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How to Respond to Inspectional Observations, Warning Letters, Import Alerts Effectively? Talking about Remediation

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General Overview

- ❑ GMP Oversight Responsibility
- ❑ Review of **FDA Form 483 Frequently Asked Questions**
- ❑ Responding to an FDA-483 in a Timely Manner
- ❑ What should a Response to a FDA-Form 483 Contain.
- ❑ What is a 90-Day Notification Letter : OAI, VAI, NAI
- ❑ Response Letter
- ❑ Warning Letter Close Out Letter
- ❑ Discussion of Common Mistake Firms Make in Responding to an FDA-483
- ❑ Regulatory Significance- What may Lead to an OAI Classification/OAI Classification
- ❑ Responding to 483s and WLs
- ❑ Closing Remarks

Definition of “CGMP” Explicitly Includes Management Oversight of Manufacturing to Ensure Quality

SEC. 711. ENHANCING THE SAFETY AND QUALITY OF THE DRUG SUPPLY.

Section 501 (21 U.S.C. 351) is amended by adding:

“For purposes of paragraph (a)(2)(B), the term ‘current good manufacturing practice’ includes the **implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.**”

A. What Does An FDA Form No. 483 Represent ?

- Investigator's description events, deficiencies or violations to CGMPs as observed by an Investigator.
- List of facts and not assumptions (based on agency standards, regulatory expectations)
- Also referred to as a written statement or opinion of an investigator based on his review of the information provided, practice(s) or conditions observed, documents presented and reviewed, statements made, or absence of any of the above- related to CGMPs violations.
- **It's not a final decision or regulatory action**

B. Are Firms Required to Respond to an FDA 483 or WLs?

- There is no legal requirement for a firm to respond to observations cited
- Most firms respond to the deficiencies listed
- The agency's current policy is to review all information firms submit as part of their response, if submitted within 15 business days, when reviewing the inspection package for issuance of a WL or other action
- Extensions to submit responses to 483 observations beyond 15 days are usually not granted

Q1: When is an FDA Form 483 issued?

- ▶ **A:** An FDA Form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) **has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic (FD&C) Act and related Acts. FDA investigators are trained to ensure that each observation noted on the FDA Form 483 is clear, specific and significant.** Observations are made when in the investigator's judgment, conditions or practices observed would indicate that any food, drug, device or cosmetic has been adulterated or is being prepared, packed, or held under conditions whereby it may become adulterated or rendered injurious to health.

Q2: What is the purpose of an FDA Form 483?

- ▶ **A:** The FDA Form 483 notifies the company's management of objectionable conditions. At the conclusion of an inspection, the FDA Form 483 is presented and discussed with the company's senior management. Companies are encouraged to respond to the FDA Form 483 in writing with their corrective action plan and then implement that corrective action plan expeditiously.

Q3: Is the FDA Form 483 intended to be an all-inclusive list of every possible deviation from law and regulation?

- ▶ **A:** No, it's not. The FDA Form 483 is a report which does not include observations of questionable or unknown significance at the time of the inspection.
- ▶ **A:** There may be other objectionable conditions that exist at the firm that are not cited on the FDA Form 483. FDA investigators are instructed to note only what they saw during the course of the inspection. Companies are responsible to take corrective action to address the cited objectionable conditions and any related non-cited objectionable conditions that might exist.

Q4: What are the implications of the FDA Form 483 for agency enforcement and what happens next?

- ▶ **A:** The FDA Form 483 does not constitute a final Agency determination of whether any condition is in violation of the FD&C Act or any of its relevant regulations.
- ▶ **A:** The FDA Form 483 is considered, along with a written report called an Establishment Inspection Report, all evidence or documentation collected on-site, and any responses made by the company. The Agency considers all of this information and then determines what further action, if any, is appropriate to protect public health.

