

RAPS 2008
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& **exhibition**

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Boston
Hynes Convention Center

Regulatory Essentials: US

Compliance & Enforcement

September 14, 2008



RAPS REGULATORY AFFAIRS
PROFESSIONALS SOCIETY

Making better healthcare products possiblesm

»»»» Leadership in motion

Compliance and Enforcement

Objectives

- Understand Prohibited Acts specified in the Federal FD&C Act
- Understand FDA Inspectional Authority, Scope and limitations
- Understand FDA Enforcement Options

FDA Inspections & Enforcement Agenda

- **FDA Mission**
- **Federal Food Drug and Cosmetic Act**
- **FDA Organization & Structure**
- **Inspections**
 - Definitions
 - Systems Approach: Quality system technique (QSIT)
 - Inspection observations (Form 483)
- **Enforcement Actions**
 - Administrative & Judicial Actions
 - Highlight Warning Letters & Other enforcement tools

FDA Mission (FDAMA 1997)

- **Promote:** Public Health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner
- **Protect:** Public Health
 - Foods are safe wholesome and sanitary
 - Drugs (Human and Vet) are safe and effective
 - Devices (Human) safe and effective
 - Cosmetics safe and properly labeled
- **Participate:** in International Harmonization Activities

Food Drug and Cosmetic Act

Violation of the Law

Federal Food Drug and Cosmetic Act

- [Chapter I: Short Title](#)
- [Chapter II: Definitions](#)
- [Chapter III: Prohibited Acts and Penalties](#)
- [Chapter IV: Food](#)
- [Chapter V: Drugs and Devices](#)
- [Chapter VI: Cosmetics](#)
- [Chapter VII: General Authority \(Inspections\)](#)
- [Chapter VIII: Imports and Exports](#)
- [Chapter IX: Miscellaneous](#)

Chapter III- Prohibited Acts and Penalties

- Prohibited Acts 301
- Injunction Proceedings 302
- Penalties 303
- Seizure 304
- Hearing Before Report of Criminal Violation 305
- Debarment,
Temporary Denial of Approval, and
Suspension 306
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- Authority to Withdraw Approval of Abbreviated Drug Applications 308
- Report of Minor Violations 309
- Proceedings in Name of United States; Provision as to Subpoenas 310

SEC. 301. Prohibited acts.

- The following acts and the causing thereof are hereby prohibited:
 - (a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded.
 - (b) The adulteration or misbranding of anyin interstate commerce.
 - (c) The receipt in interstate commerce of anythat is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.
 - (d) The introduction or delivery for introduction into interstate commerce a new drug without a new drug application (NDA)
 - (e) The refusal to permit access to or copying of any record as required by section; or the failure to establish or maintain any record, or make any report, required under section or the refusal to permit access to or verification or copying of any such required record.
 - (f) The refusal to permit entry or inspection as authorized by section 704.

Adulteration

- It consists of a filthy, putrid, or decomposed substance, or has been produced under unsanitary conditions whereby it may have been so contaminated
- It is a drug that has not been manufactured in compliance with good manufacturing practice
- Its container is composed of any poisonous or deleterious substance which may render the contents injurious to health
- Its strength, quality, or purity differs from an official compendium or that which it purports or is represented to possess
- It is a class III medical device and does not have an approved PMA and is not otherwise exempt
- It is a device that has not been manufactured in compliance with the Quality System Regulation
- It is a banned device

Misbranding: (Think Labeling)

- Its labeling is false or misleading
- Its label fails to indicate the manufacturer, packer, or distributor's name and place of business, and an accurate statement of contents
- It is a drug and its label does not contain the established name of the drug and the established name and quantity or the proportion of each active ingredient
- Its label fails to bear adequate directions for use and such warnings are necessary for the protection of users
- It is dangerous to health when used in the dosage or manner recommended by the labeling
- It is not **listed** with FDA or is manufactured in a facility not **registered** with FDA
- It is a device for which notification was not provided as required by section 510(k)
- Failure to file AER or MDR

FD&C Act Chapter VII—General Authority

- Subchapter A (U.S.C. Part A)—General Administrative Provisions
- Regulations and Hearings701
- Examinations and Investigations702
- Records of Interstate Shipment703
- **Factory Inspection704**

