail, citation, and violation that the FDA claims and why. In most cases, the FDA also requests a timeline to respond and which type of communication they request.

02.B Step 2
Perform an investigation

It is important to investigate the claims by a multidisciplinary team in order to fully understand and plan the actions needed. Employees from different functions can see and analyze the violations from different perspectives, so you'll be able to see the big picture.

The first thing that the team should assess is verifying whether the claims are reasonable.

If your team thinks that those claims are not reasonable, you have the right to disaffirm.

Nonetheless, it is quite likely that the FDA alleges reasonable violations, so your team needs to follow the next steps.

In the investigation step, it's crucial to have a well-implemented CAPA management system to handle a number of nonconformances all at once.

> Create CAPA for each nonconformance
>
> Assign a team of qualified employees and/or subject matter experts to investigate the root cause
>
> Consider if the issue may have a correlation with other systems
>
> You may have correction(s) alongside corrective and/or preventative actions

Once you find the root cause, you'll build every action based on that root cause. So make sure that you take the time to investigate and capture everything and find the root cause.

02.C Step 3
Respond to the warning letter by the deadline

Usually, the FDA states a deadline in the warning letter, so you should respond before the stated deadline with the current status of the actions. It would be better to address all issues within the deadline.

If corrective action is required, you should take the corrective action (or at least begin taking) before responding to the Warning Letter. When you respond to the warning letter, you should state that you are investigating the issue and start working to accomplish actions with a commitment of a reasonable completion date.

If the investigation or corrective actions cannot be completed within the FDA's deadline, you can respond with a rationale for a reason for the delay and the time within which you commit to complete it.

02.D Step 4
Keep the FDA in the loop with the next steps

If all planned actions or investigation can not be accomplished within the time frame, reply to the first response letter with a timeline for the completion of the investigation. Additionally, you should inform the FDA on a regular basis of the current status of the investigation / actions that you accomplished and / or you are working on.

You can find every detail that should be written in the response letter in the next section.

However, if the issue requires more time, effort, or implementation of a system, the first response should contain at least the following parts:

> The immediate corrective/ containment action taken
>
> A summary of the investigation of findings (or an explanation that the investigation is ongoing)
>
> A timeline for completion of the investigation

Keep in mind to commit with a reasonable and feasible timeline.

02.E Step 5
Determine an action plan

Once you have written the first response letter with the investigation details, it's time to focus on the actions that are required to be taken in order to eliminate or at least mitigate the issue. If allegations have merit, the appropriate actions can be planned straightforwardly.

The Corrective and Preventative Action (CAPA) Plan should carefully address the problems cited by regulators. Define a list of the actions for each FDA observation. Read below the possible corrective and preventative actions, and consider which of these actions are applicable and appropriate for your mentioned observation.

Evaluate the issues if they have any impact on products

Evaluate the issues if the products have public safety risk

- If so, take voluntary action
- If so, place a hold on current products, both on-site and on the market

Investigate Root Cause and any systemic issues

Identify CAPAs for both identified and systemic issues

If you need to improve your controls, and written procedures

- Update/generate procedures

Conduct training as needed for current, updated or new procedures with documentation of competency evidence

Perform an internal audit to the process regarding mentioned observation

- Analyze any additional gaps requiring action

Provide all objective pieces of evidence for CAPAs

Ensure test methods, processes, and computer systems are properly validated or revalidated within the timeframe

Provide sufficient copies of documents and/or records related to actions taken for mentioned observation

02.F Step 6

Provide a timeline estimate for the CAPA Plan

If the issues cited in the Warning Letter require more than 15 business days to implement fully, provide the FDA with a detailed timeline of actions beyond that timeframe. Remember to follow through on all deadlines you provide.

02.G Step 7

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.

2.H Step 8
Treat it as a learning experience

We know that when you receive a warning letter, that you'll be audited soon by the FDA. You can not say without getting stressed that "it's a learning process, enjoy and take lessons from every minute!" But keep reminding yourself that...

> It is the most effective way of learning!
>
> Think wisely, and take notes from the first day that you received that warning letter
>
> Those notes would be your guide, if you face similar issues in the future

Additionally, quality compromises continuous improvement practices. If you haven't any issues, observations, or warning letters, it does not mean that your processes are executed perfectly and you don't need to do anything. There are always opportunities to improve. If you consider your FDA interactions as opportunities to improve your processes, you can see your warning letter as a more positive experience.

