

# FDA Inspections: an investigator's perspective

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**Lori S. Lawless**  
**Medical Device Specialist**  
**Supervisory Consumer Safety Officer**  
**Food & Drug Administration**  
**Baltimore District**  
**[Lori.Lawless@fda.hhs.gov](mailto:Lori.Lawless@fda.hhs.gov)**  
**(410) 779-5442**



# Who conducts inspections for FDA?

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- The Office of Regulatory Affairs (ORA) is the lead office for all field activities at the FDA.
- Regulating more than **135,000 business establishments** that annually produce, warehouse, import and transport **\$1 trillion** worth of consumer goods.

# Who conducts inspections for FDA?

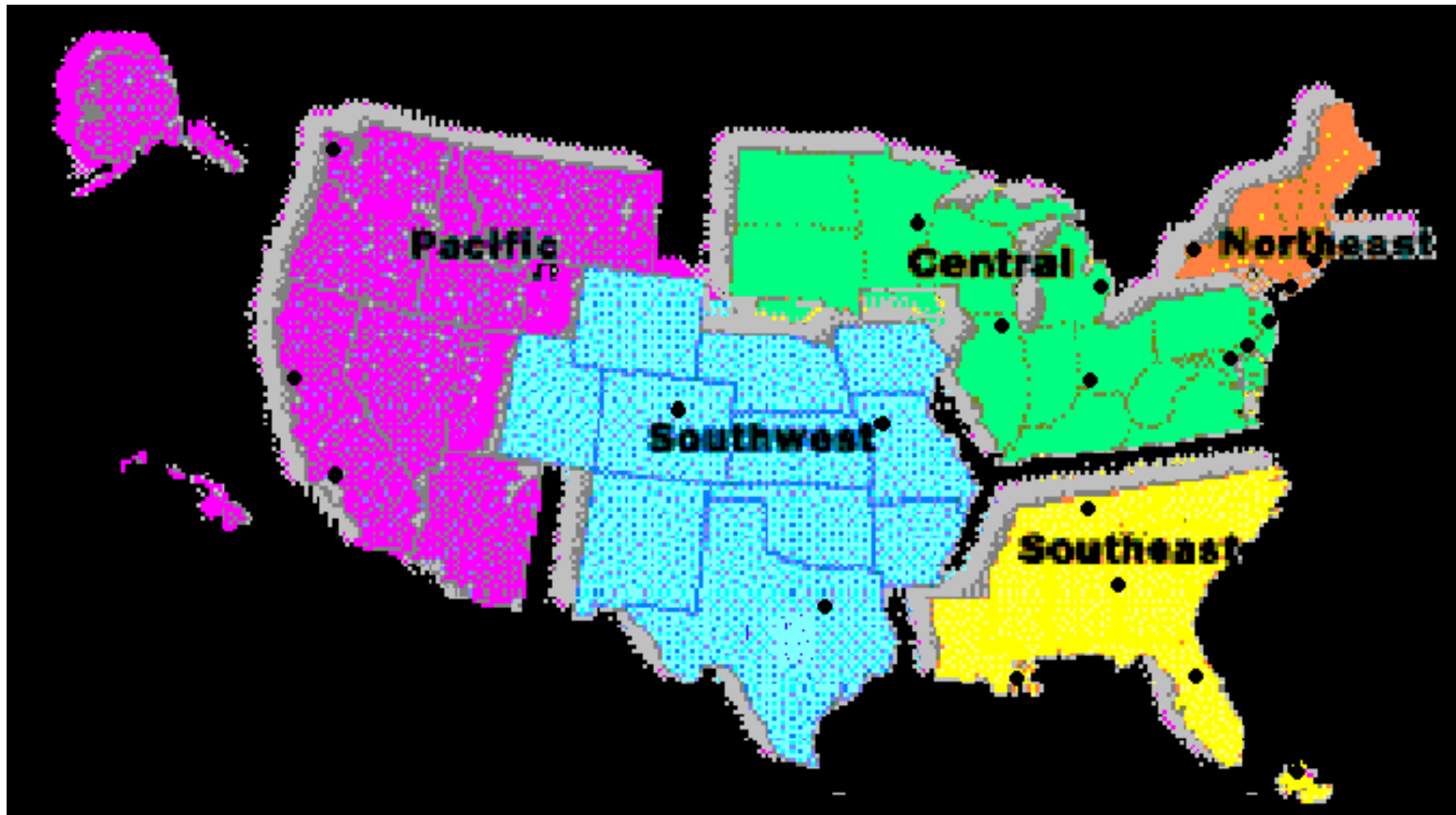
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## **Part of the Office of Regulatory Affairs**

