FDA Inspections

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Purpose of an Inspection

- Determine if operations are in compliance with the laws and regulations administered by FDA
- Evaluate manufacturing methods, facilities & controls
- Collect evidence to support regulatory action when violations are identified

Authority to Inspect

- First Food & Drug Act in 1906: No inspection authority
- 1938 FD&C Act formally authorized factory inspections
- Food, Drug & Cosmetic Act (FD&C Act), Section 704-Factory Inspection
- FD&C Act Amendments/Other Acts (IOM 2.2)

FD&C Act Section 704(a): Factory Inspections 1

- Officers or employees duly designated
- Presentation of appropriate credentials
- And a written notice to owner, operator or agent in charge

FD&C Act Section 704(a): Factory Inspections 2

- Are authorized to enter & inspect at **reasonable** times, within **reasonable** limits, & in a **reasonable** manner
- Any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are
- manufactured, processed, packed, or held,

FD&C Act Section 704(a): Factory Inspections 3

- for introduction into interstate commerce or after such introduction,
- or to enter any vehicle, being used to transport or hold food, drugs, etc
- All pertinent equipment, finished and unfinished materials, containers, and labeling therein

Inspection Coverage Add-Ons

- Prescription drugs, nonprescription drugs (human), or restricted devices … inspection shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on adulterated or misbranded
- 704(e) records maintained per 519 or 520(g) shall provide reasonable access to and to copy and verify such records.

Inspection Does Not Include:

- Inspections shall not extend to:
  - Financial data
  - Sales data (except shipping data)
  - Pricing data
  - Personnel data (except qualifications)
  - Research data (except per regulations)
- Inspection refusals - Obtain warrant

Types of Inspections 1

- Comprehensive vs. Directed
- Routine: statutory or per workplan
- Pre-approval: NDA, ANDA, PMA
- Obtain specific information for new product or process
- Follow up to reported problem: complaint
- Gather recall information
- Follow up to a regulatory action

Types of Inspections 2

- Routine - General Quality Assessment
  - QSR/Design Controls, MDR, Tracking, 510(k), Sterilization (EtO, Steam, Radiation)
- For Cause - Specific issues
  - Regulatory follow up
  - Complaint/MDR follow up
  - Recall

Types of Inspections 3

- Bio-Research Monitoring (BIMO)
  - Clinical Investigator
  - Sponsor/Monitor
  - Institutional Review Board
- Foreign firm inspections

Basic Inspectional Forms

- Separate notice for each inspection
  (Notice of Inspection Form FDA 482)
  - Attachment to FDA 482: Resources for FDA Regulated Businesses
- Completion of inspection: report in writing
  (Inspectional Observations Form FDA 483)
- If samples collected: receipt for samples
  (Receipt for Samples Form FDA 484)

Form FDA-483 Required Statement-All Inspections

- "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."

Form FDA-483 Required Statement for QS Inspections

- Required Statement. For all Quality System inspections the Form FDA-483 should contain the following statement:

  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.

Inspectional Process

- National Workplan: Risk Base/Statutory
- District determines assignment to Investigator
- Inspection made, Report written
- Classification:NAI, VAI, OAI or to Center
- Non-regulatory or Regulatory follow up
- Investigations Operations Manual (IOM) http://www.fda.gov/ora/inspect_ref/iom/

Depth of Inspection

- Facts which influence time & depth:
  - Purpose
  - History
  - Size & complexity
  - Product & process
  - Compliance Program requirements
  - Industry Problems
  - Conditions uncovered during inspection
- Investigator (CSO) & Supervisor decide time & depth

Inspectional Initiatives

- Medical Device Initiative
  - Pre-announce inspection (5 calendar days)
  - Annotated FDA 483 Inspectional Observations
  - Post Inspection Notification (PIN letter- Discontinued 01-01-01)
- FMD -145 First Party Redacted EIR to Firm
- Warning Letter Pilot (Terminated March 14, 2003)

The Inspection 1

- Pre-announce (medical device only)
- Credentials to owner, operator or agent in charge
  - Do not allow to copy (IOM 5.1.1.2)
- Issue Notice of Inspection, FDA-482
  - one per inspection - not each day (IOM 5.2.2)
  - complete legal names, person & firm, street address, date & time, sign notice

The Inspection 2

- Interview management/employees
- Obtain information (facts), observe things
- Document in diary, collect records
- Observe manufacturing processes:
  - Manufacturing Flow,
  - Sources of Contamination,
  - Sanitary Conditions,
  - Employee Practices,

The Inspection 3

- Observe manufacturing processes:
  - Formula,
  - Storage Conditions,
  - Coding, Packaging & Labeling,
  - Raw Materials, Food Colors & Additives,
  - Environmental Controls, Plant Constructions & Maintenance,
  - Use of Insecticides & Rodenticides

The Inspection 4

- Document violative practices & conditions
- How?
  - Show routes of contamination
  - Make specific and quantitative observations
  - Collect samples for testing & examination
  - Take photographs
  - Copy pertinent records
  - Accurately report observations & conversations in detail

