FDA Inspections: an investigator's perspective

FDA Inspections Summit
Bethesda, MD
October 23, 2014

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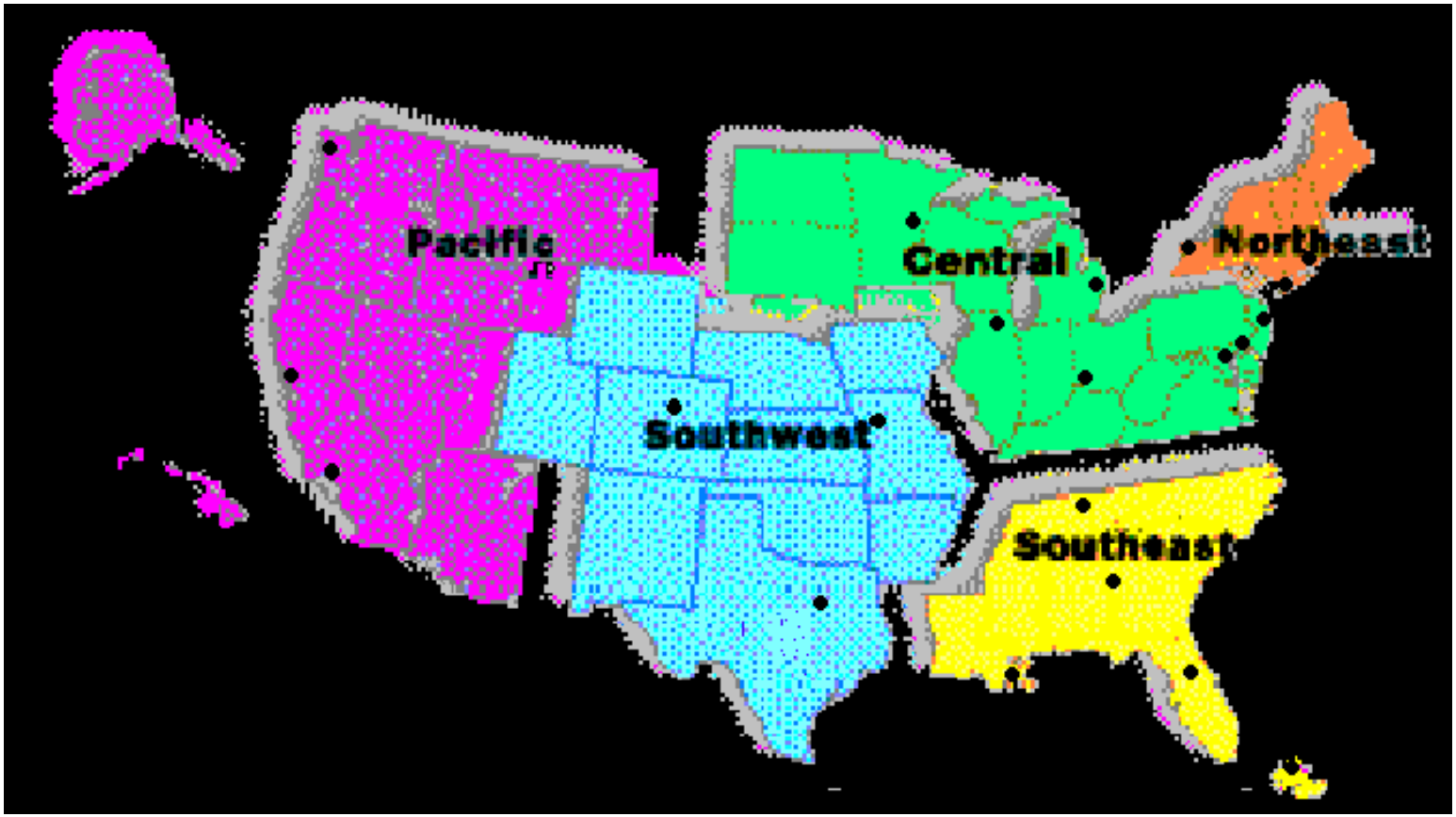
Office of Regulatory Affairs

Field Operations: Regional/District Offices



Who conducts inspections for FDA?

