


FDA Inspection Observations - The FDA-483 and Beyond

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Objectives

- Describe history and purpose of the FDA-483
- Describe the rules FDA has established for what is a reportable observation and what is not
- Explain agency guidance for evaluating the significance of FDA-483 observations resulting from drug GMP inspections
- Managing the exit discussion of the FDA-483
- Effective written response to the FDA-483





The FDA-483, History and Purpose

- The 483 was born as a result of the Factory Amendments of 1953 to the Federal Food, Drug and Cosmetic Act
- Prior to that time, FDA inspection results were not reported to management at the conclusion of an inspection
- The inspection authority also contained a “Catch-22” in that FDA had to obtain “...*permission* of the owner, operator or agent in charge...” before beginning an inspection, but the withholding of permission was a criminal act
- In *United States v. Cardiff*, (344 U. S. 174), the court held that the Federal Food, Drug, and Cosmetic Act did not compel that consent be given to warrantless inspections of establishments covered by the Act. As a result, the statute was subsequently amended to read as it does today, and the requirement for FDA to provide a report to management at the end of the inspection was added to the law

Statutory Basis of the FDA-483

- When FDA conducts an inspection in the US, the Investigator must issue a Notice of Inspection, FDA-482. The basis for this is found in Section 704(a) of the Federal Food, Drug and Cosmetic Act:
“For purposes of enforcement of this chapter, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, tobacco products, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, tobacco products, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein.”



Statutory Basis of the FDA-483

- The same section provides for the FDA-483 when it states:
“Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, tobacco product, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.”

REMEMBER...this was written in 1953, and a lot has changed in the nearly 60 years since then!!



Summary – Status of the 483

- The 483 is an initial report, by the Investigator(s) at the conclusion of the inspection, to management of the company, of the things that were observed which may, after further agency review, be deemed to be violations.
- Adulteration observations are legally mandatory for inclusion, general GMP observations are listed by policy
- The 483 is not a final agency determination of noncompliance.
- There will be substantial further review, and a more extensive report will be written about the inspection. This is called the Establishment Inspection Report, or EIR, and it will form the basis of any further action.
- The company can and should make its views known, both orally and in writing, for consideration by FDA in evaluating the significance of the 483 (more about this later in this presentation)
- The 483 is immediately available under Freedom of Information, regardless of the status of the inspection [reference 21 CFR 20.101]



The 483 and GMP Observations

- While it is true that if something in a drug manufacturing facility “consisted in whole or in part of a filthy, putrid or decomposed substance...”, etc., it could certainly be said to be in violation of GMP, what about other things that are GMP violations but not in that category?
- FDA has established, by policy, that certain things not mandated to be reported by the statute will nonetheless be reported on the FDA-483.
- Did you ever look on the back of the 483?
- The reverse side of the 483 states:
“The observations of objectionable conditions and practices listed on the front of this form are reported:
1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.”

In other words, most GMP observations are there by policy, not because they have to be by law. Filth observations must be listed by law.



What goes on the FDA-483 – and what does not??

FDA Investigations Operations Manual (IOM) Section 5.2.3 states in part:

- “All FDA-483s should adhere to the following general principles:
- Observations which are listed should be significant and correlate to regulated products or processes being inspected.
 - Observations of questionable significance should not be listed on the FDA-483, but will be discussed with the firm’s management so that they understand how uncorrected problems could become a violation. This discussion will be detailed in the EIR.”



The IOM goes on to establish the rules for what is reportable and what isn't.

