Addressing Form 483 Observations and Warning Letters

Outline

- What is a “483” Observation
- Company 483 Responses
- Quality Plan Approach to Developing Responses
- Warning Letter Responses
- Discussion Items
- Post Response Activities

What is a “483” Observation?

- Noncompliance to regulatory standards (21 CFR parts 210-211 (Drugs) and 820 (Medical Devices))
- Government Form 483
- Observations listed in the order of importance
- 483 observation structure
  - statement of the applicable regulation
  - list of “specific examples” related to this observation
  - details of specific event (lot nos. SOP nos. equipment, etc.)
  - multiple examples in same observation

What a “483” Observation is NOT!

The 483 contains inspection observations, but does not represent a final Agency determination of the firm’s compliance status

Company 483 Response

- There is no legal requirement to submit a response to the FDA
- It is in the firm's best interest to submit one
  - FDA Compliance Officer determines if further regulatory action is required. Not the Investigator.
  - A response MAY avoid further regulatory action such as a Warning Letter.
  - Response demonstrates to FDA that you acknowledge and understand the observation(s)

Company 483 Response

- It is important to respond to a 483 even when the observations do not appear to be critical in your eyes
  - You may have incorrectly evaluated the FDA investigator's opinion of the observation criticality
  - If you don't submit a response, the FDA Compliance Officer does not have your side of the story
  - A response becomes part of audit history record & will be reviewed by FDA prior to the next audit

Company 483 Response

- Demonstrates to FDA a commitment to voluntarily correct the observation

- Responses must be submitted within 15 days to to the District FDA Compliance Officer (Federal Register, Volume 74, Aug. 11, 2009, effective Sept. 15, 2009)
  - Per FR, a FDA decision on issuing a Warning Letter will not be made until after the 15 days
  - Gives audited company an opportunity to respond to the 483 observations

Company 483 Response

- Key Parts of a Good Response:
  - Cover letter
  - Copy of the issued 483 report
  - Detailed responses to each observation
  - Supporting evidence of response statements

Company 483 Response

- Cover Letter should contain:
  - Company's name and address,
  - Dates of the inspection,
  - Management statement of the firm's intention to make the necessary enhancements and to comply to regulations
  - Provide a key contact name and information for follow-up questions or communications,
  - Any explanations of the structure/organization of the response package,

Company 483 Response

- Copy of issued 483
  - Provided for reviewer's convenience
- Detailed responses to each observation
  - four (4) basic response sections
    - List observation in its entirety followed immediately by the response.
    - Response with references to attachments needed to make a point or show corrective action has occurred
    - Committed completion dates for longer term corrective actions
    - List of attachments referenced in the response

Company 483 Response

- If the company disagrees with observation:
  - You must present documented **FACTS**
  - You need to carefully determine if it is better to continue to disagree or to implement corrective actions.
  - This risk assessment needs to be made with the criticality of the observation in mind.
- Present any activities or processes that might mitigate the impact of the observation on affected product

Company 483 Response

- Example:

Observation: *Preventive maintenance is not being performed on the XXX pump used to formulate product XYZ. The operational manual describes maintenance/testing procedures that include scale calibration, ground resistance testing, and visual inspections.*

Response: Company procedure 04-QP-001 effective date 01/01/11, requires that preventive maintenance be performed per the pump manufacturers operating manual. The SOP is not clear as to the specific maintenance activities or on the documenting of the performance of the maintenance.

Company 483 Response

Response (cont'd):

The calibration of the XXX pump is performed semi-annually, and copies of the calibration reports are attached (reference attachment 1). However, ground resistance testing has not been performed per the manual. Ground resistance testing has now been completed and documentation of the testing is contained in attachment 2. SOP 04-QP-001 will be revised to make it more clear as to what maintenance needs performing and its schedule and how to document the information generated. Target completion date is 04/29/2011.