1. **Office of Regulatory Affairs (ORA): FDA investigators in FDA District Offices around the U.S.**

2. **FDA-trained Auditors from Conformity Assessment Bodies in the European Union (EU) or other partnerships/agreements**

3. **FDA-trained auditors from independent third parties accredited by FDA**

Investigators

Part of the Office of Regulatory Affairs

- More than 4,400 ORA personnel in more than 200 locations work everyday to maximize compliance of regulated products and to minimize public health risk

- Office of Criminal Investigations (OCI)

Investigators

- Also known as a Consumer Safety Officer
- Have a science background
- Work in Food, Devices, Drugs, BIMO, Blood & Biologics, and Imports
- Receive training according to discipline
- May be part of international inspection Cadre

How does FDA decide who to inspect?

- Registration database identifies who manufacturers devices for distribution in the U.S.
- Listing database identifies what devices they distribute
- FDA prioritizes inspections by risk and gives higher risk devices/situations a higher priority

How does FDA choose?

- Mandated by law, every 2 years for class II and class III device manufacturers
- Risk
- Follow up inspections to a regulatory action
- Complaints (public & industry)

What is high priority for an inspection?

- Make Class III or Class II devices
- Make implantable devices and life supporting and life sustaining devices
- Recently introduced a new device to the market
- Have had significant violations and complaints in the past

Does FDA notify the manufacturer of an upcoming inspection?

- FDA calls domestic manufacturers up to 5 calendar days before the inspection
- FDA contacts foreign manufacturers 2 - 3 months in advance to schedule inspection
- Manufacturer may be requested to send Quality System Manual or equivalent for pre-inspection review

What happens when the FDA investigator arrives at the site?

- Ask to see the top management ("most responsible person" at the firm.
- Present credentials (identification as an authorized FDA investigator)
- Issue FDA-482 "Notice of Inspection" (explains FDA's legal authority to inspect)

This is an example of Form FDA 482, Notice of Inspection

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

1. DISTRICT OFFICE ADDRESS & PHONE NO.

TO

2. NAME AND TITLE OF INDIVIDUAL

3. DATE

4. FIRM NAME

5. HOUR a.m. p.m.

6. NUMBER AND STREET

7. CITY AND STATE & ZIP CODE

8. PHONE NO. & AREA CODE

Notice of Inspection is hereby given pursuant to Section 704(a)(1) of the Federal Food, Drug, and Cosmetics Act [21 U.S.C. 374(a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264][2]

As a small business that is subject to FDA regulation, you have the right to seek assistance from the U.S. Small Business Administration (SBA). This assistance includes a mechanism to address the enforcement actions of Federal agencies. SBA has a National Ombudsman's Office that receives comments from small businesses about Federal agency enforcement actions. If you wish to comment on the enforcement actions of FDA, CALL (888) 734-3247. The website address is www.sba.gov/ombudsman.

FDA has an Office of the Ombudsman that can directly assist small business with complaints or disputes about actions of the FDA. That office can be reached by calling (301) 796-8530 or by email at ombuds@oc.fda.gov.

For industry information, go to www.fda.gov/oc/industry.

9. SIGNATURE(S) (Food and Drug Administration Employee(s))

10. TYPE OR PRINT NAME(S) AND TITLE(S) (FDA Employee(s))

[1] **Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:**

Sec. 704(a)(1) For purposes of enforcement of this Act, 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. In the case of any person (excluding farms and restaurants) who manufactures, processes, packs, transports, distributes, holds, or imports foods, the inspection shall extend to all records and other information described in section 414, when the standard for records inspection under paragraph (1) or (2) of section 414(a) applies, subject to the limitations established in section 414(d). In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products are manufactured, processed, packed, or held, inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs, nonprescription drugs intended for human use, restricted devices, or tobacco products which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualifications of technical and professional personnel performing functions subject to this

(Continued on Reverse)

Can you refuse an inspection?