Concluding the Inspection 1

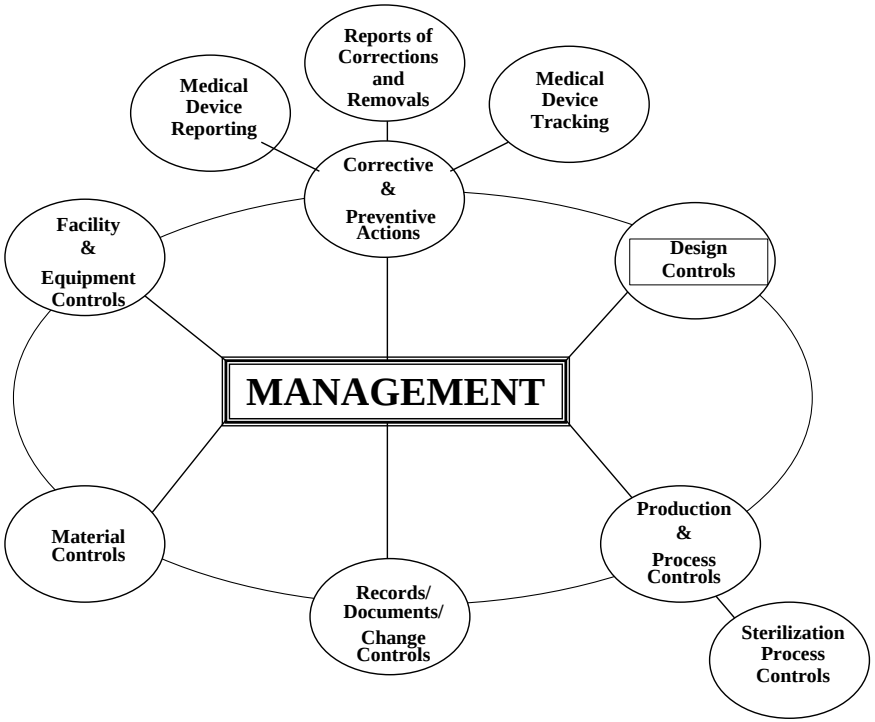
- Prior to conclusion: complete collection of samples, documentation, labels, labeling, etc.
- Issue Receipt for Samples FDA 484, Affidavit FDA 463, etc.
- Inspection is concluded with a discussion with management

Concluding the Inspection 2

- If appropriate issue Inspectional Observations FDA 483
- Discuss observations with management
- Explain observations
- Inform that observations are in your judgement violations of the FD&C Act
- Solicit/Record management's response

The QSIT Inspection Approach

- Top-down (versus Bottom-up)
- Sampling records (use tables)
- Pre-inspection activities (ask for and review documents)
- Start and end with Management



How Will Each QSIT Subsystem be Inspected?

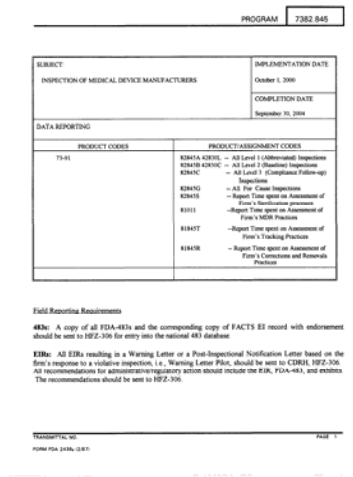
- QSIT Guide
  - Purpose and Importance
  - Objectives
  - Flow charts
  - Narratives
  - Sampling Plans

Inspection order of Subsystems

- Management Controls
- Design Controls
- Corrective and Preventive Actions (CAPA)
- Production and Process Controls (PAPC)
- Conclude with Management Controls

Compliance Program

- CP 7382.845
- Incorporates Several Program Areas
- Utilizes QSIT
- Uses Three Levels of Inspection
- Establishes OAI


PROGRAM 7382.845

SUBJECT: INSPECTION OF MEDICAL DEVICE MANUFACTURERS

IMPLEMENTATION DATE: October 1, 2000

COMPLETION DATE: September 30, 2004

DATA REPORTING

PRODUCT CODES: 73-91

PRODUCT/ASSIGNMENT CODES
- 82845A 42850L – All Level 1 (Abbreviated) Inspections
- 82845B 42850C – All Level 2 (Baseline) Inspections
- 82845C – All Level 3 (Compliance Follow-up) Inspections
- 82845G – All For Cause Inspections
- 82845S – Report Time spent on Assessment of Firm's Sterilization processes
- 81011 – Report Time spent on Assessment of Firm's MDR Practices
- 81845T – Report Time spent on Assessment of Firm's Tracking Practices
- 81845R – Report Time spent on Assessment of Firm's Corrections and Removals Practices

Field Reporting Requirements

483s: A copy of all FDA-483s and the corresponding copy of FACTS EI record with endorsement should be sent to HFZ-306 for entry into the national 483 database

EIRs: All EIRs resulting in a Warning Letter or a Post-Inspectional Notification Letter based on the firm's response to a violative inspection, i.e., Warning Letter Pilot, should be sent to CDRH, HFZ-306. All recommendations for administrative/regulatory action should include the EIR, FDA-483, and exhibits. The recommendations should be sent to HFZ-306.

TRANSMITTAL NO. PAGE 1

Compliance Program: Levels of Inspection

- **PAC 82.845A -** Level 1: Abbreviated, CAPA plus one subsystem
- **PAC 82.845B -** Level 2: Baseline (Comprehensive), The four major subsystems (MC, DC, PAPC & CAPA)
- **PAC 82.845C -** Compliance Follow-up, As directed by inspection guidance
- PAC = Program Assignment Code

For Further Information

- **Good Manufacturing Practice (GMP) Requirements - Quality System (QS) Regulation Information**
  - http://www.fda.gov/cdrh/dsma/cgmphome.html
- **QSIT Guide**
  - http://www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm

For Further Information

- **Inspection of Medical Device Manufacturers - Final Guidance for Industry and FDA**
  - http://www.fda.gov/cdrh/comp/7382.845.html
- **Investigations Operations Manual**
  - http://www.fda.gov/ora/inspect_ref/iom/
- **Office of Ombudsman**
  - http://www.fda.gov/oc/ombudsman/homepage.htm