



Best Practices in FDA 483 and Warning Letter Management and Recovery

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Agenda

- Inspection Close-Out Meetings and the 483
- What to do before you respond – minimizing the damage
- Top 483 Citations for FY2013
- Warning Letters FY2014
- Common 483 response inadequacies
- Examples of inadequate 483 responses
- Exercise – “right” versus “wrong” responses
- Best practices for responding to 483s and Warning Letters
- Warning Letters – Will my company receive one?
- Implications of a Warning Letter

Inspection Close-Out Meetings and the 483

- FDA 483 presented to Senior Management during inspection close-out . “accepting” the 483
- Form 483 – List of Observations (objectionable conditions), MAY constitute FD&C violations.
- FDA action influenced by :
 - Significance of the 483 findings
 - Company’s response
 - Inspection Report and documentation
 - Inspection History

What to do Before you Respond – Minimizing the Damage



- Use the close-out meeting to fully understand the intent and scope of the observations
 - Remember that everything you say goes in the EIR
 - Ask for clarifications where needed
 - Correct any misperceptions or inaccuracies in the 483
 - Only observations that are shown to be factually incorrect (and supported by objective evidence) are likely to be modified or removed
 - Annotation (only for medical device 483s)
 - Reported corrected, not verified
 - Corrected and verified
 - Promised to correct
 - Under consideration
 - Promise a written response
 - FDA commits to reviewing responses submitted within 15 days of inspection close-out

Top 483 Citations FY2013 – Medical Devices



21 CFR	Violation
820.100(a)	CAPA Procedures – lack of or inadequate
820.198(a)	Complaint Handling Procedures – lack of or inadequate
820.100(b)	CAPA Documentation
820.75(a)	Process Validation – lack of or inadequate
803.17	MDR Reporting Procedures – lack of
820.50	Purchasing Control Procedures – lack of or inadequate
820.90(a)	NCMR Procedures – lack of or inadequate
820.30(i)	Design Change Procedures – lack of or inadequate
820.181	Device Master Record – not maintained
820.22	Quality Audit Procedures – lack of or inadequate

Source: FY 2013 Inspectional Observation Summaries, <http://www.fda.gov/ICECI/Inspections/ucm381526.htm>

Top 483 Citations FY2013 – Pharmaceuticals



21 CFR	Violation
211.22(d)	Quality control unit – procedures not followed or inadequate
211.192	Production record review – failure to investigate discrepancies
211.100(a)	Production and process controls – no written procedures
211.160(b)	Laboratory controls – lack of scientifically sound and appropriate
211.67(b)	Equipment cleaning and maintenance – procedures not established or followed
211.113(b)	Control of microbiological contamination – procedures not established or followed
211.67(a)	Equipment cleaning and maintenance – inadequate cleaning
211.165(a)	Release testing – inadequate to assess conformance with specifications
211.110(a)	Sampling and in-process testing – lack of procedures to monitor variability
211.166(a)	Lack of written stability program

Source: FY 2013 Inspectional Observation Summaries, <http://www.fda.gov/ICECI/Inspections/ucm381526.htm>

Common Response Inadequacies



- Failure to perform “systemic corrective action”
- Failure to provide reasonable and responsive timelines for correction
- Failure to provide objective evidence (e.g., revised standard operating procedures, review findings)
- Failure to provide evidence of training to updated procedures
- Failure to assess all “affected” product
- Failure of response, procedure, or documentation to address the violation
- Failure to address specific examples noted in 483 questions
- Failure to consider or conduct retrospective reviews
- Arguing with or dismissing FDA's concerns
- Re-training is not always the solution!!!!

Examples of Inadequate 483 Responses



- *We find that your August 5, 2014 response is not adequate to address the above violations. You have indicated that some of these observations will **not be completed until January 16, 2015**. Your firm did not provide **any documentation that these items will be addressed swiftly**.*
- *We have reviewed your response and have concluded that it is not adequate. Your response to the observation was to cease distribution of the Adjustable Laser Probe and to voluntarily recall the product. This response **does not address the corrective action necessary to address the cause of the observation to prevent its recurrence**. The observation merely used this device as an example of a deviation. You must assure that design control procedures are adequately established for all applicable devices.*

Examples of Inadequate 483 Responses

- *We reviewed your firm's response and conclude that it is not adequate. While a procedure titled SOP-004, Internal Quality Audits was submitted in your response, **no evidence of implementation or training** on this procedure was provided. In addition, your firm **did not provide evidence that it conducted a quality audit as required as a corrective action to this observation**. Lastly, your firm **did not provide evidence that it retrospectively reviewed all quality system procedures to ensure they were documented, as required**.*
- *We reviewed your firm's response and conclude that it is not adequate. While a procedure titled SOP-006, Supplier Evaluation and Monitoring was submitted in your response, **no evidence of implementation or training on this procedure was provided**. In addition, your firm **did not provide evidence that it evaluated (b)(4) as a supplier as a correction to this observation**. Also, you **did not provide evidence that you retrospectively reviewed all suppliers to ensure they were evaluated, as required**.*

Exercise 1:

What's wrong with this response?

