

# 483s: How to Manage Them and How to Respond

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# Topics We Will Address

- What is a FDA 483
- FDA's Inspection Classification Scheme
- Close-out of Inspection
- Minimizing Number of 483 Observations
- You Received a 483, What Now
- 483 Response
- Steps you can Take to Avoid a Warning Letter

# What is a FDA 483

- Form 483 intended to eliminate possibility of FDA action against a firm without prior notice

# What is a FDA 483

- The document presented by an FDA investigator at the conclusion of a facility inspection
  - Represents the opinion of the investigator(s)
  - Will be reviewed at the District Office
  - Has an associated Establishment Inspection Report (EIR)
- It is addressed to the highest official at the facility and is signed by the investigator(s)
- Available under FOIA (see 21 CFR 20.101(a)), thus providing public scorecard

# What is a FDA 483

- It lists the alleged deficiencies or issues of non-compliance in the manufacturer's quality system
  - Lists only significant observations
  - Observations of lesser significance are discussed with management and included in the narrative report (EIR)
- Each inspection (via the EIR) will be classified into one of three categories (NAI, VAI, or OAI)

# Inspection Classifications

- **NAI** (No Action Indicated) – No objectionable conditions or practices were found during the inspection
- **VAI** (Voluntary Action Indicated) - Objectionable conditions are found but the District is not prepared to take or recommend any administrative or regulatory action
- **OAI** (Official Action Indicated) – Regulatory and/or administrative sanctions will be recommended

# Close-out of Inspection

- Close-out provides opportunity for clarification of misunderstandings
- Deficiencies corrected during inspection can and should be pointed out
- Not a substitute for a full written response

# Close-out of Inspection

- Do take full advantage of opportunity to gain understanding of issues as FDA sees them and where practical, make commitments about corrective action
- Company should make clear formal response will follow in writing within certain time period after inspection
- Do point out any immediate corrective actions taken during inspection, and ascertain whether FDA inspection team deemed actions sufficient to address concern

# Close-out of Inspection

- Do challenge FDA inspection team as appropriate to explain basis of citations
- Keep questions and challenges focused on issues and not directed personally at investigator
- Such discussion can potentially result in deletion of an item from 483

# Minimizing the Number of Observations in a 483

- Address issues raised during the inspection as much as possible prior to the inspection closeout
- Ask the inspector to annotate the 483 to reflect corrective action where possible

# You Received a FDA 483, What Now

- Create a response team to identify an initial strategy and assign responsibilities
- Prioritize observations by importance (those most likely to impact product quality)
- Use project management tools to identify required tasks, assign responsibilities, and track until closure
- Establish a goal to respond to FDA within two weeks (if the 483 is broad, it may require more time)

# You Received a FDA 483, What Now

- Develop a comprehensive corrective action plan
  - This investigation may uncover additional deficiencies not identified during the inspection. If so, include them in your overall CAPA plan.
  - Adhere to your CAPA and document change control systems when making changes

# You Received a FDA 483, What Now

- Contact District and/or Center to inform them of anticipated date of response
- Compare this and any previous 483s for recidivist issues
- Draft and submit an FOI request for the EIR
- Hold regular response team meetings to monitor progress

# The 483 Response: Drafting the Cover Letter

- Address it to the District Director, with a courtesy copy to the lead investigator
- State the reason for the submission
- Discuss the commitment of management with executive responsibility to address the issues
- Address any issues raised in the 483 that relate to management responsibilities
- Raise respectfully any significant points of disagreement and where these issues are located in the response documents

# The 483 Response: Drafting the Cover Letter

- If this is a preliminary response with open action items, provide a time frame for updating the response
- Solicit FDA's prompt feedback on the satisfactory nature of the response
- Where the 483 observations are extensive and show multiple systemic deficiencies or product health risk issues, indicate your desire to meet with FDA

## The 483 Response: Responding to the Observations

- Re-state the observation exactly as it is written on the 483
- Address the specific examples cited in the observation
- Address the implied systemic issue raised by the observation

# The 483 Response: Identify Root Cause(s)

- Demonstrate in response company made adequate effort to identify root cause
- Consider providing:
  - Description of company investigation, including any testing
  - Discussion of alternative theoretically possible root causes that were rejected
  - Discussion of additional circumstances that support conclusion that identified root cause was correct one
  - Process helps remove agency doubt that company can prevent most deficiencies on its own

