Writing a Flawless 483 Response

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FDANEWS

Agenda

FDA response requirements
responding to 483 observations
responding to a warning letter

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Requirements
Usual inspection outcomes
What FDA looks for in your response
Example failures

FDA RESPONSE REQUIREMENTS

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FDA Requirements

1. Respond to 483 observations in 15 business days or less
   - day 16: ORA and Center make enforcement decision
   - FDA only recognizes US Federal holidays and weekends as non-business days
2. Unwritten "three strikes" can *almost* guarantee stronger enforcement
   - 3 inadequate responses to 3 previous inspections
   - 3 warning letters from 3 previous inspections
3. Re-inspection within 6-18 months
   - exception: another trigger comes first (recall, etc.)
   - response to 483s dictates re-inspection priorities and tactics

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Usual Inspection Outcomes

1. **Warning Letter (WL)**
   - supposed to be issued within 45-60 days
   - cites significant issues (*i.e.*, not all FDA 483 observations)
   - cites predicate regulations and internationally harmonized guidance
2. **Untitled Letter**
   - issued within 45-90 days
   - provides "warning" (FDA views with same as WL)
   - not typically made public
3. **Untitled "Untitled Letter"**
   - as per Untitled Letters
   - FDA perceives low risk to general public safety
   - sufficient progress on closing deficiencies within 15 days
   - only outcome guaranteed to not provoke re-inspection
   - often difficult to actually determine you received

Our Goal

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> " As a general rule, a Warning Letter should **not** be issued if the agency concludes that a **firm's corrective actions are adequate and that the violations** that would have supported the letter **have been corrected**."
>
> FDA, *Regulatory Procedures Manual*, § 4-1-3 #3
> http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm

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FDA's Response Assessment

- Is the response timely?
- Is the response complete, well organized, and supported by appropriate documentation?
- Is the response easily understood (e.g., clearly written)?
- Is the response grammatically correct?
- Has the response been both spell-checked and proof-read?
- Is the response from an officer of the company?
- Has the company adequately addressed each of the specific inspection observations?
- Has the firm provided **objective evidence of corrections**?
- Does the firm seem to understand the specific inspectional observations and their impacts on compliance and product safety (and efficacy)?

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FDA's Response Assessment

- Does the firm appear to have an adequate remediation plan?
- Does the remediation plan include specific timelines and milestone commitments?
- Does the remediation plan speak to example measures of effectiveness or other independent completion verifications?
- Does the remediation plan address any larger systemic issues?
- Does the remediation plan discuss other corporate site impacts or impacts to other products?
- Has the firm volunteered to submit updates and progress reports?
- Has the firm incorporated good compliance best practices to govern its long-term remediation activities?

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> "We **know** within 60 seconds or less if **you get it** or not."
>
> - former FDA CDRH chief, Tim Ulatowski, December 2006

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Real-World Responses that Guaranteed a Warning Letter

- "You cited us on a technicality"
- "…this was the fault of a research coordinator [or other low level employee or contractor]…"
- "Protocol had rules that weren't scientifically based so we didn't feel the need to follow"
- "We got verbal approval"
- "Too much paperwork and fine print to follow"
- "The data set was too complicated to do a full analyses"
- "As to the forged signatures, those 4 were within an acceptable statistical margin of error given the number of documents your inspector looked at"
- "We maintain everything in email and your investigators refused to spend the time [for 18,000+ emails] necessary to review them all"
- "Fifteen days is not enough for us to comply"

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Warning Letter Excerpt

" Your response states that general CGMP training would be given to contract employees, but you do not address **why** contractors were not trained prior to our inspection or the effect of this deficiency on product quality."

Warning Letter to Mark Biosciences, July 2014
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm409898.htm

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Warning Letter Excerpt

" Your responses **continue to be specific spot fixes** and have failed to achieve the necessary **systemic approach** to comprehensively address the violations."