- 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)

# Office of Regulatory Affairs

## Field Operations: Regional/District Offices



# Who conducts inspections for FDA?

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- 1. FDA investigators in FDA District Offices around the U.S.**
- 2. FDA-trained Auditors from Conformity Assessment Bodies in the European Union (EU)**
- 3. FDA-trained auditors from independent third parties accredited by FDA**

# How does FDA decide who to inspect?

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- **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 decide who to inspect?

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- **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 inspection?

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- **Device manufacturers that:**
  - **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 in the past**



# Does FDA notify the manufacturer of an upcoming inspection?

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- **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?

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- **The FDA investigator will:**
  - **Ask to see the top management**
  - **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.	
2. NAME AND TITLE OF INDIVIDUAL		3. DATE	
4. FIRM NAME		5. HOUR	a.m.
TO 6. NUMBER AND STREET			p.m.
7. CITY AND STATE & ZIP CODE			8. PHONE NO. & AREA CODE
<p>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)]<sup>1</sup> and/or Part F or G, Title III of the Public Health Service Act [42 U.S.C. 262-264]<sup>2</sup></p>			
<p>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 <a href="http://www.sba.gov/ombudsman">www.sba.gov/ombudsman</a>.</p> <p>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 <a href="mailto:ombuds@oc.fda.gov">ombuds@oc.fda.gov</a>.</p> <p>For industry information, go to <a href="http://www.fda.gov/oc/industry">www.fda.gov/oc/industry</a>.</p>			
9. SIGNATURE(S) (Food and Drug Administration Employee(s))		10. TYPE OR PRINT NAME(S) AND TITLE(S) (FDA Employee(s))	
<p><sup>1</sup> Applicable portions of Section 704 and other Sections of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:</p> <p>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</p>		<p>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</p> <p style="text-align: right;">(Continued on Reverse)</p>	

# What happens during the inspection?

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- **Investigator may tour the facility to get an idea of layout, workflow, and areas that may need closer inspection**
  
- **This helps the investigator decide how to organize the inspection**



# What happens next?

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- **The investigator will:**
  - **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 is QSIT?

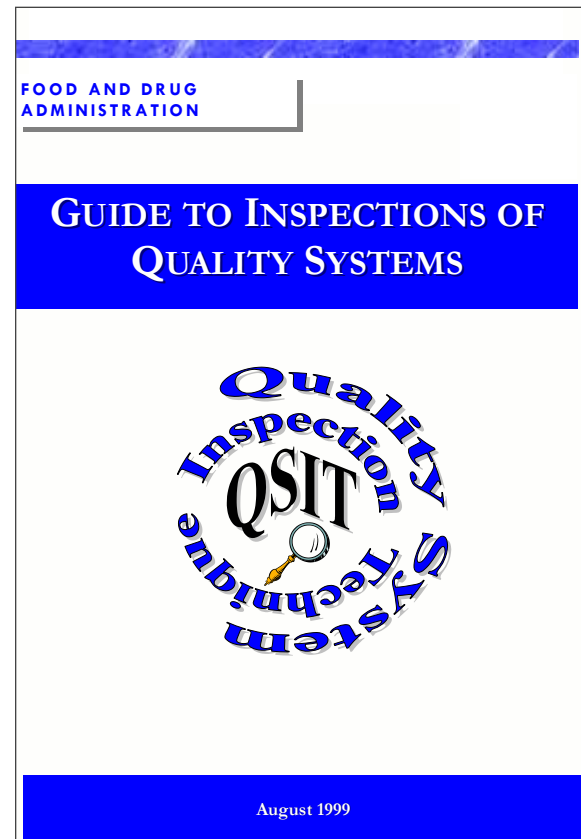
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- **Identifies 4 major subsystems to evaluate and states the purpose and importance of each subsystem**
- **Provides flowcharts and inspectional objectives to cover during inspection**
- **Offers advice on inspection**
- **Provides tables for statistical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

