DEALING WITH FDA 483’s, WARNING LETTERS, and OTHER ENFORCEMENT ACTIONS

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Dealing with 483 Observations at the Conclusion of an Inspection

- At the conclusion of an FDA inspection, you may be issued a 483 (Inspectional Observations)
- These are always considered to be significant as issues of questionable significance should not be listed on a FDA 483
- Discuss any observations carefully with the inspector to ensure that they have a correct understanding of the situation and you agree that it is stated accurately and relates to regulated product in the US market
- My advice is try and avoid a mad dash to fix everything before the end of the inspection
  - While this does show you take matters seriously, it rarely resolves the 483 issue which is considered significant, and the issue probably still needs a CAPA to find the root cause and solve the underlying problem
Dealing with 483 Observations at the Conclusion of an Inspection

- For Medical Device inspections, you have the opportunity to annotate the observations
  - Many companies request to do this so that the 483 will have their comments noted thereon
- Some attorneys will advise to formally agree to any violation or sign any affidavits offered by the investigator
- Keep in mind the 483 will eventually become a public document available through Freedom of Information (FOI)
Dealing with 483 Observations, Your Reply to the Agency

- Upon receiving a 483, take the time to put together an action plan that will effectively deal with the problems cited as well as the root cause of the failure
  - A CAPA or CAPAs are almost always appropriate in this case
- Although not strictly required, a reply should always be sent into the District to explain how you intend to deal with the observations and provide any new information
  - Send the reply in within 15 days in order to possibly avoid the matters being escalated to a Warning Letter
  - Your reply shows you take the issues seriously, understand, and are working diligently to resolve the observations
Dealing with 483 Observations, Your Reply to the Agency

As part of your reply:

- Ensure commitments for corrections come from a senior quality or management representative who has authority and responsibility.
- Normally respond by citing the observation and then citing your response, action plan, and your evidence of correction.
- Break long multiple observations into smaller parts to be sure and address each problem.
- Describe how you plan to correct not only the specifics cited, but also indicate how the underlying root cause and systemic issues will be addressed.
- Set expectations for realistic times to resolve the issues.
- Supply evidence of corrections (updated procedures, reports, notifications, training files, etc.)
Dealing with 483 Observations, Your Reply to the Agency

- A reply, together with supporting documentation could mitigate any further action from the District
- If supporting documentation is not yet available, give the District an expected plan to close out the items, stick to the plan, and follow through with subsequent documentation
- You will receive acknowledgement that your reply has been received
- Always feel free to discuss matters with the District to be sure your corrective action plan will meet their expectations
- You will know the matters have been resolved if you get an EIR report
Keep In Mind...

- Although a 483 is a notice of violation, it does not normally preclude you from manufacturing or shipping your products:
  - Products are always to be manufactured in accordance with QSR
  - If FDA feels like more serious action is required, they will take it
Where can things go from here?

- A hierarchy of options:
  - 483 Observations
  - Warning Letter
  - Seizure
  - Injunction
  - Criminal Prosecution
If the Warning Letter Comes

- These are attention getters!
  - Usually addressed to the CEO or other significant management representative
  - Investors, competitors, and customers hear about them and start asking questions
  - An open warning letter can effect certain product submissions and prevent issuance of certificates to foreign government for your international markets
  - For a foreign establishment the issues may land you on the import hold list, effectively taking you off the US market
  - For a major manufacturer with significant issues, the cost resolving Warning Letters can run into the millions
  - You are now at risk at subsidiaries in other districts; if each plant has similar problems stemming from corporate management there may be a cluster of Warning Letters forthcoming
RECOVERY FROM A WARNING LETTER (WL)

- Acknowledge the receipt of the WL (certified mail) to the FDA and inform them you will respond in 15 working days or give justified reason for a later date for their consideration.

- Assemble a team to address the WL with a minimum of QA & RA as members and designate a leader who understands the issues (usually not the legal department).