Importance of Responding to an FDA-483 in a Timely Manner

- ▶ The FDA Form 483 **does not constitute a final agency determination** and firms are encouraged to respond to the FDA Form 483 in writing with their corrective action plan with supporting documentation within 15 business days from the issuance of the FDA Form 483 expeditiously.
- ▶ **IMPORTANCE OF TIMELINESS RESPONSE AND PROPOSED CORRECTIONS**

Importance of Responding to the FDA-483

- Does not automatically mean that a Warning Letter, Import Alert or Reg. Action will not be taken.
- Responding to the deficiencies/violations is an opportunity for firms to explain what happen, provide additional supporting information, clarify misunderstanding (if any).
- Is an opportunity to provide the CAPA, a reassessment plan, additional findings and share improvements made?

**SO, YOU RECEIVED A FORM 483,
LIST OF INSPECTIONAL
OBSERVATIONS REFERENCING
SOME OF THE FOLLOWING
DEFICIENCIES/VIOLATIONS**

HOW DO YOU RESPOND?

Most Common Mistake Firms Make in Responding to an FDA-483

- ▶ Submission of incomplete responses
- ▶ Reference to work that will be done but no inclusion of protocols and plans
- ▶ Lack of timelines in proposed projects
- ▶ No information of the interim measures regarding significant GMP deficiencies
- ▶ Not expanding investigations into other batches, products and systems potentially affected by the deficiencies.
- ▶ Incomplete assessment of product in the market

Most Common Mistake Firms Make in Responding to an FDA-483

- ▶ Deficient or absence of risk assessment
- ▶ Deficient or incomplete retrospective review of OOS affected systems, people implicated in wrongdoings.
- ▶ Reference to investigations or assessment done but such assessment was not submitted for review.
- ▶ No explanation for not providing all the information during the inspection to the investigators and only submitting after 483 was issued.

Firms have the Right to Disagree With the Observations Presented by an Investigator:

- ▶ 1. Include your rationale with supporting scientific data and not only an opinion.
- ▶ 2. Provide data (e.g., documents, photos, evidence, videos...) to support your disagreement.
- ▶ 3. Indicate when additional information became available and why it was not presented to the inspection team

Transparency is Essential

1. The information must be accurate, reliable, complete...good,bad,ugly.
2. Do not **over-react, and do not threaten with shutdown** or recalling- product with risk to ptx. will not be allowed in the market.
3. Extra-texting, short/long term remediation, third part certification...

Industry Role and Communication

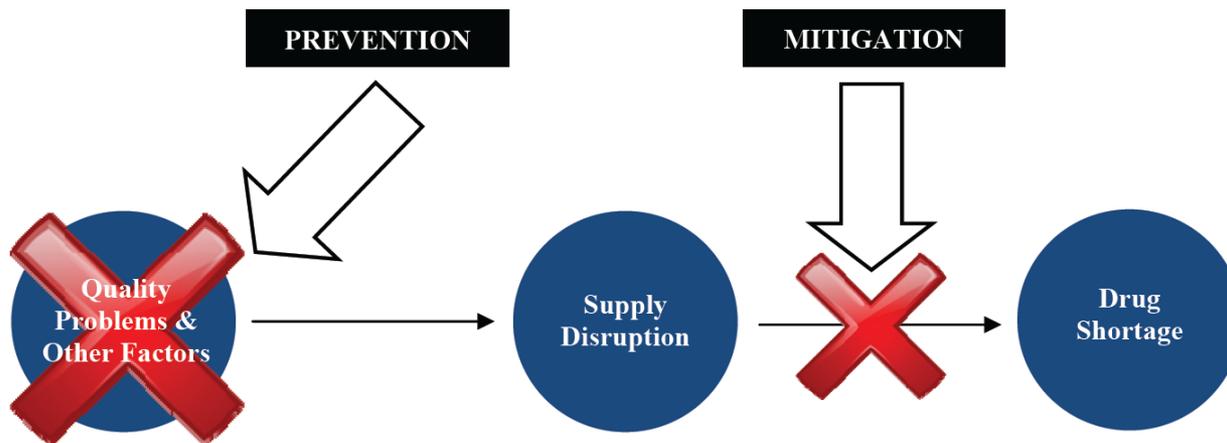
- **Early notification is key!**
- Mandatory reporting of discontinuance or meaningful disruption of supply
- Voluntary details on supply interruption and proposals for mitigation/prevention of shortages
- Engage FDA Drug Shortage Staff when submitting any shortage-related communications
→ drugshortages@fda.hhs.gov