FD&C Act Chapter VIII—Imports and Exports

- Imports and Exports 801
 - “Appears”
 - Detention

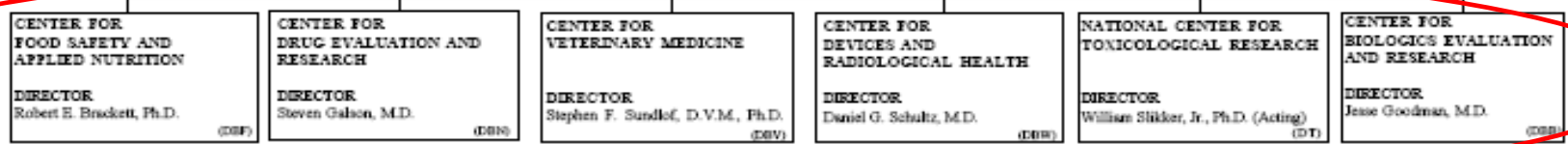
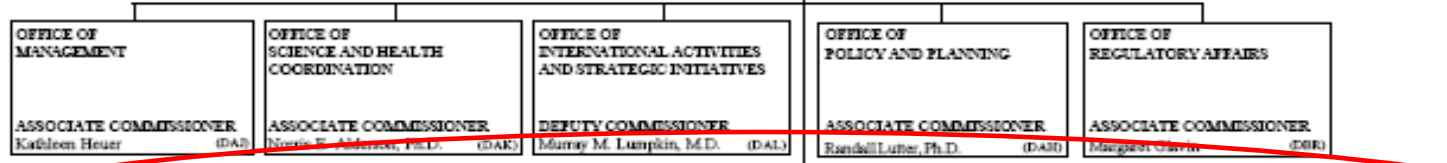
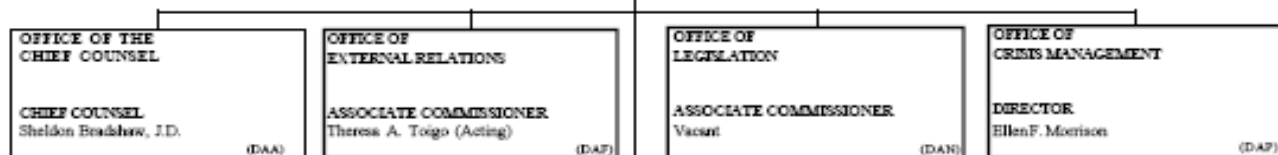
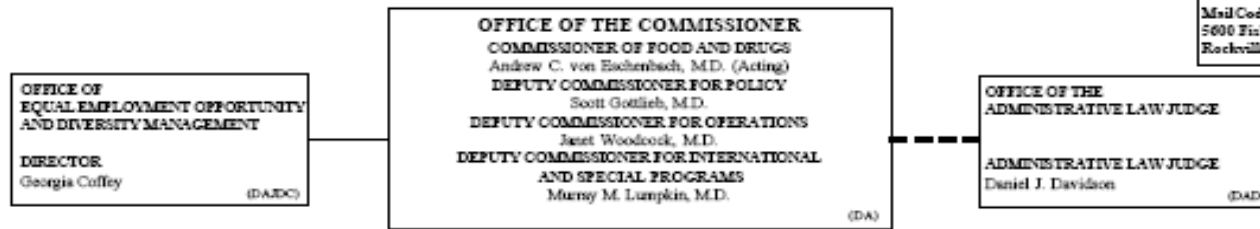
PHS, HHS, FDA

Levels of Review “Checks and Balances”