- Under section 704 of the FD&C Act, FDA is authorized to enter establishments
- They are further authorized to inspect “at reasonable times and within reasonable limits and in a reasonable manner”
- FDA can also seek an Administrative Inspection Warrant from a United States District Court

What happens next?

- Gather information about size and structure of company, who are the responsible officials, what products are manufactured there

- Evaluate the manufacturer's Quality System using the Quality System Inspection Technique (QSIT)

What happens during the inspection?

- Investigator may tour the facility to get an idea of layout, workflow, and areas that may need closer inspection. (Start Big, Get Small)

- This helps the investigator decide how to organize the inspection

What happens during the inspection?

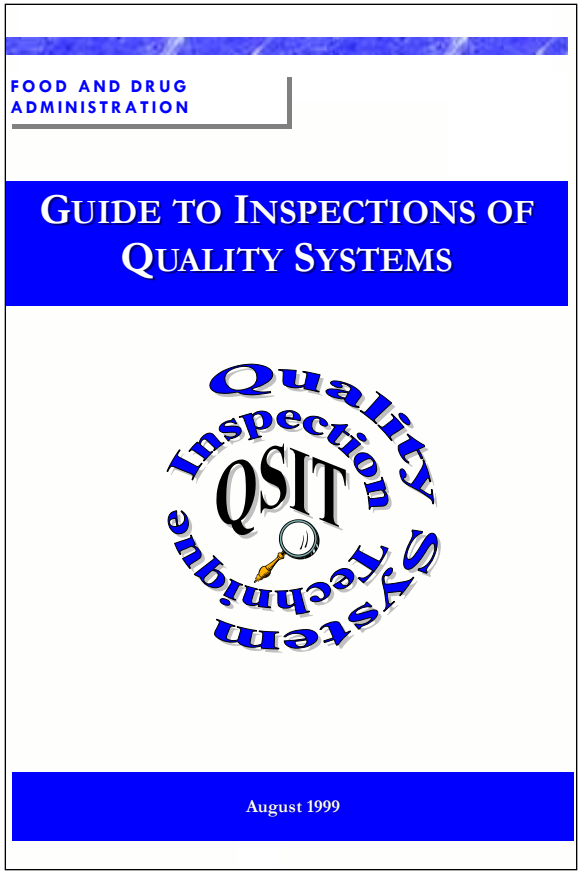
- The Investigator may request to interview employees, take samples (484 Receipt for Sample) and make copies of documents
- The Investigator may also request to take pictures during the inspection

What is QSIT?