Warning Letter to Boston Scientific, January 2006
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2006/ucm075775.htm

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Warning Letter Excerpt

" We realize that Eli Lilly Company has multiple locations. This letter is an official notification that FDA expects **all of your locations to be in compliance**. We **recommend all of your locations be evaluated** and that corrective action be taken corporate-wide if deficiencies are found."

Warning Letter to Eli Lilly, March 2001
http://www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/2001/UCM078265.pdf

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Warning Letter Excerpt

" According to your response, you scheduled training on manual integration for all analysts who use Empower-2 software. You have not show **how** you will ensure that your test methods are appropriate to determine whether your API conforms to established standards and specifications."

Warning Letter to Interpharma Praha, October 2016
http://www.fda.gov/downloads/ICECI/EnforcementActions/WarningLetters/2001/UCM078265.pdf

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5-step action plan
Parsing the Form FDA-483
Drafting the response
Response do's and don'ts

RESPONDING TO A FDA-483

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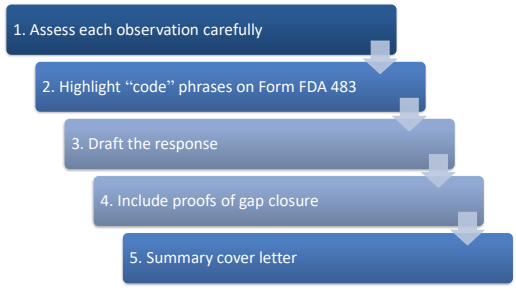
Five Step Action Plan



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Assess Each Observation

- Does it require a response?
- Determine the scope of each observation
- Are there system-wide implications?
- Are there implications for other sites?
- Are there implications for other products?
- Are there supplier implications?
- Conduct a rapid root-cause analysis (5 Whys technique)
- Identify the specific regulatory requirements (citations and any related guidance documents)
- Involve SMEs and outside experts as appropriate
- Parse the FDA-483 for specific code phrases

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483 Code Phrases

"without justification …"
- no documented decision-making (risk assessment, valid statistical methods, etc.)

"taken no action …"
- no records (written documents, samples, etc.) proving otherwise

"inadequate _____ [investigations, supplier oversight, etc.] …"
- missing records, signatures, analyses; no monitoring, etc.

"not established a statistically sound method for …"
- do not choose the 1970s "three random samples"

"repeat observation …"
- make sure to review any previous inspections and responses

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Draft Your Response

Use the Inspection Observation-Closure Matrix

Outline three remediation plans

1. immediate/short-term
2. longer-term
3. monitoring/recurrence prevention (continuous improvement and show "how" prevents problems)

Know when to seek outside expertise and help

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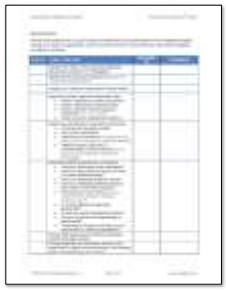
Checklist: Inspection Response

- In reference material
- Written up in several industry magazines and newsletters



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Draft Your Response

- Outline response
  - review with Site Inspection Response Team
  - review with functional area impacted
  - review with senior management team
- Do **NOT** commit to timeframes that force you to hire more full-time employees
  - find outside experts to advise you on how to comply with what you have today
  - use outside expert's advice to justify long-term plans

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Draft Your Response

- Verify observation closure
  - document using the matrix to verify
  - proof of "quick win" closures
  - proof of any "above and beyond" activities
  - proof of long-term plans (timeline and milestones)
- Submit proof along with summary, cover letter
  - FDA ***must receive*** within 15 working days (3 weeks)
  - FDA will not review any response received on day 16+

Case Study

7-page cover letter

Split into 2 sections

- Point-by-point discussion of actions for each the four 483 observations
- Additional steps taken at a systemic standpoint and overall continuous improvement and monitoring level

Six different appendices

- Revised SOPs and forms
- Long-term timeline, etc.