# The 483 Response: Description and Documentation

- Description shall reflect company's understanding of what is needed to correct immediate problem and general principles (current good practices) that should govern any long-term program to correct deficiency
- Provide documentation of corrective action commitment signed by the person responsible for the documented activity

# The 483 Response: Responding to the Observations

- Identify realistic, yet suitably aggressive time frames for actions that will require a longer period to implement
- Include with your narrative response references to supporting documentation
- Provide as attachments all supporting documentation and evidence of corrective and/or preventive actions taken
- Check and recheck every factual assertion to make certain there are no mistakes
- Determine whether there is confidential information in responses

## The 483 Response: Responding to the Observations

- If you believe the investigator erred in a given observation, indicate what the investigator reviewed during the inspection, what you offered, and why you believe that facts support a finding of satisfactory compliance on the given issue. It is okay to disagree.
- Where a deficiency cited will require time to enact permanent corrective action, identify the measures to be established to provide greater control in the short term (“the band-aids”).

# Band-Aid Actions

- **Example:** FDA cites a failure to assure the acceptability of certain raw materials and components used as evidenced by complaints and complaint investigations
  - **Short Term Solution:** Pledge to conduct heightened inspection of such materials during manufacturing until the long-term actions (i.e. supplier corrective actions, audits, and enhanced incoming quality assurance procedures) can be established

# Example of a Good Response

- Inspectional Observation
  - Instruments 12, 16 and 382, which were in use during the manufacture of Lots 5, 6 and 7 of Product X had exceeded due dates for their next scheduled calibrations
  - GMP requirement: 21 CFR 211.68(a)

# Example of a Good Response

- Elements of Successful Written Response:
  - Instruments were calibrated and found to be within limits (records attached)
  - Usage in manufacture of Product X has no effect on quality
  - Calibration program to be reviewed to assure no other such instances
  - Review of program along with any needed corrections will be completed in 60 days; documentation will be submitted

# Example of Good Response

- Key Features of Each Element:
  - Immediate corrections made when possible and adequately documented
  - Effect of deviation on product quality is objectively assessed
  - Systemic and/or global ramifications of observation are addressed
  - Target date set for ongoing actions, with promise to submit documentation

# What Not to do in a 483 Response

- Argue about the overall 483 in your response to a particular observation
- Imply that the investigator “doesn’t understand” your business
- Include unrealistic time commitments for actions planned
- Fail to address systemic issues pointed out by examples cited

# What Not to do in a 483 Response

- Do not include agreement with FDA's criticisms
- Agreement with FDA's criticisms can be used against company as an admission in future litigation
- FDA usually interested in explanations of what a company will do in future to comply than in confession of past sins
- Careful writing required to avoid damaging admission while satisfying FDA

# Steps You Can Take to Avoid a Warning Letter

- Do:
  - Develop active company compliance culture and convey that attitude to FDA investigators
  - Correct most observations when FDA investigator is onsite; ensure any remaining issues are in process of being addressed and communicate this to investigator in writing before inspection is completed
  - Ensure senior management is involved in initial meeting, during the inspection and in subsequent communications with FDA

# Steps You Can Take to Avoid a Warning Letter

- Do:
  - Ensure all communication with FDA investigator and agency is professional, that issues are addressed and proof is provided of each issue, including copies of final, signed-off documents
  - Guarantee that promised action is taken and documented and that copies are provided to agency
  - Ensure responses are timely

# Steps You Can Take to Avoid a Warning Letter

- Don't:
  - Convey negative attitude when speaking to investigators
  - Say that “it costs too much to implement that”
  - Say that “that’s the responsibility of our QA manager” or “senior management is too busy”
  - Request meeting immediately after inspection; spend time developing detailed and solid 483 response

# Where to Get More Information

- Investigators Operations Manual
  - [http://www.fda.gov/ora/inspect\\_ref/iom/iomoradir.html](http://www.fda.gov/ora/inspect_ref/iom/iomoradir.html)
- Regulatory Procedures Manual
  - [http://www.fda.gov/ora/compliance\\_ref/rpm/default.htm](http://www.fda.gov/ora/compliance_ref/rpm/default.htm)
- Information on Submission of FOI requests
  - <http://www.fda.gov/opacom/backgrounders/foiahand.html>.