COMPOUNDING PHARMACY OWNER SUMMIT

Closing 483 Files: You Have to Ask, Dude!

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Objective

To gain understanding of how to use the U.S. Food & Drug Administration (FDA) regulatory standards to successfully close an FDA Form 483

Terminology

- FMD-145: Field management directive (FMD) that provides criteria and instructions for releasing one copy of an establishment inspection report (EIR)
- Close-out: a letter issued when, based on FDA's evaluation, the firm has taken corrective action to address violations

What is an FDA Form 483?

- Issued by FDA's Office of Regulatory Affairs (ORA)
- Notice to firm management at the conclusion of an inspection that an investigator has observed conditions that may constitute violations of the Federal Food, Drug, and Cosmetic Act and related acts

What to know about a 483

- Observations are listed by the investigator in order of significance
- Does not constitute a final FDA determination of whether there is a violation
- The FDA considers the Form 483, EIR, all evidence or documentation collected on-site, and any responses made by the company to determine what further action, if any, is appropriate

Most common 483s

- Absence of written procedures
- Data integrity issues
- Failure to investigate the discrepancies
- Cleaning, sanitizing, and maintenance
- Environmental monitoring

What should I do after I receive 483 observations?

- Take active interest, ask questions and seek clarification during close-out meeting with investigator
- Prepare and submit a written response
- Implement corrective action plan
- Update FDA every four to six weeks
- Prepare for reinspection

How to respond

- Investigator will provide instructions on how to submit a response
- Submit written response within 15 business days of receipt of 483
- Responses should be comprehensive and well organized

What should a response include?

- Any immediate action taken
- Documentation/evidence
- Actions completed
- Corrective action plan with realistic timelines
- Address attention to all observations/violations

What happens after investigator issues 483?

- Report is reviewed and endorsed by investigator's supervisor
- Then it is reviewed by the assigned compliance officer, ORA and Center for Drug Evaluation and Research (CDER)
- FDA will reach out if they find a need to recommend recall or to collect samples
- Meetings with FDA are typically not granted until at least the report and response have been reviewed

How is a 483 successfully closed?

- If your response satisfies regulators and the matters are deemed resolved, the FDA will send a close-out letter or EIR to acknowledge response has been received and resolved
- If your response does not satisfy regulators, a warning letter or enforcement action may ensue

Standard for closing out a 483

21 C.F.R. § 20.64(d)(3) states:

> **(d) Records for law enforcement purposes shall be subject to the following rules:**
>
> **. . .**
>
> **(3) The consideration of regulatory enforcement action based upon a particular record shall be deemed to be closed within the meaning of this section:**
>
> **(i) If it relates to administrative action, when a final decision has been made not to take such action or such action has been taken and the matter has been concluded. . . . 21 C.F.R. § 20.64(d) (emphasis added)**

Tips for requesting a close-out

- **Demonstrate that you've met the standard:**
  - When did you respond to 483?
  - When did you send updates?
  - How much time has elapsed?
  - Have all corrections been implemented?
  - Did FDA take further action?
- **Request that FDA issue the EIR!**
- **Keep an eye out for upcoming guidance from FDA on this topic – 2023 CDER Guidance Agenda**

Close-outs

- Close-out letters should be issued within 65 working days of having all necessary information
- FDA may or may not choose to conduct a follow-up inspection

FMD-145

- FDA releases a copy of the EIR to the firm
- Copy released only after inspections are closed and firm is in compliance
- Inspections resulting in agency action are not eligible for release of EIR until the inspection is closed
- EIR is transmitted within 45 calendar days of closing inspection

Q&A

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