"Include specific factual observations of:

1. Foods, drugs, devices, or cosmetics consisting in whole or in part of filthy, putrid, or decomposed substances.
2. Undesirable conditions or practices, bearing on filth or decomposition, which may reasonably result in the food, drug, device, or cosmetic becoming contaminated with filth.
3. Insanitary conditions or practices which may reasonably render the food, drug, device, or cosmetic injurious to health.
4. Careless handling of rodenticides or pesticides.
5. Results of field tests (organoleptic examination of fish, crackout of nuts, etc.) if the results revealed adulteration.
6. Observations of faulty manufacturing, processing, packaging, or holding, of food, drug, or device products as related to current good manufacturing practice regulations including inadequate or faulty record keeping.
7. Observations of faulty can closures and/or deviations from recommended processing times and temperatures.
8. Deviations from the animal proteins prohibited in ruminant feeds requirements (21 CFR 589.200043).
9. Results of analytical laboratory findings which reveal adulteration."



Certain other types of observations relevant to the pharmaceutical industry are also to be reported, according to IOM section 5.2.3.2.2; for example:

- Observations indicating non-conformity with commitments made in a New Drug Application, New Animal Drug Application, or in an antibiotic certification or certification exemption form
- Observations, forming the basis for product non-acceptance (of products) under the Government Wide Quality Assurance Program (GWQAP).
- Observations indicating non-conformity with the postmarketing adverse drug experience reporting requirements



Non-Reportable Observations

It is possible for FDA to make observations during an inspection that the agency will consider to be violations, and may even be cited in Warning Letters or other actions subsequently, but which are not to be reported by Investigators on a 483.

Those are:

- Label and labeling content, (with certain exceptions stated).
- Promotional materials.
- The classification of a cosmetic or device as a drug.
- The classification of a drug as a new drug.
- Non-conformance with the New Drug Regulations, 21 CFR 312.170 (New Drugs for Investigational Use in Human Beings: Exemptions from Section 505(a) unless instructed by the particular program or assignment.
- The lack of registration required by Section 41571 and 510 of the FD&C Act. The lack of registration per 21 CFR 1271 Subpart B, Procedures for Registration and Listing, promulgated under Section 361 of the PHS Act.
- Patient names, donor names, etc. If such identification is necessary, use initials, code numbers, record numbers, etc.
- Corrective actions. Specific actions taken by the firm in response to observations noted on the FDA 483 or during the inspection are not listed on the FDA 483, but are reported in the EIR. Except as described in IOM 5.2.3.4.
- The use of an unsafe food additive or color additive in a food product.



Determination of Significance of 483 Observations in Drug GMP Inspections

Reference: FDA Compliance Program 7356.002, Drug Manufacturing Inspections, Part V, Regulatory/Administrative Strategy. Provides general guidance, and illustrates by example (but not all inclusive) the sorts of things that would be deemed significant on a system – by – system basis.

Quality System:

- 1) Pattern of failure to review/approve procedures.
- 2) Pattern of failure to document execution of operations as required.
- 3) Pattern of failure to review documentation.
- 4) Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints.
- 5) Pattern of failure to assess other systems to assure compliance with GMP and SOPs.



Facilities and Equipment System:

- 1) Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated avenues of contamination, such as airborne or through unclean equipment
- 2) Pattern of failure to validate cleaning procedures for non-dedicated equipment. Lack of demonstration of effectiveness of cleaning for dedicated equipment.
- 3) Pattern of failure to document investigation of discrepancies.
- 4) Pattern of failure to establish/follow a control system for implementing changes in the equipment.
- 5) Pattern of failure to qualify equipment, including computers.



Materials System:

- 1) Release of materials for use or distribution that do not conform to established specifications.
- 2) Pattern of failure to conduct one specific identity test for components.
- 3) Pattern of failure to document investigation of discrepancies.
- 4) Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations.
- 5) Lack of validation of water systems as required depending upon the intended use of the water.
- 6) Lack of validation of computerized processes.

Production System:

- 1) Pattern of failure to establish/follow a control system for implementing changes in the production system operations.
- 2) Pattern of failure to document investigation of discrepancies
- 3) Lack of process validation.
- 4) Lack of validation of computerized processes.
- 5) Pattern of incomplete or missing batch production records.
- 6) Pattern of nonconformance to established in-process controls, tests, and/or specifications.