- We have reviewed our process as described in the 483 and we respectfully disagree with this finding as procedure XYZ has been in place for many years with no issue and we believe it to be compliant as is. However, we have revised the procedure to address the specific example listed in the 483 and we have retrained all applicable employees on this procedure to ensure it is implemented appropriately. We have also quarantined the product referenced in the example and will disposition it in accordance with our procedures.

Exercise 1:

What's wrong with this response?

- Argumentative without providing evidence to support position
- No updated procedure provided
- No evidence of re-training provided
- No corrective action plan
- No timelines for disposition of quarantined product
- No commitment to review other product that may be affected

Exercise 2:

What's right with this response?

- We have opened CAPA 123 to investigate and fully understand the root cause of this issue and to develop comprehensive corrective actions in order to prevent recurrence. As immediate corrections to this observation, we have taken the following actions:
 - We have revised our XYZ procedure to address the specific example in the 483 as well as the other areas where this issue may arise (see Attachment 1 for revised procedure).
 - We have retrained all applicable employees on this procedure to ensure it is implemented appropriately (see Attachment 2 for evidence of re-training to the revised procedure).
 - We have quarantined the product referenced in the example and will disposition it in accordance with our procedures by October 31, 2014.
 - We have arranged for a retrospective review of other products that may have been impacted by this same issue to be performed and will ensure they are also appropriately dispositioned. This retrospective review will be completed by November 30, 2014 and the results will be provided in our monthly update to this response.
- The CAPA 123 root cause investigation is currently underway; a copy of the CAPA investigation and corrective action plan will be provided in our next monthly response.

Exercise 2:

What's right with this response?

- Objective evidence provided for completed actions
- Immediate corrections made, timelines provided for longer term corrective actions
- Addressed example in 483, but also looked beyond the immediate issue to see what other product could be impacted
- Commits to providing updates on a periodic basis
- Commits to performing a retrospective review for other potentially impacted product

Response Best Practices (483 and WL)



- Describe comprehensive correction action plan whenever possible (correction, corrective action, preventive action where applicable)
- Perform or Consider the need for retrospective reviews to evaluate past actions/product/records when identified deficiencies have been in place for an extended period of time
- Correct as much as possible in the first 15 days and provide realistic (but responsive) timelines for the longer term corrective actions
- Provide evidence of completed corrections with the response: updated procedures, training records, CAPA plans, reports, etc.
- Remember that a new procedure is not “implemented” until the SOP has been approved and training has been completed
- Address all examples cited in the 483, but also look beyond the immediate example to determine what other products or processes could be affected.
- Review the observation thoroughly before discounting it as FDA often has a broader perspective and it may take a while to understand their concerns. However, if you disagree, provide a firm discussion and objective evidence to support your position and request a meeting to discuss the observation further if you think it is warranted.
- Ensure corrective actions are completed and sustainable

Why even the best response may not prevent a Warning Letter ...

C.P. 7382.845 Inspection of Medical Device Manufacturers

- Situation I – Official Action Indicated (OAI)
 - Total failure to define, document, or implement a quality system or one of the seven subsystems.
- Situation II – Voluntary Action Indicated (VAI)
 - Minimal probability...that the establishment will produce nonconforming and/or defective finished devices. The Form FDA-483, Inspectional Observations, will serve to inform the establishment of any objectionable findings.
- IMPORTANT NOTE: A Situation II should not be assigned if the inspection documented major deficiencies and the firm responds only with **promised corrections, corrective actions and preventive actions**. In order for an inspection to be classified as Situation II, FDA must have **documented evidence of effectively implemented corrections and corrective actions taken on any and all major deficiencies observed during the inspection**.
- Bottom Line: A promise to correct may not be enough...

Implications of a Warning Letter

- Competitive disadvantage
- “Damaged/tarnished reputation”
- Resources spent in remediation/responses
- Legal liability
 - Consumer litigation
 - Shareholders litigation

- Positive News
 - Close-Out Letters implemented for Warning Letters issued after 9/1/2009

- In response to the FDA Warning Letter, XYZ stated in a press release that “XYZ takes all correspondence from the FDA seriously and will be responding to the agency with our improved system and procedure implementations to address the FDA’s concerns shortly. As the issues referenced by the FDA were never at any time regarding the manufacturing quality or safety of any product, we believe that we will be able to resolve this matter in a timely fashion.”

Thank You!

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