Writing a Flawless 483 Response

cerulean associates LLC
lean compliance + FDA consulting

FDANEWS

Agenda

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

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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insert new 30day FDA letter

- from contract pharma FDA presentation
- started on October 1
- example

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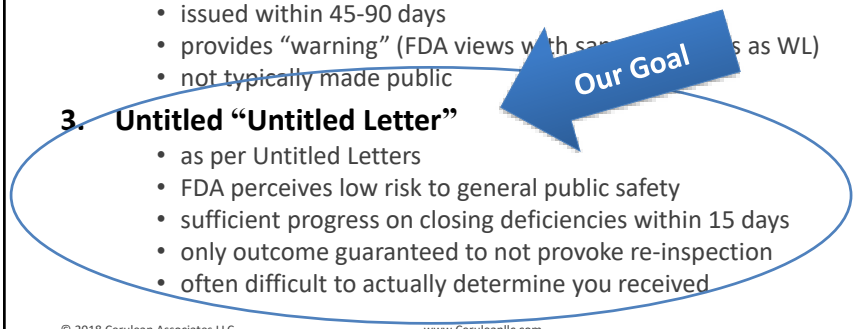
Usual Inspection Outcomes

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. **<u>Untitled Letter</u>**
   - 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



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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?

"We **know** within 60 seconds or less if **you get it** or not."

- former FDA CDRH chief, Tim Ulatowski, December 2006

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"

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

In other words, if you've been in non-compliance for OVER ONE YEAR on something, you must explain WHY you were non-compliance and HOW you will ensure this **will not** happen in the future

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

REMEMBER
FDA is looking for **short-term, immediate fixes** you *completed* **BEFORE** you sent in response
PLUS
Longer term, systemic fixes (that may entail project plans, new systems, etc.)

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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

IF you are a multi-site company, ONE of your responses **WILL** be your plan (and broad timeline) to conduct assessments of non-compliance at your other sites

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Warning Letter Exc

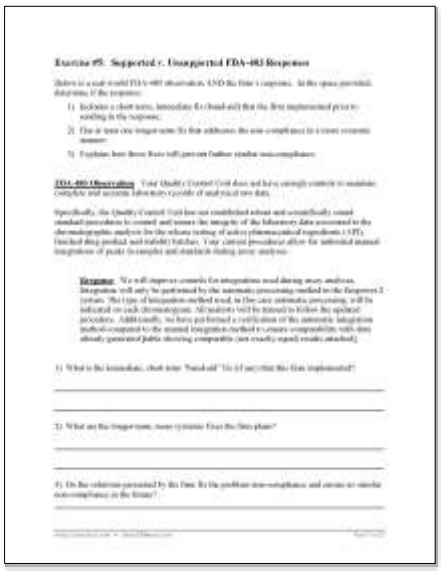
Lots of statements but no proof and no details on root causes, corrective actions, etc.

"Your investigation stated that you reanalyzed the crude sample and concluded that it met the specification. **You provided no further details on the root causes and on the effect of using a system that failed SST to test your raw material**.

Your response stated that no product in distribution was found to be OOS, but **you included no data to support this conclusion**. Your response is inadequate. You identified additional data integrity issues, but **failed to provide details regarding the corrective measures your firm has implemented**."

Warning Letter to Kyowa Hakko Bio Co., Ltd., August 2018
https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm617419.htm

Interactive Exercise



Warning Letter Excerpt

" According to your response, you scheduled training on manual integration for all analysts who use Empower-2 software. You have not shown **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

Any FDA-483 observation says "You've been in non-compliance for a while with…" and so your response MUST show **HOW** you will STOP being in non-compliance going forward

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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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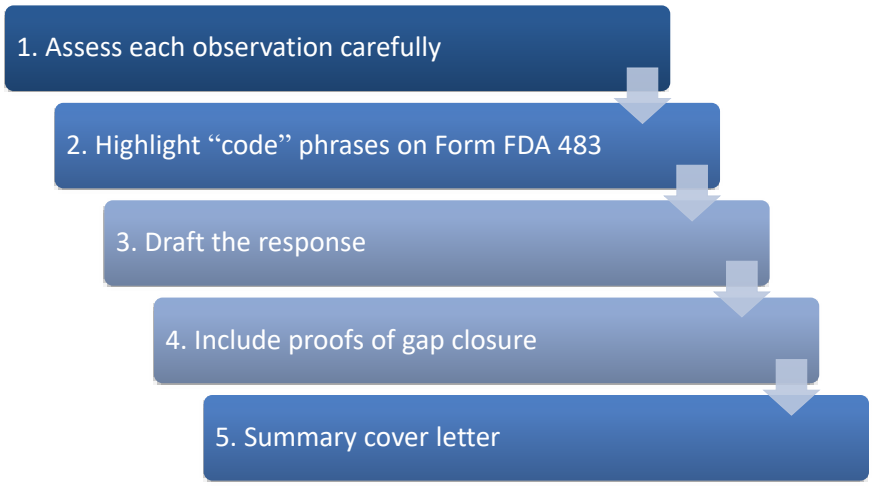
Five Step Action Plan