Organizational Chart of FDA

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION

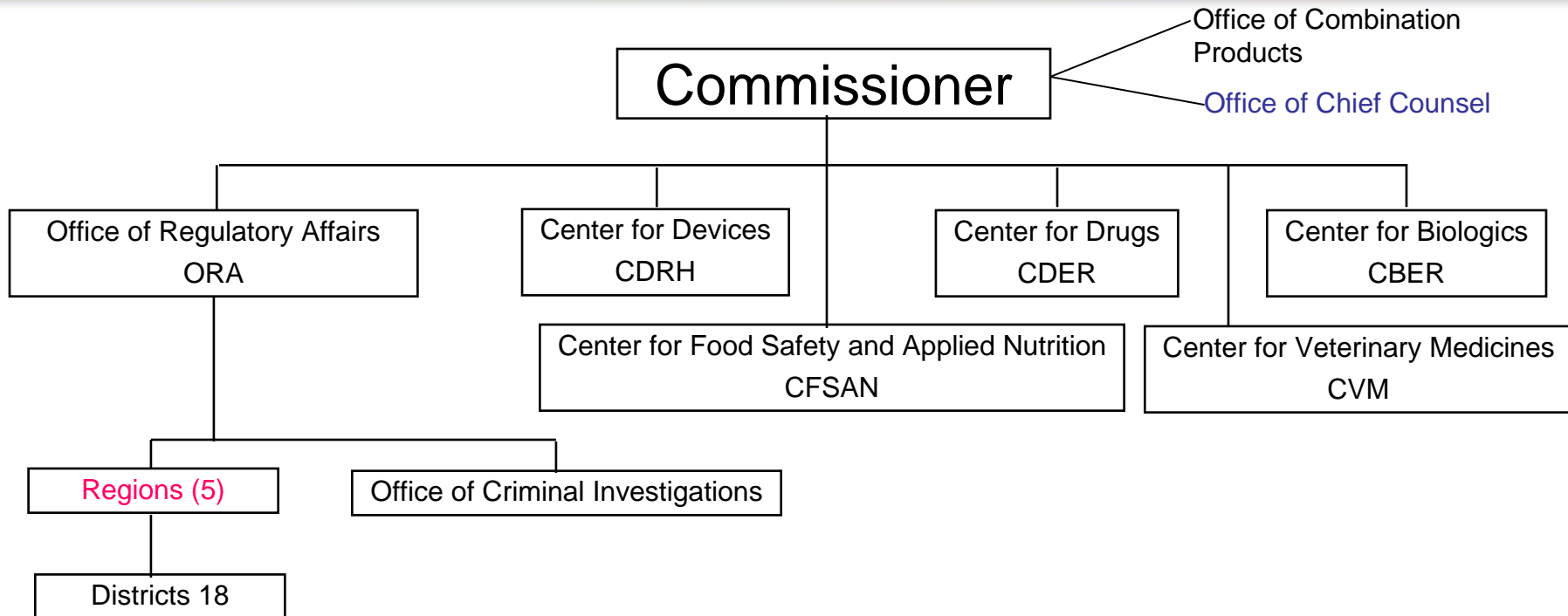
Main Tel: (301) 827-2410
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 5000 Fisher Lane
 Rockville, MD 20857



--- Reports directly to the Secretary, HHS

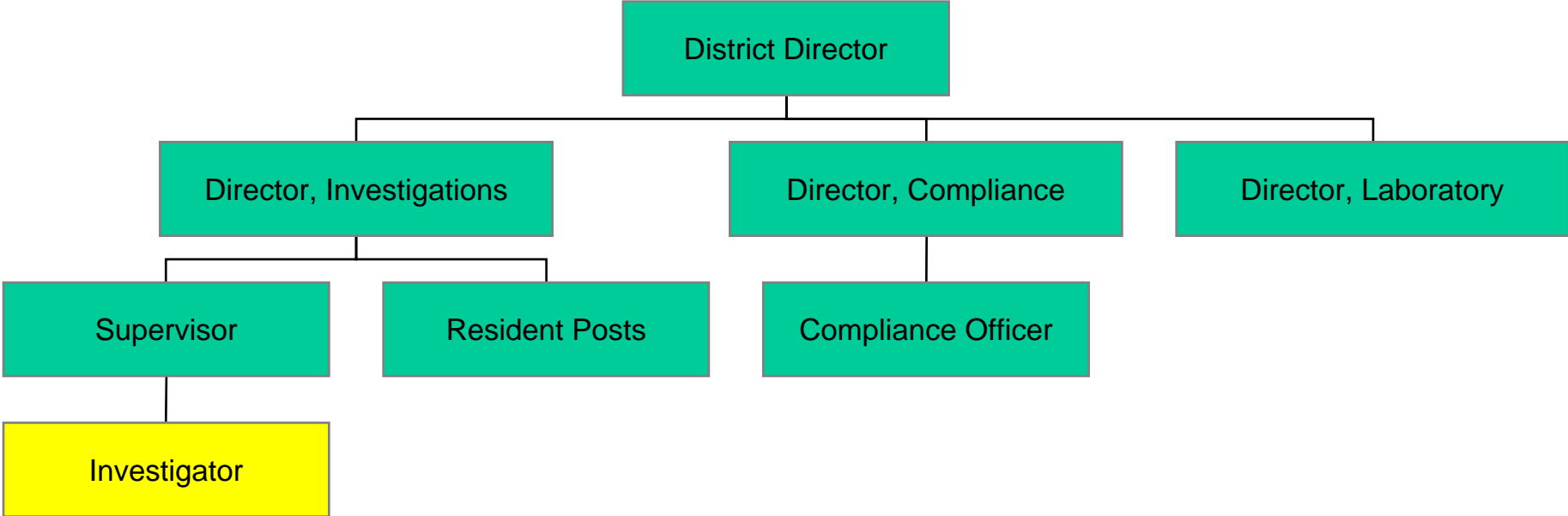
Prepared by the Division of Management Systems, OMF, OM-05-01-06