Communication with FDA

- Before making a decision to shut down a manufacturing facility:
 - Contact FDA's Drug Shortage Staff at drugshortages@fda.hhs.gov
 - ◁ Propose ways to address issues while maintaining supply of medically necessary drugs

Drug Shortages

- Drug shortages are significant public health threat
- Encourage manufacturers to prioritize high quality manufacturing and ensure supply and capacity



Debris located on equipment immediately above filling areas can potentially fall into the filling area and into products being filled. How do you Respond?



How do you Respond?



Discoloration top of a HEPA filter screen; black spots too numerous to count observed on the HEPA filter supporting grid. Part of HEPA filters runs directly above filling machine. How do you respond?



Stainless steel sieve worn out, discoloration and corrosion. How do you Respond?



Compression Machine (suppose to be stainless steel). How do you response?



DEFICIENCIES CITED:

- OOS Investigations/Process Deviations
- Potential- Questionable Data Integrity Practices
- Process Performance/Control Issues
- Trends in unknown root cause determination
- Maintenance Issues, recurrent equipment fixes
- Improvised process changes/equipment modifications
- Foreign Particles
- Increase or recurrent presence of unknown peaks
- Increased # complaints, rejects, recalls
- Poor designs, questionable process flow
- Equipment not reliable- frequent parameter changes

- Conclusions not supported- No CAPA, no FAR
 - Not verifying or addressing previous similar failures
 - Previous inadequate CAPAs not addressed
 - Not extended investigation to other lots,
 - Retesting to invalidate, and not to determine root cause “Testing into Compliance”
 - Ignoring data or evidence that does not support conclusions (e.g., record shows sonication was performed, disregarded to indicate analyst did not sonicate)
-
- **HOW DO YOU RESPOND TO A 483?**
 - **WHAT DO YOU SUBMIT IN 15 DAYS?**



Responding to an FDA Form
483,
List of Inspectional
Observations

Responding to the FDA Form 483

- Firms should address the following:
 - Extent of the problem (by regulators/internally)
 - Justification for scope of retrospective review
 - Batches, timeliness covered, products, lines affected
 - Risk assessment/criticality/severity/likelihood of recurrence
 - Voluntary market action (why no action)
 - Aggravating/mitigating factors
 - Comprehensive remediation plan

Responding to the FDA Form 483

- ❖ Include detailed information and supporting documentation about:
 - WHAT happened?
 - WHEN? timelines and cut of date justification
 - WHO was involved/responsible, and how was this determined?
 - WHY did it happen? Deficient SOPs, poor QU oversight and how this is being corrected
 - HOW did it happen, gap analysis?

Common deficiencies found in 483 and WL responses (not all inclusive):

- Incomplete or limited information included
- Lacks supporting data (e.g., protocol, report, data of testing, good/bad results, limited explanation)
- Fails to address unmet commitments from previous inspections and how new commitments will prevent recurrence
- Fails to address repeated issues at site inspected or other facilities within the network

Con't

- Fails to address a global correction plan
- Response ONLY addresses specific 483 example
- Lacks clarification of issue and assumes investigator is correct
- Describes corrections or CAPA but provides no evidence (e.g., we tested retain samples, but do not explain the rational of approach, neither includes batches tested and results; validated the method of process cited, but lacks a review of other methods and processes)

Con't

- Inadequate, limited retrospective review
- Response includes limited review & corrections No explanation for discrepancies between what was said, collected or presented during the inspection and information submitted in the response.
- No indication of when information in the response was created or generated and intend to give message it was available all the time.

