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A Review of 483 Observations, the Top Med Device Issues Sited & Proper Response

Introduction

The FDA is allowed to visit your company to perform an inspection. In the course of the inspection they may bring some issue to your attention in the form of an observation (aka a 483). This article reviews what a 483 looks like, some of the more common issues flagged in medical device companies, and how to respond.

Authority

What gives the right for the FDA to inspect your site? Section 7b of the Federal Food, Drug, and Cosmetic Act gives the FDA the authority. It states:

(b) Written report to owner; copy to Secretary. 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**, 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

The 483 is issued in accordance with FDA policy to:

"..assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration"

Scenarios

There are three typical inspection scenarios with respect to 483s:

1) **Pre-Approval Inspections (PAI)** – Process and data check to seek approval to go market with your product
2) **Routine GMP inspections** – Usually every 2-3 years to make sure your company is following good GMP practices
3) **"For-cause" inspections** – where the FDA has a specific reason or issue to investigate

The Anatomy of a 483 Observation Letter

483 is simply the name of the FDA form. There are a few samples of 483 letters on the Office of Regulatory Affairs (ORA) Freedom of information Act (FOIA), reading room website.

Let's look at one 483 example letter. Click here to download a report for a medical device company done last year. The components repeated on each page include:

- The FDA district/regional office that performed the inspection is listed. This is then followed by a *Firm Establishment Identifier* (FEI) which is a number issued by the office.

- The date(s) of inspection (which can range from days to months) and the name and address of the facility that was inspected are noted next.

- The name and title of the individual to whom the 483 is issued to (usually the most responsible individual physically present in the facility). In this case, it is the company CEO.

- The type/classification of the business. In this example, it is listed as a Medical Device Manufacture.

- At the bottom (footer), there is a place for all the investigator signatures and dates.

Page one also contains a standard disclaimer:

"This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above"

The middle section of each page contains the meat of the report. This is where the the detail of the observation(s) are described. Each observation is numbered 1 to N. In this case, this particular medical device manufacturer has accumulated 15 observations.

What Are Some of the Top Medical Device Observations?

In 2010, the top 15 issues sited as part of 483 Observations from medical device manufacturers were (From FDA SITE):

Ref No	ShortDesc	LongDesc	Frqncy
21 CFR 803.17	Lack of Written MDR Procedures	Written MDR procedures have not been [developed] [maintained] [implemented]. Specifically, ***	119
21 CFR 820.100(a)	Lack of or inadequate procedures	Procedures for corrective and preventive action have not been [adequately] established. Specifically, ***	118
21 CFR 820.100(b)	Documentation	Corrective and preventive action activities and/or results have not been [adequately] documented. Specifically, ***	114
21 CFR 820.75(a)	Lack of or inadequate process validation	A process whose results cannot be fully verified by subsequent inspection and test has not been [adequately] validated according to established procedures. Specifically, ***	87
21 CFR 820.198(a)	General	Complaint handling procedures for [receiving] [reviewing] [evaluating] complaints have not been [established] [defined] [documented] [completed] [implemented]. Specifically, ***	81
21 CFR 820.50	Purchasing controls, Lack of or inadequate procedures	Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been [adequately] established. Specifically, ***	70
21 CFR 820.198(a)	Lack of or inadequate complaint procedures	Procedures for receiving, reviewing, and evaluating complaints by a formally designated unit have not been [adequately] established. Specifically,***	66
21 CFR 820.198(c)	Investigation of device failures	Complaints involving the possible failure of [a device] [labeling] [packaging] to meet any of its specifications were not [reviewed] [evaluated] [investigated] where necessary. Specifically, ***	64
21 CFR 820.22	Quality audits - Lack of or inadequate procedures	Procedures for quality audits have not been [adequately] established. Specifically, ***	60
21 CFR 820.22	Quality Audit/Reaudit - conducted	Quality [audits][reaudits] have not been performed. Specifically, ***	58
21 CFR 820.30(i)	Design changes - Lack of or Inadequate Procedures	Procedures for design change have not been [adequately] established. Specifically,***	57

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Ref No	ShortDesc	LongDesc	Frqncy
21 CFR 803.50(a)(1)	Report of Death or Serious Injury	An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury. Specifically, ***	53
21 CFR 820.30(a)	Design control - no procedures	Procedures for design control have not been established. Specifically,***	53
21 CFR 803.50(a)(2)	Report of Malfunction	An MDR report was not submitted within 30 days of receiving or otherwise becoming aware of information that reasonably suggests that a marketed device has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. Specifically, ***	51
21 CFR 820.75(a)	Documentation	Process validation [activities] [results] have not been [documented] [approved] [adequately documented] [adequately approved]. Specifically, ***	46

CAPA and MDR related issues rank supreme in 483 issues listed in 2010. Many of them have to do with the lack of setting and/or documenting a procedure.

Preparing a Response to an 483 observation

Do you have to respond to a 483 observation? Yes, you do. In the past, observation responses by companies were considered optional. But today the FDA is proactive in calling for the automatic issuing of Warning Letters to companies that fail to respond to the FDA 483s within 15 days (since 9/15/2009).

Anita Richardson, as part of 5th annual FDA and Changing Paradigm conference in 2009 outlined a solid framework for writing an effective 483 response. Her points were:

Assess each observation

- Focus on specifics
- Focus on system-wide implications
- Focus on global implications
- Consider affected products
- Consider root-cause analysis
- Focus on the regulatory requirement(s) associated with the observation
- Develop action plan to achieve immediate, short-term, and long-term correction and to prevent recurrence
- Know when to seek outside assistance

In addition, she presented a few specific tips including:

1) Include a commitment/statement from senior leadership
2) Address each observation separately
3) Note whether you agree or disagree with the observation
4) Provide corrective action accomplished and/or planned; tell FDA the plan
   - Be specific (e.g. observation-by-observation)
   - Be complete
   - Be realistic
   - Be able to deliver what you promise
   - Address affected products
5) Provide time frames for correction
6) Provide method of verification and/or monitoring for corrections
7) Consider submitting documentation of corrections where reasonable & feasible

We hope this has been a helpful overview on 483s. Call SPK and Associates today for guidance in software engineering best practices with a focus on avoiding 483 observation letters.

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