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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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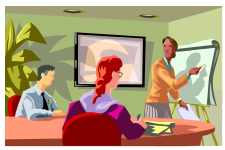
Draft Your Response

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

Draft Your Response

FDA has learned to be very skeptical of any responses that include "We will hire ___ new employees…"

- 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

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)

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 executive 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

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)

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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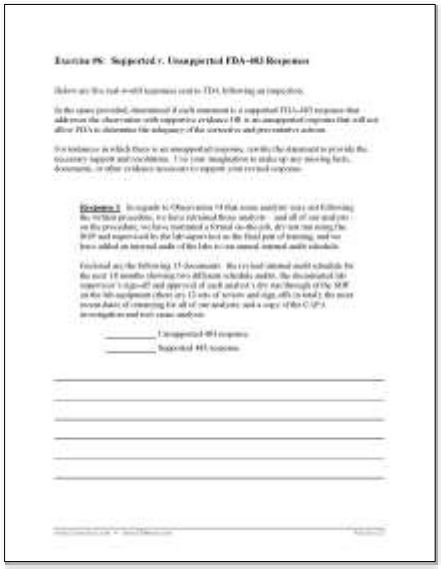
Interactive Exercise



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RESPONDING TO A WARNING LETTER

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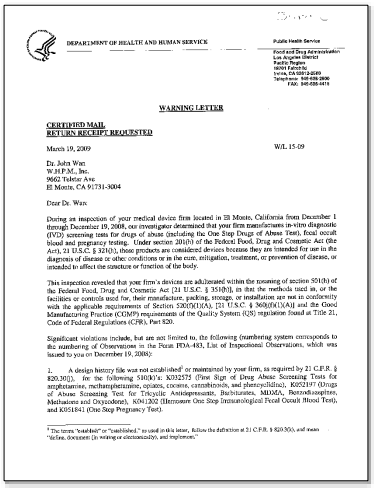
Quick Warning Letter Points

- 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



DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service

Food and Drug Administration
Los Angeles District
Pacific Region
19701 Fairchild
Irvine, CA 92612-2520
Telephone: 949-608-2906
FAX: 949-608-4416

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

March 19, 2009

WL 15-09

Dr. John Wan
W.H.P.M., Inc.
9602 Tobler Ave
El Monte, CA 91731-3004

Dear Dr. Wan:

During an inspection of your medical device firm located in El Monte, California from December 1 through December 19, 2008, our investigator determined that your firm manufactures in-vitro diagnostic (IVD) screening tests for drugs of abuse (including the One Step Drugs of Abuse Test), fecal occult blood and pregnancy testing. Under section 201(h) of the Federal Food, Drug and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are considered devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or intended to affect the structure or function of the body.

This inspection revealed that your firm's devices are adulterated within the meaning of section 501(h) of the Federal Food, Drug and Cosmetic Act [21 U.S.C. § 351(h)], in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the applicable requirements of Section 520(f)(1)(A), [21 U.S.C. § 360j(f)(1)(A)] and the Good Manufacturing Practice (GMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (CFR), Part 820.

Significant violations include, but are not limited to, the following (numbering system corresponds to the numbering of Observations in the Form FDA-483, List of Inspectional Observations, which was issued to you on December 19, 2008):

1. A design history file was not established[1] or maintained by your firm, as required by 21 C.F.R. § 820.30(j), for the following 510(k)'s: K032575 (Five Sign of Drug Abuse Screening Tests for amphetamine, methamphetamine, opiates, cocaine, cannabinoids, and phencyclidine), K052197 (Drugs of Abuse Screening Test for Tricyclic Antidepressants, Barbiturates, MDMA, Benzodiazepines, Methadone and Oxycodone), K041202 (Hemosure One Step Immunological Fecal Occult Blood Test), and K051841 (One Step Pregnancy Test).

[1] The terms "establish" or "established," as used in this letter, follow the definition at 21 C.F.R. § 820.3(s), and mean "define, document (in writing or electronically), and implement."

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

If you receive your

2nd or 3rd warning letter…

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bring in outside expertise now.

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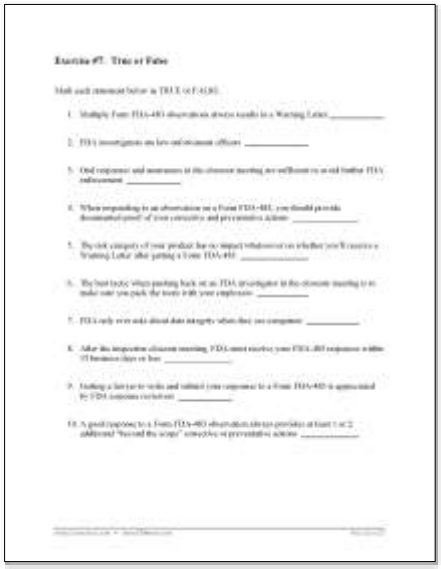

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