03.
Structure of a response

You need to provide information to the FDA that is easily understood and navigated, with a structure like this:

03. A Cover letter

03. B Appendix 1 - Body of the response

03. C Appendix 2 - List of attachments

03.D Appendix 3 - List of planned and completed actions

03.A Cover Letter

A cover letter should address the following items

- The purpose of the letter and any terms used later in the letter
- Discuss management's commitment to resolving the issues identified in the warning letter (with executive responsibility)
- Identify and address any issues that relate to the management responsibilities
- In case observations indicate systemic deficiencies or product health risk issues, request a meeting with FDA
- Any points of disagreement should be identified
- Explain the appendices and make a commitment for the next update response
- You should designate the cover letter and response as confidential and not subject to disclosure under the Freedom of Information Act (FOIA)
- The planned response schedule (i.e. every six weeks or once a month) should be defined.
- Close with contact details

03.B APPENDIX 1 The Response

Insert a paragraph that explains planned and completed actions the company will take and has taken in response to the FDA observations in this appendix.

List appendices and explain what information each of them contains. Check the following items that you cover in this appendix of your response letter:

> Details of correction(s)
>
> Timelines for the correction(s)
>
> Corrective Action(s)
>
> The steps taken to identify, examine, and correct any example of the same type of issue not specifically identified by the FDA
>
> Any actions that are taken based on the impact of the product that has been manufactured. Describe how you determined there was no impact
>
> It is necessary to take any interim corrections or measures in order to ensure compliance until permanent corrections can be made.
>
> Preventative Action(s) (if any)
>
> Attachments (documents or records) such as copies of updated procedures, data collected, reports or summary reports, etc

An example of APPENDIX 1 - **The body of the response**

In this appendix...

> List each FDA observation
>
> Insert a response following the general statement
>
> Provide attachments with the evidence to support the response

To maintain a high level of efficiency, it is a good idea to separate completed actions from those that are currently in the planning stages.

FDA Observation 1

Copy observation verbatim, including annotation, if any.

Response

Copy the response here.

Completed Actions

Copy the completed actions here.
See Appendix 2, Attachment XX for a copy of the [DESCRIBE RECORDS] records.
If there is no "completed" action, then delete this row.

Date Completed

On [MONTH DAY, YEAR, COMPANY [STATE COMPLETED ACTION]].
If there is no "completed" action, then delete this row.

Planned Actions

Copy the planned actions here.
See Appendix 2, Attachment XX for a copy of the [DESCRIBE RECORDS] records.
If there is no "planned" action, then delete this row.

Date Completed

By [MONTH DAY, YEAR, COMPANY] will [DESCRIBE PLANNED ACTIONS].
[COMPANY] also plans to complete [DESCRIBE RECORDS] by [MONTH DAY, YEAR].
[COMPANY] considers this item to be closed.
If there is no "planned" action, then delete this row.

03.C APPENDIX 2
List of attachments

This appendix includes a list of Attachments such as procedures, training records, protocols, reports, etc.

An example of APPENDIX 2 – **List of Attachments follows**

Attachment	Title/Description	Number of Pages
1.		
2.		
3.		
4.		

03.D APPENDIX 3 List of planned and completed actions

This appendix includes a list of Actions/ Accomplishments, the number of each warning letter observation and a brief description of the planned and completed actions.

As you provide updated responses, this appendix should contain the actions planned and completed. It is a useful tool to remind the FDA of the current status of the planned and completed actions.

An example of APPENDIX 3 – **List of planned and completed actions follows**

Observation	**Planned Actions** *(Month, Day, Year)*	**Completed Actions** *(Month, Day, Year)*	**Number of Pages**
1.			
2.			
3.			
4.			

04.

How Scilife helps companies avoid FDA warning letters

Understanding FDA Warning Letters and how to respond appropriately is critical for pharmaceutical companies. If you do ever receive a warning letter from the FA, following the 8 steps outlined above will help you get back on track.

However, taking proactive actions in the first place to prevent violations is a safer, more effective, and cost-saving approach. The likelihood of receiving complaints and investigations is decreased by focusing on quality rather than solely compliance.

Discover how Scilife Smart Quality Platform can help you stay fully compliant at all times and avoid receiving any future warnings

Talk to a Scilife expert

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