Company 483 Response

- Address any potential impact on affected products & actions taken to mitigate this impact
- Be sure to address each and every portion of the observation
- For longer term corrective action commitments:
  - State the committed corrective action in detail
  - Be realistic about the commitments
  - Give a specific completion date

Company 483 Response

- Supporting Documentation – Includes:
  - Copies of revised documents & training records for completed corrective actions
  - Copies of any document referenced in support of a statement made in the response
- Status Updates
  - Regular updates (monthly)
  - Provide details & documentation for newly closed
  - Summarize status of open commitments
  - Analyze existing target dates. Request extension if absolutely needed.

Quality Plan Approach to Responses

- Complex 483 observations with multiple observations require careful planning & organization
- Need to have the subject matter experts within your firm review propose responses to each observation.
- Use of a Master Compliance Plan (MCP) / Quality Plan is recommended
  - Advantage - uses multiple teams to address all observations simultaneously
  - Disadvantage - Coordinating multiple teams to ensure timely completion of all draft responses can be challenging

Quality Plan Approach to Responses

- MCP is a format for creating and assigning responsibilities to individual teams:
  - Each has a leader who may or may not draft team members
  - Each team is responsible for evaluating and researching the assigned observation(s)
  - Team drafts responses to key aspects of the observation with the supporting documentation
  - Team develops short term and long term corrective actions and target completion dates
  - Short term commitments should be completed prior to response submission when possible

Quality Plan Approach to Responses

- Work teams remain responsible for implementation of longer term corrective action commitments until complete
- Team submits draft response & documentation to the MCP Coordinator for assembly into one cohesive package
- MCP Leader has management Team review responses & finalizes the response package.
- Consider having a Third Party Consultant review the response package or assist in response preparation
- Independent internal audit team verifies proper implementation & effectiveness to close commitment

Warning Letter Responses

- Agency position is that Warning Letters are issued only for violations of regulatory significance
- It is the FDA‘s practice to give individuals & firms an opportunity to take voluntary and prompt corrective action before it initiates an enforcement action
- Issued to achieve voluntary compliance and to establish prior notice (warning)
- FDA expectation is that most individuals and firms will voluntarily comply with the law

Warning Letter Responses

- Warning Letter responses are even more critical than 483 responses
  - The Warning Letter means that FDA has major concern(s) about your company's regulatory compliance
  - 483 response letter may not have reduced or eliminated FDA's concerns
  - Responses and corrective actions were either not presented adequately or were deemed inadequate by the FDA
  - Warning letter will identify specific deficiencies

Warning Letter Responses

- Thoroughly evaluate the Warning Letter. Assign Project Leadership responsibility to one person
- If you don't understand anything about the Warning Letter, call or meet with the FDA
- It is strongly suggested to utilize the services of a third party expert on FDA regulations and regulatory actions to guide and review response letter
- Remember to address how you will ensure integrity of your process & quality of product during correction period
- Submit regular status update to FDA

Discussion Items

- No 483? You are not done!
- Obtain a copy of Establishment Inspection Report (EIR)
- Refer to the section General Discussion or Discussion Items
  - Section contains topics of concern discussed with management but not 100% resolved
  - Topics for follow-up at next inspection

Discussion Items

- Treat Discussion Items Internally as an observation
- Address them – Don’t ignore them!
- Correct them or create defense rationale
- Utilize the information to enhance your current system

Post Response Activities

- Organize all the audit documentation into a central document and store
- Readiness for future FDA Inspection
- Readily available internally as a reference document for future questions

For Consideration:

- Highlight SOP changes resulting from 483 corrective actions

In Summary

- A 483 response is beneficial to your firm!
- 483 responses due to the FDA within 15 days
- Carefully evaluate each 483 observation & respond to ALL parts of the observation
- Responses must address both the specific observation correction AND global corrective actions
- Include any mitigating processes or systems that show the observation made does not impact the product.

In Summary

- Provide & retain supporting documentation
- Utilize an organized and effective system such as MCP to evaluate and respond to 483 observations. (Develop a system now, not later when the inspection happens!)
- Commitments need to be realistic and ACCOMPLISHED ON TIME!
- Provide regular status updates to FDA
- Utilize third party consultant experts as necessary
- Use EIR Discussion Items to enhance your systems

?? QUESTIONS ??