Medical Device Inspections

FDA Small Business
Regulatory Education for Industry (REdI)
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Office of Regulatory Affairs

• 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.
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)
Office of Regulatory Affairs
Field Operations: Regional/District Offices
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)
Investigator Tools

• Federal Food, Drug, and Cosmetic Act

• 21 Code of Federal Regulations (800-1299)

• Quality Systems Manual: A Small Entity Compliance Guide on-line
Investigator Tools

- Compliance Policy Guides
- 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

• DSMICA
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
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.
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

- Design Controls
- Corrective & Preventive Actions
- Production & Process Controls
- Material Controls
- Management
- Equipment & Facility Controls
- Records, Documents, & Change Controls
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 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 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 “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 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 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.
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 Devices Observations Used in Turbo EIR

<table>
<thead>
<tr>
<th>Cite ID</th>
<th>Count</th>
<th>Reference No.</th>
<th>Citation Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>3130</td>
<td>1686</td>
<td>21 CFR 210.100(a)</td>
<td>Procedures for corrective and preventive action have not been [adequately] established. Specifically, ***</td>
</tr>
<tr>
<td>630</td>
<td>1179</td>
<td>21 CFR 203.17</td>
<td>Written MDR procedures have not been [developed] [maintained] [implemented]. Specifically, ***</td>
</tr>
<tr>
<td>4189</td>
<td>1063</td>
<td>21 CFR 20.198(a)</td>
<td>Complaint handling procedures for [receiving] [reviewing] [evaluating] complaints have not been [established] [defined] [documented] [completed] [implemented]. Specifically, ***</td>
</tr>
<tr>
<td>3696</td>
<td>1074</td>
<td>21 CFR 20.100(b)</td>
<td>Corrective and preventive action activities and/or results have not been [adequately] documented. Specifically, ***</td>
</tr>
<tr>
<td>546</td>
<td>975</td>
<td>21 CFR 20.75(a)</td>
<td>A process whose results cannot be fully verified by subsequent inspection and test has not been [adequately] validated according to established procedures. Specifically, ***</td>
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<tr>
<td>3415</td>
<td>833</td>
<td>21 CFR 20.22</td>
<td>Quality [audits][reaudits] have not been performed. Specifically, ***</td>
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<tr>
<td>2327</td>
<td>786</td>
<td>21 CFR 20.22</td>
<td>Procedures for quality audits have not been [adequately] established. Specifically, ***</td>
</tr>
<tr>
<td>2371</td>
<td>704</td>
<td>21 CFR 20.30(a)</td>
<td>Procedures for design control have not been established. Specifically, ***</td>
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<tr>
<td>3103</td>
<td>692</td>
<td>21 CFR 20.30(j)</td>
<td>Procedures for design change have not been [adequately] established. Specifically, ***</td>
</tr>
<tr>
<td>479</td>
<td>668</td>
<td>21 CFR 20.50</td>
<td>Procedures to ensure that all purchased or otherwise received product and services conform to specified requirements have not been [adequately] established. Specifically, ***</td>
</tr>
</tbody>
</table>
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
Providing Industry Education and Assistance – CDRH Resources

• **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

• **Device Advice – Online Regulatory Information**
  – Searchable by topic
  – dsmica@fda.hhs.gov
Providing Industry Education and Assistance – CDRH Resources

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