Case Study

Result:

Untitled "Untitled Letter"
(13 pages)

Response Specifics

- Send written response to Center contact
  - consider cc'ing investigators involved and district office
  - make sure you send EXACT copies of the response to each
- Address observations **point-by-point**
  - note whether you agree or disagree with each observation
  - immediate actions taken to fix specific non-compliance
  - longer term actions taken to address larger issues
  - proof (records generated, plan with progress, etc.)
  - specify any consultants used to help implement fixes (*Note:* be cautious about claiming that you hired ex-FDA, ex-HHS, or ex-DOJ consultants … *this is a divisive issue in FDA* … and could be personal)

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Practically Speaking

- Tone of your letter must provide assurance as to how seriously you take your responsibilities for compliance and product safety and efficacy
- Letter needs to come from top management
- Consider including specific verification or effectiveness measures (target metrics) … very good to show "how" fix fixes
- Hiring a consultant to conduct additional gap analyses is a long-term, systemic activity (this will not suffice to resolve specific FDA-483s and may only be one of many long-term actions)
- Think twice before wasting everyone's time if you will not include resolution evidence and long-term plans

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Additional Suggestions

- Allow time for an independent, "fresh set of eyes" to review prior to submission
- Plan for delivery at FDA no later than 14 days
- Keep in mind your target audience at FDA: compliance directors (not the investigators)

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Response Do's

- **DO** thank the FDA investigators for taking the time to inspect and provide insight
- **DO** provide a list of documents enclosed in the response
- **DO** offer to keep FDA up to date with progress – provide date (within 15 days) of next progress status update and what to expect you'll have done
- **DO** respond to each observation, one by one, with specific actions and proof
- **DO** take ownership and accountability for the issues
- **DO** explain any special, unique circumstances surrounding an observation

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Response Do's

- **DO** include "above and beyond" actions for each observation
- **DO** identify additional preventative or continuous improvement actions
- **DO** describe how you will improve your compliance self-monitoring
- **DO** be direct, factual and well-organized
- **DO** include a timetable with specific, realistic milestones
- **DO** provide assurances (as appropriate) that product safety/efficacy is secure

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Response Don'ts

- Do **NOT** commit to timeframes that require you to hire more full-time employees within the next 30-90 days
- Do **NOT** spend time in your response praising (or defending) your company or personnel
- Do **NOT** spend time in your response on typical PR language about your mission statement, your commitment to the environment, your community works, etc.
- Do **NOT** devolve into legalism (response should clearly come from management, not your legal counsel)
- Do **NOT** blame everything on lack of or poor training
- Do **NOT** cite practices at other firms

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Response Don'ts

- Do **NOT** ignore or guess at root causes of issues
- Do **NOT** make blatantly unrealistic commitments, timelines, and milestones
- Do **NOT** simply assert your willingness or commitment to comply
- Do **NOT** submit a sloppy response (spelling errors, unorganized, etc.)
- Do **NOT** ask for more time (this is not filing a tax extension)

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Interactive Exercise

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RESPONDING TO A WARNING LETTER

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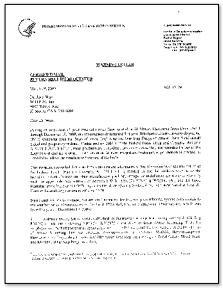
Quick Warning Letter Points

- Public
- FDA's conclusion that you are breaking the law and regulations
- It is too late to argue facts
- Issuing office will assess the adequacy of your response



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Responding to a Warning Letter

- Two week (10 business days) turnaround time
- Respond to the assigned Compliance Officer
- Include a **clear acknowledgement** that you are not in compliance with the law (FDCA) and the specific regulations/guidances cited
- Assess and respond to each item point-by-point
- Provide a corrective action, remediation plan – FDA will inspect to this (and the other areas at your firm they didn't get to such as production, warehousing, etc.)
- Provide a specific timeline with milestones
- Make clear that you understand the root causes

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If you receive your

2nd or 3rd warning letter…

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bring in outside expertise now.

Interactive Exercise

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