Common deficiencies found in 483 and WL responses include:

- Failure to address the what, when, why, how, who regarding the findings (extent of issues).
- Failure to include a comprehensive assessment
- Response only addressing specific 483 citation
- No explanation of why new information was not made available to the investigators
- Firms often forget to address important parts or comments made in the WLs, and only submit high level reviews and general overviews

WHAT DOES THIS MEAN ?

“...a comprehensive evaluation of the extent of the inaccuracy of the reported data. As part of your comprehensive evaluation, provide a detailed action plan to investigate the extent of the deficient documentation practices. . .”

~ recent FDA warning letter

What is FDA expecting to see in a comprehensive evaluation?

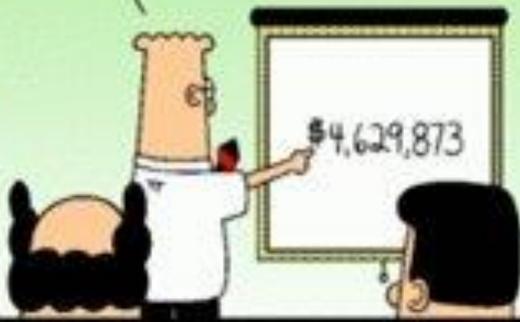
- Thorough and complete evaluation of past occurrences
- List of records reviewed and findings
- Drug application data reviewed and findings (methodology)
- Details of period covered, lot numbers, products, analytical test, **results** (passing and failing).
- Assessment of all systems potentially affected
- Full Transparency

Points to Consider

- 483 observations are NOT all inclusive.
- Firms should review all records collected by investigators during inspection (e.g., investigations, validations, media fill reports...), even if only 1-2 were cited on 483.
- Recommend responding to verbal observations as these are normally included and discussed in EIR
- Firms commit to respond to “non written/or” deficiencies, and then choose not to address

Don't Make Up Stories

I DIDN'T HAVE ANY ACCURATE NUMBERS SO I JUST MADE UP THIS ONE.



www.dilbert.com scottadams@aol.com

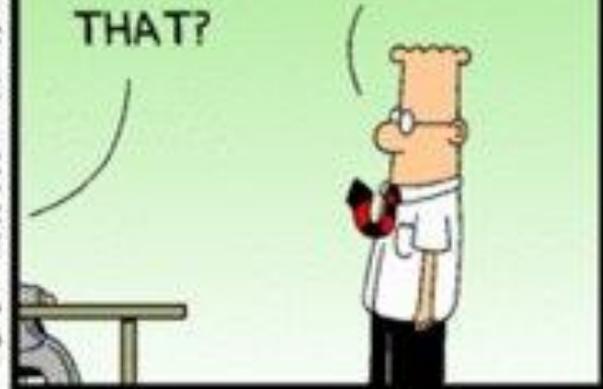
STUDIES HAVE SHOWN THAT ACCURATE NUMBERS AREN'T ANY MORE USEFUL THAN THE ONES YOU MAKE UP.



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HOW MANY STUDIES SHOWED THAT?

EIGHTY-SEVEN.



Closing Thoughts

- A response to an inspection deficiency and WL should be comprehensive and include assessment of current state of compliance and extent of the problems.
- A response should include detailed roles and responsibilities of the independent 3rd party.
- CAPA should be complete or with information on how the effectiveness will be monitored and demonstrated-submit updates to the agency.
- Demonstrate sustainability

Closing Thoughts

To assure quality, well designed and appropriately implemented processes, systems, and procedures, along with the COMMITMENT of Senior and Executive Officers, providing the necessary resources and management oversight are essential. Regulators are interested in sustainable and effective quality systems, that will assure patients receive safe and effective medicines.



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