- Create a Quality Improvement Plan.
WL RECOVERY

- Determine if you have the in-house knowledge and expertise to address the issues, if not seek an experienced outside help
- Very carefully study the WL and the FDA Form 483
- Break down the WL into the individual issues in the WL
WL RECOVERY

- Review your notes from the FDA Inspection to refresh your memory
- Review the areas that the FDA indicated were inadequate
- The Warning Letter was issued either because your 483 response was inadequate or your violations were too concerning to the FDA
WL RECOVERY

- Assign each issue to a group to provide a response to each individual item in the WL.
- Have the committee review each group findings for accuracy, responsiveness and confidence in the Root Cause, Corrective Action and time frame to implement.
- Remember the response must be provided to the FDA within 15 working days.
- Give the FDA an estimate of the time to complete all Corrective Actions that can not be completed in the 15 day window.
- For prolonged corrective action plans submit a timeline and the quality improvement plan to FDA.
Quality Systems Improvement Initiative Planning Example

System Teams
- Management Control Team Phase I/II
- CAPA Team Phase I
- Design Control Team Phase I
- Production & Process Control Team Phase II
- Material Control Team Phase II
- Facility & Equipment Control Team Phase II
- Document Control Team Phase I

Phase I
- Ph. I Estimated Completion 9/30/10
- Estimated Completion 9/30/10
- Estimated Completion 9/30/10

Phase II
- Ph. II Estimated Completion 12/31/10
- Estimated Completion 12/31/10
- Estimated Completion 12/31/10
- Estimated Completion 12/31/10

Audit Phase
- Quality System 3rd party Audit of New System
WL RECOVERY

- The FDA will be happy to meet with you to discuss your plan.
- Once they agree your action plan is complete they will inform you of the estimated date for a follow-up inspection and close out.
- Many times new organizations do not understand the significance and ramifications of a WL.
- Insure Management is aware of the regulatory significance of a WL and involved because if the issues are not adequately addressed it can get even worse.
- Deep rooted quality problems are usually due to lack of management commitment and do not get fixed without it.
Like the 483 response, your written response should take each item addressed by the FDA stated verbatim followed by your reply

Send the response certified mail or FedEx

The management representative for quality is the appropriate contact person for your firm, although some CEOs will want to take responsibility for this

Ask if they would like an electronic copy

Be prepared to answer their questions and justify your timelines
WL RECOVERY

- Consider a face to face meeting if appropriate and if the FDA agrees
- The FDA will schedule a follow-up Inspection dependent on your response time frame
- Conduct a thorough and rigorous mock follow-up audit for security, completeness and adequacy of your implementation (A third party provides a fresh, independent, unbiased assessment)
WL RECOVERY

- Your responses and Corrective Action plan need to fully answer and resolve the issues on the WL.
- This process can easily take a year or more because of internal corrections and the need for an FDA reinspection.
- Once your WL is resolved remember this is all on the record for the next Investigator’s audit.
WL RECOVERY

- Follow up internally periodically to confirm that the issues listed do not revert back to the WL state
- Manage your QSR compliant Quality System
- Try and avoid institutional amnesia...repeating the same mistakes a few years later
Escalation Beyond a Warning Letter

- Every year a few companies push the limits to cause FDA to take legal action...why?
- FDA can bring Injunctions, Consent Decrees, Fines, Seizures, and Criminal Prosecution to bear
- Why would you go there? These actions can really affect your business!
- A Consent Decree amounts to a court order to bring you into compliance with supervision of operation from FDA
- FDA is solely concerned with public safety and compliance with the law...not the viability or profitability of your business
Don’t make my day!

- There is a cadre of experienced consultants out there working independently or subcontracting for major consulting firms who are constantly busy on remediation projects.
- WL’s and Consent Decrees are public information; in the past few years, actions such as these at Cordis, Stryker, Boston Scientific, Gambro, Terumo, Hospira, and many other firms have kept my friends and I busy on major quality system remediation projects.
- It’s pretty reliable work, but wouldn’t it be better if I could stay away from these long term projects...
- Preventive Action is always better than Corrective Action, but it seems that corrective action gets more attention.
Negotiating with Regulators

- Understand that some things are not negotiable. Safety, laws, ..... 
- A lot of things are! Inspection dates, Submission strategies.....
- They are not consultants, and will usually not act as such.
- If possible, work from a win-win point of view. Our company will benefit, and public health will benefit...
- Problems of yours such as how long it will take, how many people you will need, how much it will cost, etc. are usually not of significant concern to Regulators
- Avoid negative relationships
- If people on your staff cannot deal with regulators without losing their cool...do not expose them to those situations
Understand the Rules

- You cannot expect Regulators to create special rules for you.
- You should be aware of what others have had to do.
- You need to know the Regulations and Guidelines thoroughly.
- If you do not agree with the Regulations, take it up in the proper channels, not with reviewers or inspectors.
- Avoid work-around approaches to bypass rules or personnel. Examine all legitimate options and select the one that works best for you.
Questions?