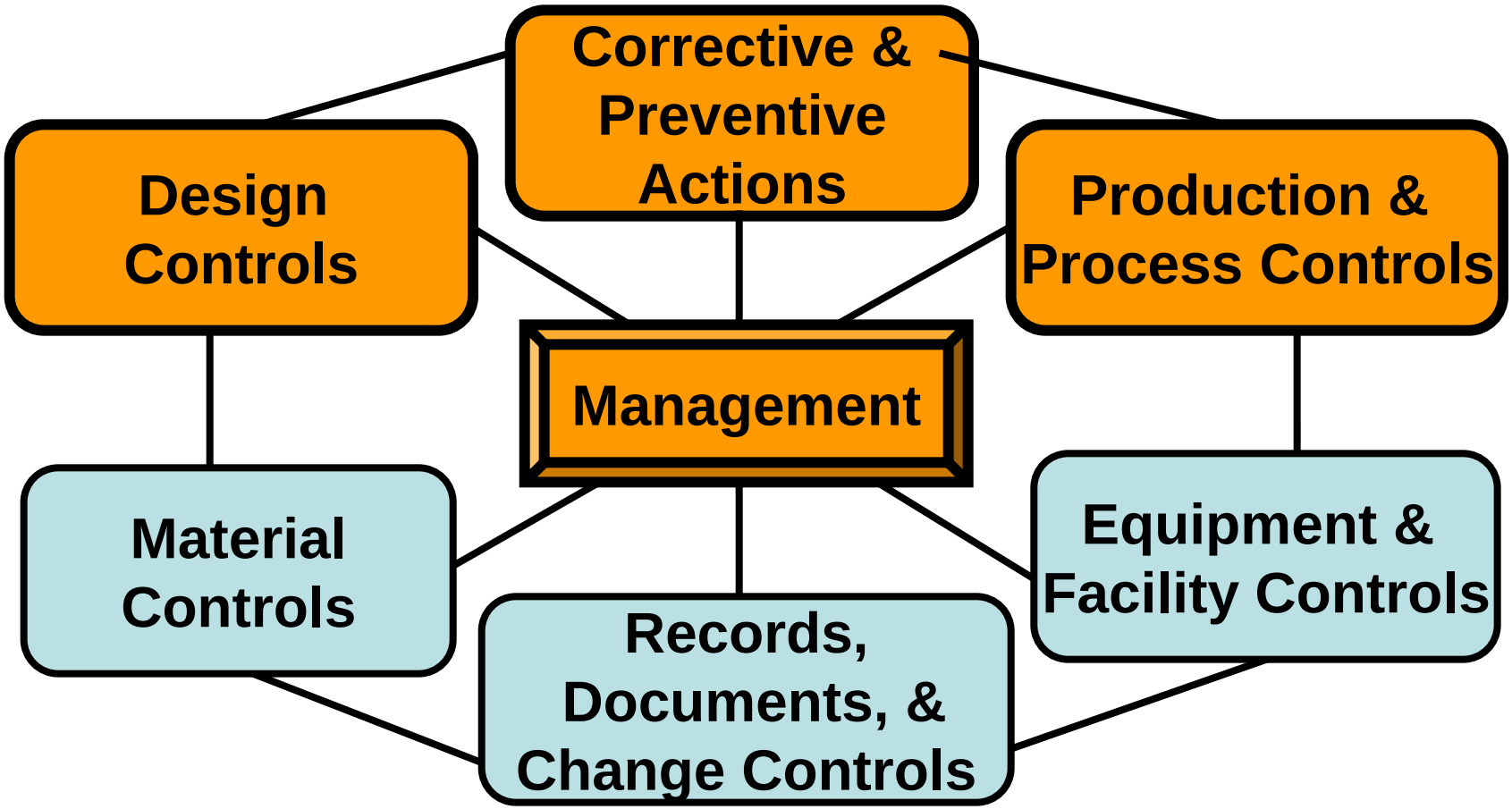
- Identifies 4 major subsystems to evaluate and states the purpose and importance of each subsystem
- Provides flowcharts and inspectional objectives to cover during inspection
- Offers advice on inspection
- Provides tables for statistical sampling of records for review

What is QSIT?

- **http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm**



Subsystems of the Quality System



Does FDA conduct different types of inspections?

- Investigator may conduct 1 of 4 types of inspections for medical devices:
  - Level 1 – Abbreviated QSIT
  - Level 2 – Baseline QSIT (Comprehensive)
  - Compliance follow-up
  - “For Cause”

What is a Level 1 abbreviated inspection?

- Is conducted after firm has had a Level 2 inspection, and quality system was in compliance with requirements
- Covers CAPA plus one other major subsystem
- Covers a different subsystem each time

What is a Level 2 baseline (comprehensive) inspection?

- Covers all 4 main subsystems
- Is conducted when the firm has never had Level 2 inspection and every 6 years thereafter, resources permitting
- Provides an overall evaluation of the firm's quality system

What is a compliance follow-up inspection?

- Is conducted to verify adequate correction of previous violations or document continuing violations to support possible regulatory action
- Is conducted to follow up on information indicating serious problems at firm
- May include elements of QSIT

What is a “For Cause” Inspection?

- Initiated at the request of CDRH, ORA Headquarters, Regional or District Directive
- Dictated by the source of information and may differ from typical QSIT approach
- These inspections are generally more in depth in particular areas than typical QSIT inspections
- Conducted as the need arises
  - Important note in CP, if the Investigator encounters a serious public health risk during the QSIT inspection the investigator may switch to a for cause inspection

What does FDA look for in the Management Subsystem?