Organizational Chart of FDA



Each Center has a product approval and a compliance office.

Organizational Chart of FDA District



Team
Inspections

Inspections

- Authority
- Definitions
- Types of Inspections
- Pre-Announced/Unannounced
- Preparation & Planning



FDA's Authority to Inspect FD&C Act 704

- For purposes of enforcement of this Act, officers or employees..., upon presenting appropriate **credentials and a written notice (FDA-482)** to the owner, operator, or agent in charge, are authorized to
- A) To enter at **reasonable times** and inspect within **reasonable limits** and in a **reasonable manner**
- Any factory, warehouse, establishment where product is manufactured, processed, packaged, or held and any vehicle used for transport

Legal Authority 704(B)

- Access to equipment, Finished & Unfinished, Materials Containers and Labeling
- Records, Files, Papers, Processes, Controls & Facilities
- No access to:
 - Financial data (except shipment data & 21 CFR 54)
 - Personnel data (except training records, qualification data, org charts)
 - Pure research (a fuzzy line)
 - *Internal audit reports (under normal circumstances)*

Inspection (IOM 502)

- An inspection is a **careful, critical, official examination** of a facility to determine its compliance with laws...
- Inspections may be used to **obtain evidence to support legal actions** when violations are found

Definitions

- Investigator Operations Manual (IOM)
- FDA Form 482 – Notice of Inspection
- Credentials- 2 part picture ID
- FDA Form 483 – List of Inspectional Observations
- EIR – Establishment Inspection Report
 - Turbo EIR

Reasons for Inspections

- Statutory Requirement (Biennial)
- Inspection Assignment
- Compliance Follow-up
- Pre-Approval
- Complaint
 - Informant, consumer, trade
- Recall

Types of Inspection

- The kind and type of inspection is defined by the program, assignment, or district
- **Comprehensive Inspection** - directs coverage to everything in the firm subject to FDA jurisdiction to determine the firms compliance status
- **Directed Inspection** - directs coverage to specific areas to the depth described in the program, assignment (Recall, CAPA, QSIT)

Depth or Scope of Inspection

- Current Compliance Program
- Nature of Assignment
- Knowledge of Industry (Infusion pumps, Stents)
- Company History (Past violations, Recalls)
- Conditions found During the Inspection

Team Inspections

- **Team Inspections**
- Individuals well versed in an analytical or inspectional technique or technology
- One investigator will be designated as the team leader
- The team leader is in charge of the inspection

Team Biologics

- Core Team of Specially trained Investigators and Compliance Officers conduct the inspections
- Located in the District Offices
- Reporting to Office of Regional Operations (ORO)
- Cooperation with CBER