Packaging and Labeling System:

- 1) Pattern of failure to establish/follow a control system for implementing changes in the packaging and/or labeling operations.
- 2) Pattern of failure to document investigation of discrepancies.
- 3) Lack of validation of computerized processes.
- 4) Lack of control of packaging and labeling operations that may introduce a potential for mislabeling.
- 5) Lack of packaging validation.



Laboratory Controls System:

- 1) Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations.
- 2) Pattern of failure to document investigation of discrepancies.
- 3) Lack of validation of computerized and/or automated processes.
- 4) Pattern of inadequate sampling practices.
- 5) Lack of validated analytical methods.
- 6) Pattern of failure to follow approved analytical procedures.
- 7) Pattern of failure to follow an adequate OOS procedure.
- 8) Pattern of failure to retain raw data.
- 9) Lack of stability indicating methods.
- 10) Pattern of failure to follow stability programs.



Managing the Exit Discussion of the FDA-483

- At the conclusion of the inspection the 483 is presented to top management.
- The company has an opportunity to present its view of each observation.
- It is advisable to use this opportunity to ensure you understand each observation from FDA's viewpoint, even if you strongly disagree with the observation.
- If you do not understand FDA's view you will be seriously hampered from forming an appropriate response.
- Have the "right people" present – Not too many!
- Agree on discussion strategy
- Control the environment
- Do not make commitments you cannot keep; keep time lines reasonable
- Present any disagreement calmly, logically, back up with facts



Simple four-step strategy:

- Step 1: Verify that the 483 is factually correct
- Step 2: Ensure that the wording is not misleading
- Step 3: Understand FDA's reason for each citation
- Step 4: Request deletion of item(s) you believe are incorrectly cited; provide your rationale



Written Reply to the 483

In the *Federal Register* of August 11, 2009 FDA posted a new policy regarding timeliness of the written response to a 483.

Key point:

- **If you want your response to be considered by FDA as part of their overall decision whether to issue a Warning Letter, you must get your written response to the agency within 15 business days.**

The law does not require that you respond to a 483 at all, either orally or in writing. But everyone does, almost without exception, and if you do not, it will be seen as very anomalous and quite negative.



An effective outline for response to each item...

1. In response to this observation, we are taking the following actions: [list what you are doing]
2. We believe this approach is reasonable because [state]:
 - A. Your assessment of the reason(s) why the observation occurred; "root cause"
 - B. Your assessment of the impact on product quality
 - C. Your assessment of the scope of impact (other batches, other products) and how you determined the scope
3. We will complete these actions by [date]
4. We will take the following steps to ensure these actions had the intended effect [list; generally, this will be audit or monitoring]



Pitfalls to Avoid

- The bottom line is, you cannot avoid responsibility, and your answers to FDA's questions must be truthful
- Bearing that in mind, here are some things to watch out for:
 - Do not use excuses such as:
 - No one objected to this during our last inspection!
 - Everyone in the industry does it this way!
 - The investigator was out to get us!
 - The investigator is inexperienced and doesn't get it!
 - Do not admit that a condition or practice represents a "violation" of GMP; avoid terms that condemn your actions or those of your company or your colleagues
 - Do not provide FDA with documents that exceed the scope of the agency's inspection authority; if FDA requests something you are not certain you should release, do not refuse, but clear the request with your management and/or legal counsel before you provide it



Summary

- The FDA-483 is the FDA Investigators' report to management of the conditions or practices he/she observed which, in his/her opinion, may constitute violations of law
- The observations are not a final agency determination of noncompliance
- There is extensive further review before any decision to escalate the agency response is made
- Companies have both oral and written opportunities during and after the inspection to make their views known, to dispute, or to offer corrective action plans
- The 483 is the first step in what can become an escalating enforcement process. Effective response to the document is the key to preventing further regulatory action.