- Has a Quality Policy been established?
- Has a management representative been appointed?
- Has Management with Executive Responsibility conducted management reviews?
- Have quality audit procedures been established and have quality audits been conducted?
- Has a quality plan been established?
- Have quality system been procedures established?

What does FDA look for in the Design Control Subsystem?

- Have design procedures and plan been established?
- Have design inputs or requirements for device been identified?
- Have design outputs or specifications for device been developed?
- Has design verification been conducted?
- Has design validation been conducted?

What does FDA look for in the Design Control Subsystem?

- Has software been validated?
- Has risk analysis been carried out?
- Have design reviews been conducted?
- Has design transfer to manufacturing been completed successfully?

What does FDA look for in the Corrective and Preventive Action Subsystem?

- Have CAPA procedures been established?
- Are sources of data analyzed to identify nonconforming product and quality problems?
- Is a statistical analysis conducted across data sources?
- Are investigations conducted to identify root cause of failures?

What does FDA look for in the Corrective and Preventive Action Subsystem?

- Is nonconforming product controlled?
- Are corrective actions and preventive actions appropriate and effective and carried out?
- Are those responsible are told about CAPA activities?
- Does management review CAPA activities?

What does FDA look for in the Production and Process Control Subsystem?

- Are processes controlled and monitored?
- Are rejects and nonconforming product handled appropriately?
- Is equipment adjusted, calibrated and maintained?
- Are all manufacturing processes validated or fully verified?
- Is software validated?
- Are production employees trained and qualified?

What about the other subsystems?

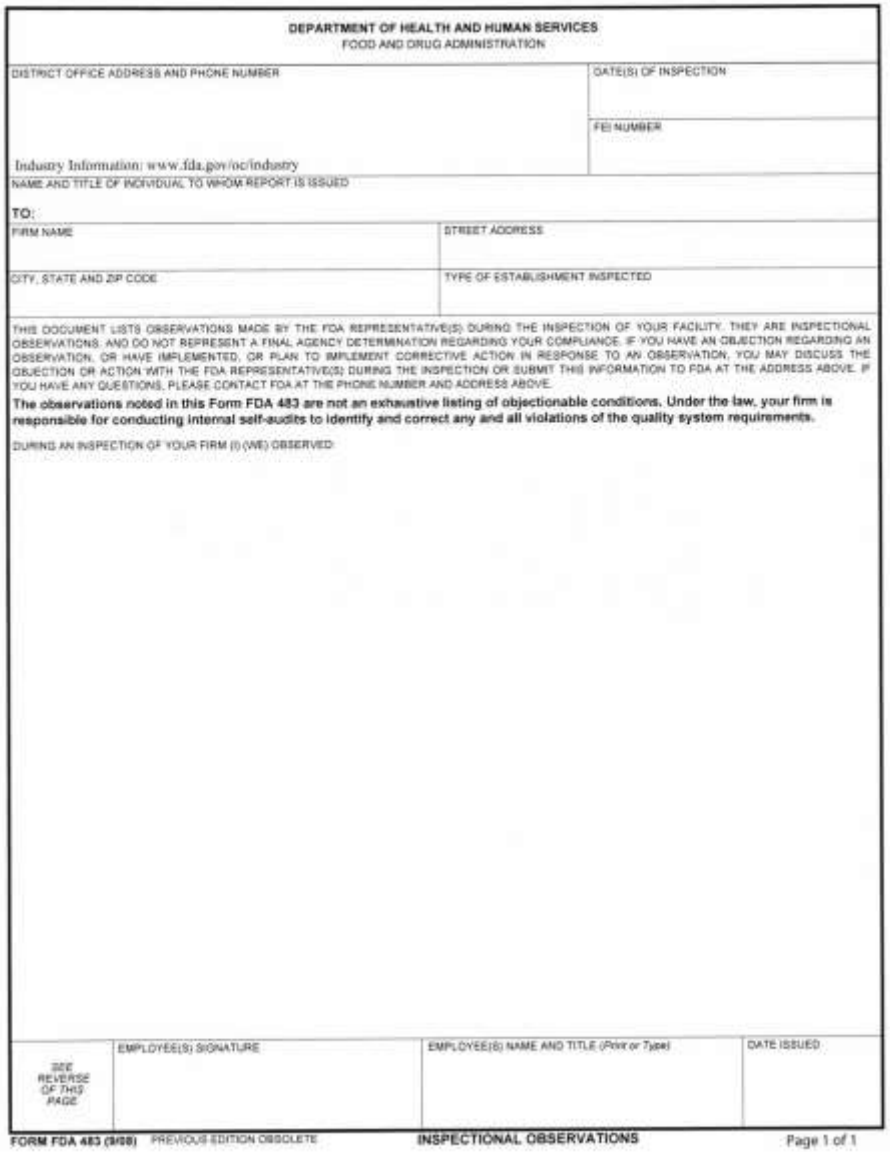
- The other three subsystems are covered through links with the four main subsystems:
  - Records, documents and change control
  - Facility and equipment control
  - Material control