# What is QSIT?

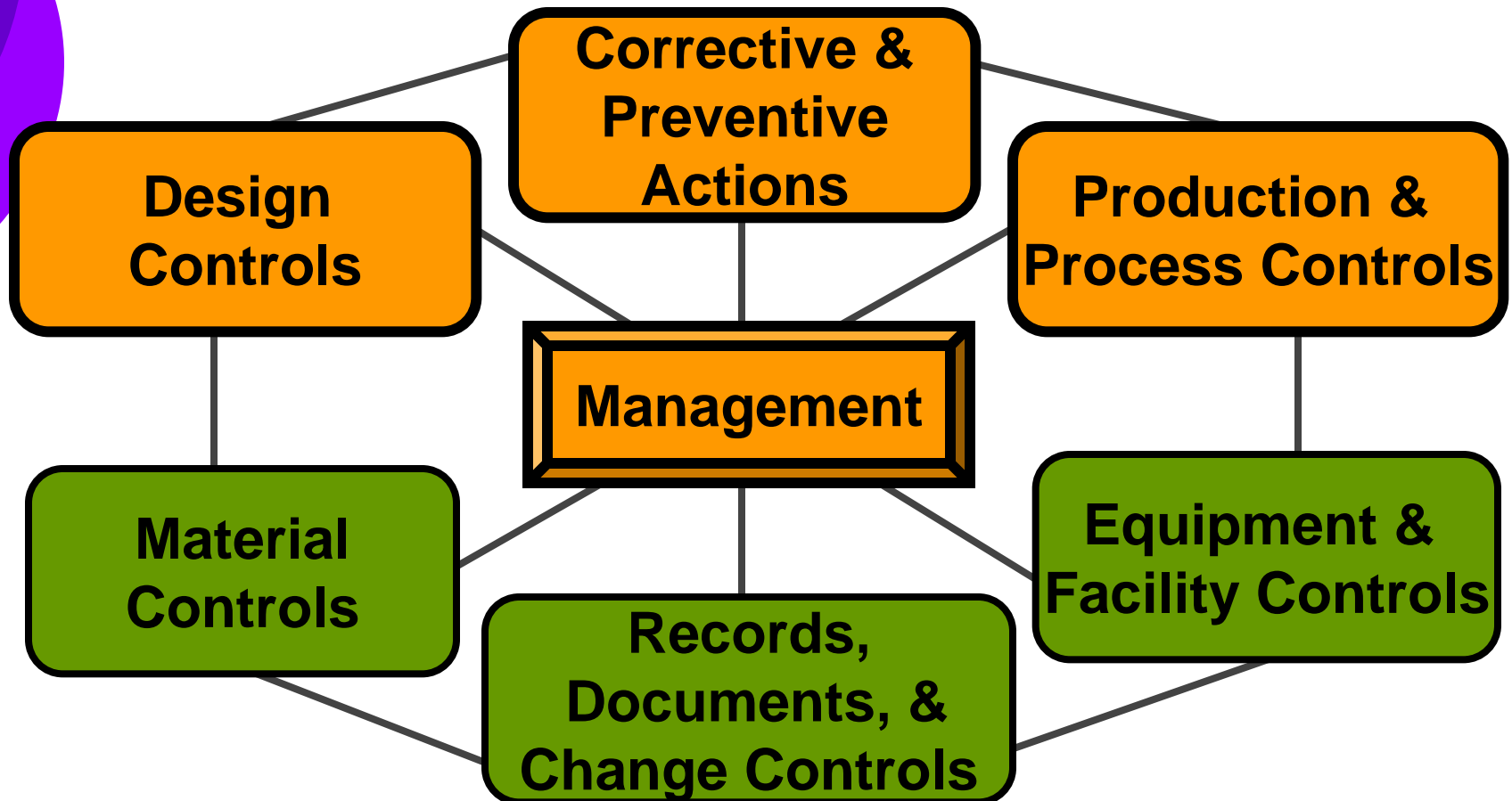
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<http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074883.htm>