Foreign Inspections

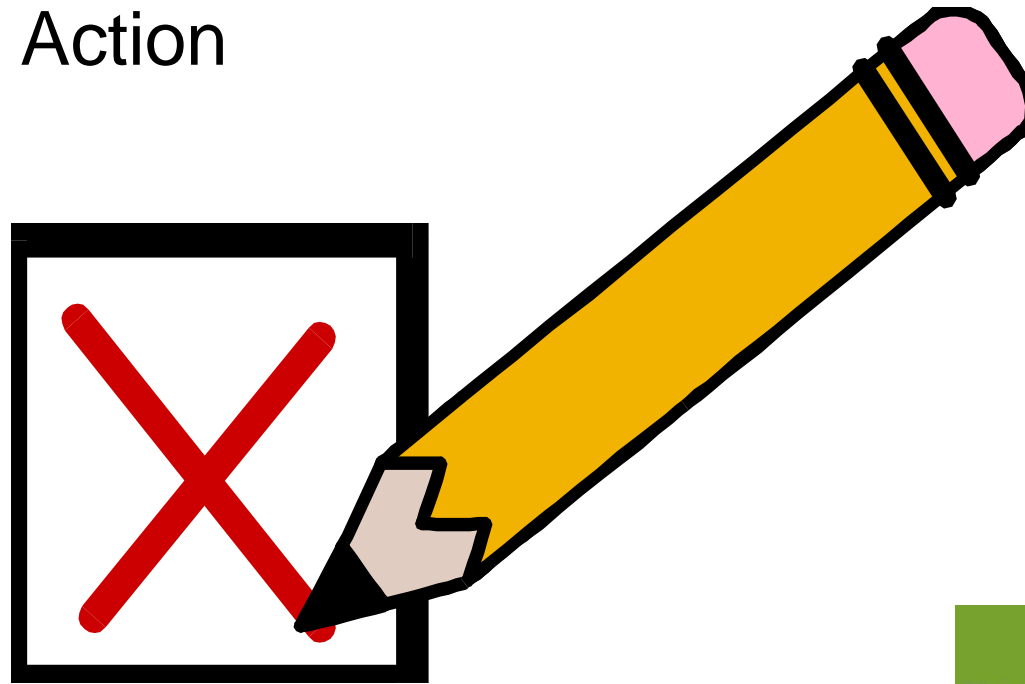
- International Companies must comply with the requirements
- Voluntary Consent for inspection
- Notice of Inspection **Not** required
- Pre-announced several weeks in advance
- Same Inspection Process and Compliance Programs
- Limited time (4-5 days)
- Enforcement options are limited (Detention)

Third Party Inspections

- MDUFMA 2002
- Amends 704
- Allows inspections (Class II & III)
- Company conditions
- Inspection by **accredited persons** (third parties)
- Currently 16 listed

Inspection Classification

- OAI: Official Action Indicated
- VAI: Voluntary Action
- NAI: No Action



Pre-Announced Inspections

- Pre-announced (Medical Device Initiatives 4/3/96)
 - Medical Device mandated with Conditions
 - Drugs & Biologics, others at District Discretion
- Conditions
 - No more than 5 days in advanced
 - Appropriate People & Records available
 - Non- Violative QS/GMP history

Unannounced Inspections

- Compliance Follow-up
- Failure to meet Pre-announced requirements
- Short Deadline Assignments
- Urgent, Hazard -to-Health Situations
- GWQAP
- District Discretion



Systems Approach to Inspections

**An Inspection Approach
Not a type Inspection**

Subsystems/Systems

Medical Devices

(QSIT)7382.845

- Management Controls
- Design Controls
- CAPA
- Production and Process Controls
- Facility & Equipment
- Materials Controls
- Records/Documents/Change Controls

Drugs- CP7356.002

- Quality System
- Facilities and Equipment System
- Materials System
- Production System
- Packaging & Labeling System
- Laboratory Control System

Enforcement Actions

FDA Seven Principles: of Enforcement

- Published in 1990
- Expects compliance and provides information to industry to facilitate its efforts to comply
- Monitors industry compliance and may afford industry the opportunity to correct violations before initiating enforcement action
- Meters its enforcement responses to the severity of the violation
- Does not tolerate fraud, intentional violations, or gross negligence
- Bases its enforcement actions on science.
- Cooperates with local, state, federal, and international public health officials
- Maximizes enforcement resources

Elements of Proof: “JIVR”