What happens at the end of the inspection?

- Meet with management to discuss the inspection
- Present the FDA 483 “List of Observations” of any significant observations
- Discuss the observations

This is an example of the FDA Form 483, Inspectional Observations.

The header identifies the FDA district office that performed the inspection, the date(s) of inspection, name and address of the facility that was inspected, the name and title of the individual to whom the 483 is issued to (usually the most responsible individual physically present in the facility), a brief description of the type of facility, and the facility's FEI (FDA Establishment Identification) number.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

Industry Information: www.fda.gov/oc/industry

DATE(S) OF INSPECTION

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO:

FIRM NAME

STREET ADDRESS

CITY, STATE AND ZIP CODE

TYPE OF ESTABLISHMENT INSPECTED

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 observations noted in this Form FDA 483 are not an exhaustive listing of objectionable conditions. Under the law, your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED

FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS Page 1 of 1

FDA-483 “Inspectional Observations”

- The content of a 483 may be handwritten, typed, completed in a PDF file and printed, or completed via the FDA's computer system called **Turbo EIR**.

- The observations listed on this form do not represent a final agency determination regarding your compliance. An additional statement only included for medical devices is that the observations are not an exhaustive listing of objectionable conditions. Under law your firm is responsible for conducting internal self-audits to identify and correct any and all violations of the quality system requirements.

- If the firm has promised and/or completed a corrective action to an FDA 483 prior to the completion of the inspection, the FDA 483 should be annotated.

FDA-483 "Inspectional Observations"

- **Turbo EIR?**
  - Links citations to underlying regulations and statutes
  - Provides uniform FDA-483s and EIRs
  - Improves data analysis

What are annotations to the 483?

As of 1997, the FDA established an annotation policy for medical device inspections. The investigator(s) should offer to annotate the 483 with one or more of the following:

- *Reported corrected, not verified*
- *Corrected and verified*
- *Promised to correct*
- *Under consideration*

The actual annotation of the 483 occurs during the final discussion with the firm's management; if the firm prefers no annotation, then annotation will not be performed. The annotations may be after each observation, at the end of each page, or at the bottom of the last page prior to the investigator's signature(s).

The term “verified” means “to confirm; to establish the truth or accuracy”. In this case, the investigator must do the verification. In some situations, they will not be able to verify the corrective action unless there is further district or Center review or until there is another inspection of the establishment. If the firm has promised correction and furnishes a date or timeframe for completion, this may be added to the annotation. If the investigator and firm have “agreed to disagree” about the validity of an observation, the observation may be annotated with “under consideration” or no annotation is used, based on the firm’s decision.