# What are the four main subsystems?

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# Does FDA conduct different types of inspections?

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- Investigator may conduct 1 of 3 types of GMP inspections for medical devices:
  - Level 1 – Abbreviated QSIT
  - Level 2 – Baseline QSIT (Comprehensive)
  - Compliance follow-up
- “For Cause”

# What is a Level 2 baseline (comprehensive) inspection?

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- **An inspection that:**
  - **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 Level 1 abbreviated inspection?

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- **An inspection that:**
  - **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 compliance follow-up inspection?

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- **An inspection that:**
  - **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?

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- **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?

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- **Has a Quality Policy been established?**
- **Has a management representative been appointed?**
- **Has Management with Executive Responsibility conducted management reviews?**

# What does FDA look for in the Management Subsystem?

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- **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?

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- **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?

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- **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?

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- **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?

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- **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?

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- **Are processes controlled and monitored?**
- **Are rejects and nonconforming product handled appropriately?**
- **Is equipment adjusted, calibrated and maintained?**



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

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- **Are all manufacturing processes validated or fully verified?**
- **Is software validated?**
- **Are production employees trained and qualified?**



# What about the other subsystems?

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- **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?

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

# What happens at the end of the inspection?

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## ○ **Turbo EIR?**

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



# What happens at the end of the inspection?

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**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***

# What should the manufacturer do after the inspection?

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- **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?

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- **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?

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- **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?

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



# Warning Letter

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- **FDA sends “Warning Letter” describing manufacturer’s violations of FDA regulations and requesting a reply within 15 days**



# Warning Letter

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- **FDA inspects the manufacturer 6 - 12 months after sending the Warning Letter to confirm correction of deficiencies**





# Summary

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- **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**



# Providing Industry Education and Assistance – CDRH Resources

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- Device Advice – Online Regulatory Information
  - Searchable by topic
  - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/>
  - [dsmica@fda.hhs.gov](mailto:dsmica@fda.hhs.gov)
  
- CDRH Learn – Online Regulatory Training Tool
  - Over 50 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/>

# Providing Industry Education and Assistance – CDRH Resources

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- **Federal Food, Drug, and Cosmetic Act**
- **21 Code of Federal Regulations (800-1299)**
- **Guidance Documents (can be accessed from [www.FDA.gov](http://www.FDA.gov) website under Medical devices CDRH Device Advice)**
- **Quality Systems Manual: A Small Entity Compliance Guide on-line**
- **Compliance Policy Guides**
- **Quality System Inspection Techniques (QSIT)**
- **Compliance Program Guidance Manual**
  - **CP 7382.845 Inspection of Medical Device Manufacturers available on-line**

# Providing Industry Education and Assistance – CDRH Resources

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## ○ CDRH Learn – Regulatory Topics

- Overview of Regulatory Requirements: Medical Devices
- Guidance Documents and Standard Operating Procedures (SOPs)
- Premarket Notification Process - 510(k)
- Investigational Device Exemption Process – IDE
- Bioresearch Monitoring (BIMO)
- Device Establishment Registration and Listing
- CDRH Regulated Software: An Introduction
- Quality System Regulation 21 CFR Part 820
- Medical Device Recalls
- Medical Device Reporting (MDR)
- Export Certificates for Medical Devices
- Regulation of Radiation-Emitting Products
- Global Initiatives
- Medical Devices In the Home
- Unique Device Identification (UDI) System