- *Jurisdiction* The product is subject to the provisions of the *FD&C Act*. For example, it meets the act’s definition of a drug or medical device
- *Interstate Commerce* the product is in interstate commerce
- *Violation* The product is adulterated, misbranded, or otherwise in violation of the act
- *Responsibility* Enforcement actions directed at individuals or companies must establish responsibility for the violations
 - *FD&C Act* has a unique “**strict liability**” standard that does not require evidence of intent

“Direct Reference” Authority

- Allows some steps in the enforcement process to be skipped
 - Medical Device Warning Letters

Administrative vs. Judicial Actions

- λ **Administrative** enforcement tools are those that FDA may initiate without using the US court system or the assistance of the Department of Justice.
- λ **Judicial** actions involve the US court system of Dept of Justice

Administrative Actions Examples

- **Notice of Violation (NOV)**
 - **Untitled letter**
 - **FDA 483 List of observations**
 - **Meetings**
- **Warning letter**
 - **Corporate Warning Letter**
- **Detention of Medical Devices**
- **License revocation/suspension (biologics)**
- **Debarment (Generic Drugs)**
- **Application Integrity Policy (Fraud Policy)**
- **Disqualification for Clinical Investigators**
- **Withhold approval (pre-market inspections)**
- **Delay, Suspend or Withdraw Product applications**
- **Civil money penalties**
- **Recall (Voluntary/Mandatory)**
- **Import Detention/Alert**
- **Publicity**

Judicial Enforcement Options

- **Seizure**
- **Injunction**
- **Consent Degree**
 - **TRO Temporary Restraining Order**
- **Prosecution**
- **Criminal Sanctions**
- **Civil Money Penalty for Radiation Emitting Products**

Warning Letter

- Titled Letter
- 1990 Dr. Kessler
- Replaced the NAFL & Regulatory Letter
 - Paper Tiger
- Significant “Violations”
- “Promise to Sue”
- Direct Reference Authority
 - Medical Device QS

Warning Letter (cont)

- Warning Letters are Appropriate
- Violations are of Regulatory Significance
- Voluntary Action can be expected
- Policy is clear & unambiguous
- Failure to correct necessitates further enforcement action
- Direct Reference Authority to the Field
- W/L are NOT Appropriate
- A History of Repeat Violations
- Violations are Intentional/Flagrant
- Reasonable Possibility of serious injury or death
- Title 18 (false statements, conspiracy, mail or wire fraud)

Warning Letters (cont'd)

- Immediately available under FOIA
- Communicates the possible imposition of other sanctions (Govt. Contracts, Application delay, Export Certificates)
- Requests a 15 Day response
- May require use of third Party consultant

- There is no legal requirement that FDA issue a Warning Letter before proceeding to court to initiate an enforcement action

Warning Letters (cont'd)

- Spring 2002: All Warning Letters reviewed by FDA's Office of the Chief Counsel and the appropriate FDA Center division before issuance
 - speak with one voice – consistency
 - likely fewer WLs but greater potential for more aggressive follow-up, if problems persist
 - look for words like “recidivist,” “persistent,” or “recurring,” which should tell you FDA is very concerned
- WLs are typically sent to the CEO, President, or other senior official

Judicial Actions: Seizure

- A civil action taken to remove a **product** from commerce because it is in violation of the law
- Complaint filed with the U.S. District Court where the product is located.
- A U.S. marshal is then directed by the court to take possession“ arrest” the goods until the matter is resolved.
- **Mass Seizure** is a massive seizure of raw materials, in process or finished product

Injunction/ Consent Decree

- **Injunction:** A civil action authorized by the FD&C act taken against an **individual or firm** seeking to stop/“restrain” violation of the law. The “preponderance of evidence” standard for civil action is less than that for a criminal action
- **Primary FDA enforcement tool**
 - Chronic violations
 - agency has not had success with other enforcement options

Injunctions & Consent Decrees (cont)

- 4 **Consent Decrees:** negotiated with and agreed to by Company
- 4 **TRO** (Temporary restraining order): Immediate Stop order associated with critical health issue
- 4 The violation of an injunction is punishable as contempt of court