Top 10 Device Observations Used in Turbo EIR

Cite ID	Count	Reference No.	Citation Text
3130	1686	21 CFR 820.100(a)	Procedures for corrective and preventive action have not been [adequately] established. Specifically, ***
630	1179	21 CFR 803.17	Written MDR procedures have not been [developed] [maintained] [implemented]. Specifically, ***
4189	1093	21 CFR 820.198(a)	Complaint handling procedures for [receiving] [reviewing] [evaluating] complaints have not been [established] [defined] [documented] [completed] [implemented]. Specifically, ***
3696	1074	21 CFR 820.100(b)	Corrective and preventive action activities and/or results have not been [adequately] documented. Specifically, ***
546	975	21 CFR 820.75(a)	A process whose results cannot be fully verified by subsequent inspection and test has not been [adequately] validated according to established procedures. Specifically, ***
3415	833	21 CFR 820.22	Quality [audits][reaudits] have not been performed. Specifically, ***
2327	786	21 CFR 820.22	Procedures for quality audits have not been [adequately] established. Specifically, ***
2371	704	21 CFR 820.30(a)	Procedures for design control have not been established. Specifically,***
3103	692	21 CFR 820.30(i)	Procedures for design change have not been [adequately] established. Specifically,***
479	658	21 CFR 820.50	Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been [adequately] established. Specifically, ***

What should the manufacturer do after the inspection?

- Send a letter to FDA identifying how they have corrected observations or will correct them
- Provide documentation of any corrections that have been completed
- Provide a timetable or estimated completion date for future corrections

What happens next?

- Investigator returns to office to write an “Establishment Inspection Report” or EIR
- Inspection is classified based on inspectional findings
- Compliance officer decides whether to recommend regulatory action

How does FDA classify inspection reports?

- NAI – No Action Indicated
- VAI – Voluntary Action Indicated – some deficiencies identified but not serious
- OAI – Official Action Indicated – serious deficiencies identified, and FDA must take action to assure correction

What actions can FDA take to address OAI inspections?

- Warning Letter
- Seizure
- Injunction
- Civil penalties
- Criminal

Warning Letter

- FDA sends “Warning Letter” describing manufacturer’s violations of FDA regulations and requesting a reply within 15 days
- FDA inspects the manufacturer 6 - 12 months after sending the Warning Letter to confirm correction of deficiencies

Investigator Tools

- Federal Food, Drug, and Cosmetic Act
- 21 Code of Federal Regulations (800-1299)
- Compliance Policy Guides

Investigator Tools

- Quality System Inspection Techniques (QSIT)
- Compliance Program Guidance Manual
  - CP 7382.845 Inspection of Medical Device Manufacturers available on-line

Investigator Tools

- **Investigations Operations Manual**
  - 5.2.1.1 Preannouncements
  - 5.6.2 Medical Device Quality System/ GMP
  - 5.6.9 Device Inspection Reports
  - 5.10.4.3.9 Manufacturing/Design Operations
    - Specific Instructions for medical device EIRs
  - 5.10.4.3.16 Additional information
    - Specific Instructions for medical device EIRs

Investigator Tools

- Previous Establishment Inspections Reports
- Training Courses
- Other investigators or FDA Labs
- DICE (Division of Industry and Consumer Education)

Investigator Tools

- Guidance Documents (can be accessed from www.FDA.gov website under Medical Devices CDRH Device Advice)
- Internet
- Other Federal, State and Local agencies
- FDA Recognized Consensus Standards

Providing Industry Education and Assistance – CDRH Resources

- CDRH Learn – Online Regulatory Training Tool
  - Over 80 Medical Device and Radiological Health modules
  - Video and PowerPoint presentations available 24/7
  - Certificate of completion upon passing post-tests
  - Many modules are translated into Chinese and Spanish
  - http://www.fda.gov/Training/CDRHLearn/
- Device Advice – Online Regulatory Information
  - Searchable by topic
  - http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/
  - **DICE@fda.hhs.gov**

Providing Industry Education and Assistance – CDRH Resources

- CDRH Learn – Regulatory Topics
  - How to Market Your Device
  - Registration & Listing
  - Postmarket Activities
  - Unique Device Identification (UDI) Systems
  - Specialty Technical Topics
  - Radiation-Emitting Products
  - In Vitro Diagnostics (IVD)

Summary

- Who conducts inspections for FDA
- Quality System Inspection Technique (QSIT)
- How FDA conducts inspections
- What should a manufacturer do after an inspection
- Enforcement actions FDA can take when manufacturers do not comply with regulation