Consent Decrees *(cont'd)*

- The decree may require:
 - Third Party certification (verified by FDA)
 - audit reports to be provided to FDA
 - Disgorge of financial (“ill gotten gain”)
 - Abbott \$100 M
 - Schering Plough \$500M
 - Eli Lilly \$24M
 - payment of fines per day for failing to meet schedules proposed by the consultants and approved by FDA
 - Continue in Perpetuity until one party petitions for

Disgorgement

- Disgorgement, a strategy employed successfully by the Federal Trade Commission
 - **Based on premise that a company is not entitled to profits gained by “illegal” means**
 - **Not intended to take away all profits, but big enough to garner attention and dissuade repeat behavior.**

Criminal Prosecution

- **Prosecution:** A criminal action taken against a company or individual charging violation of the law.
 - Proceeded by Section 305 hearing
 - Appropriate notice and opportunity for hearing
 - Contempt of civil order
 - Title 18 violation
 - Assault on federal employee performing duty
 - Conspiracy to defraud US
 - Mail fraud

Prosecutions (cont)

- Prosecutions take two forms:
- Misdemeanor
 - Violation of one or more *FD&C Act* prohibitions.
 - Does not involve intent or even knowledge.
- Felony
 - involve intentional violations and/or a defendant that has been previously convicted of violating the *FD&C Act*.
- The Department of Justice and the regional US Attorney must approve prosecutions proposed by FDA.
- In such an environment, particularly at the US Attorney level, misdemeanor prosecutions proposed by FDA are not always perceived as high priority among other competing prosecutions of bank robbers, kidnappers, murders, etc. As a result, FDA rarely pursues a misdemeanor action.

Individual Responsibility

- 4 Under the FDC Act, individuals may be held liable on the basis of their holding a “responsible position” within the company to prevent or promptly correct violations of the FDC Act (Dotterweich 1943)
- 4 FDA may prosecute top corporate executives, even if they had no direct involvement in the allegedly unlawful conduct (Park 1975)
 - 4 “Strictly liability” statute for criminal misdemeanors; criminal intent is not required to support a conviction

Criminal Investigations

- 4 Office of Criminal Investigations (OCI)
 - 4 focuses on fraud, false statements, and other serious criminal misconduct, rather than routine GMP/QSR violations
 - 4 comprised of many former FBI, DEA, and U.S. Customs Service officials

Civil Money Penalties

- Seven laws permit FDA to pursue civil monetary penalties six are administrative. Violations of the *Radiation Control for Health and Safety Act* is judicial
- 1995, FDA published final regulations
 - civil *National Childhood Vaccine Injury Act of 1986*
 - Up to \$100,000 per violation
 - *Prescription Drug Marketing Act of 1987*
 - \$50,000 to \$1,000,000 per violation
 - *Safe medical Devices Act (SMDA) of 1990*
 - \$15,000 per violation with a maximum of \$1,000,000 per proceeding
 - *Generic Drug Enforcement Act of 1992*
 - Up to \$250,000 for individuals and \$1,000,000 for companies per violation
 - *Mammography Quality Standards Act of 1992*
 - \$10,000 per violation
 - *Food Quality Protection Act of 1996*
 - \$50,000 to \$250,000 per violation, not to exceed \$500,000 per proceeding

Practice Question

When an FDA inspector arrives at a Company he or she must present :

- Form FDA 482 and credentials
- EIR
- Form FDA 483 and Notice of Inspection
- Form FDA 484

Practice Question

- The following are characteristics of FDA GMP inspections except:
 - A. Results of internal audit findings are required to be provided to the FDA Inspectors upon request
 - B. Biennial inspections of manufacturing facilities take place to verify compliance with regulations.
 - C. The FDA may inspect the drug product sponsor and any manufacturing subcontractors.
 - D. FDA inspections may be conducted due to serious non-compliance with GMP regulations

Practice Question

Which is a type of administrative enforcement tool that FDA may use outside the US court system or the Department of Justice?

- A. Application Integrity Policy
- B. Seizure
- C. Injunction
- D. Disgorgement

References

- Fundamentals of Regulatory Affairs
Chapter 7
- www.fda.gov
- Investigations Operations Manual
- Regulatory Procedures Manual
- Food Drug and Cosmetic Act

Questions ??

Thank You

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