SURVEILLANCE AND ENFORCEMENT

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Objectives

- Identify laws and regulations enforced by FDA for biological products
- Provide an overview of enforcement actions
- Provide an overview of recalls
  - Definitions, recall types, recall classifications
- Provide an overview of fatality reporting

Laws and Regulations Governing Biological Products

- Food, Drug, and Cosmetic Act (FD&C Act)
- Public Health Service Act
  - Sections 351 and 361
- Title 21, Code of Federal Regulations
  - Drugs – Parts 210 and 211
  - Blood, Blood Components, and Blood Derivatives – Parts 606-660
  - Devices – Part 820
  - Human Tissues Intended for Transplantation – Parts 1270 and 1271

Overview of Enforcement Actions

- Regulatory tools used by FDA to bring establishments, who violate the laws that FDA administers, into compliance
  - License Suspension
  - License Revocation
  - Warning Letter
  - Seizure
  - Injunction
  - Prosecution

License Suspension

- Title 21 Code of Federal Regulations Part 601.6 (21 CFR 601.6)
  - Suspension provides for immediate withdrawal of the authorization to introduce or deliver for introduction, biological products into interstate commerce
    - Reasonable grounds for revocation
    - Danger to health

License Suspension

- Outcomes
  - Reinstatement
    - Establishment demonstrated correction and compliance
  - Revocation
  - Interdiction of personnel
  - Criminal prosecution

License Revocation

- Cancellation of a license and the withdrawal of the authorization to introduce or deliver for introduction, biological products into interstate commerce
  - Requested by the manufacturer, or
  - Grounds exist for the Agency to initiate action

License Revocation

- 21 CFR 601.5
  - FDA is unable to gain access
  - Licensed product manufacturing is discontinued
  - Management fails to report a significant change in the manufacturing process
  - Good Manufacturing Practices (GMP) deficiencies
  - New method of manufacturing
  - Product is not safe and effective for its intended use

License Revocation

- Notice of Intent to Revoke
  - Inspectional findings show recurring significant issues that represent a breakdown of process controls or operations
  - Opportunity to demonstrate or achieve compliance
- Direct Revocation
  - Evidence of willful conduct
    - knowingly committed a prohibited act, or
    - acted with careless disregard of the regulations
  - No opportunity to demonstrate or achieve compliance

Warning Letters

- Written communication notifying a firm that a product, practices, operations, or other activities are in violation of the law
  - Offers firms an opportunity to achieve voluntary compliance
  - Corrections must be made promptly
  - Serves as prior notice should the agency decide to pursue additional action against firms who continue to operate in violation of the law

Seizure

- Removal of a violative product or article from the market by taking it into possession or placing it into constructive custody of the court
  - Action of choice when FDA wants to remove violative product (licensed and/or unlicensed) from distribution channels

Injunction

- A civil process initiated to stop or prevent a violation of the law and to correct the conditions that caused the violation to occur

Prosecution

- U.S.C. 18
- U.S.C. 21 (FD&C Act)
- U.S.C. 42 (PHS Act)

Recalls - Definitions

- Recall – a firm's removal or correction of a distributed product that FDA considers to be in violation of laws that it administers, and against which FDA would take legal action.
- Market Withdrawal – a firm's removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by FDA.
- Correction – repair, modification, etc. of a product without its physical removal to another location.

Recalls – Definitions (cont)

- Recalling Firm – the firm who initiates a recall or who has primary responsibility for the manufacturing and marketing of the product to be recalled
- Recalls are a means of:
  - Protecting the public health and well-being
  - Retrieving products that present a risk of injury or gross deception or are otherwise defective

Recall Types

- Firm initiated (voluntary)
  - Most common
  - Initiated by a firm independently and under any circumstances to remove or correct a distributed product
  - Initiated by a firm when informed by FDA that the product in question violates the law, but the agency has not specifically requested a recall

Types of Recall Actions

- FDA Requested
  - The Commissioner or his designee may request a firm to initiate a recall when the following exists:
    - Urgent situation
    - Risk of illness or injury or gross consumer deception
    - Firm has not initiated a recall
    - Necessary to protect public health and welfare

Types of Recall Actions

- FDA Ordered
  - Initiated by a firm in response to an order for such an action
    - Mandatory Recall of Human Tissue Intended for Transplantation – PHS Act, Section 361
    - Licensed Biological Products – PHS Act, Section 351
    - Mandatory Device Recalls – Safe Medical Devices Act, Section 518
    - Human Tissue Intended for Transplantation – PHS Act, Section 361

Recall Classifications

- Three types of recall classifications
  - Class I
  - Class II
  - Class III

Recall Classifications

- Class I – a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death

Recall Classifications

- Class II – a situation in which use of, or exposure to a violative product may cause temporary or medically reversible adverse consequences, or where the probability of serious adverse health consequences is remote.

Recall Classifications

- Class III – a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences

Non-Blood Biologic Recalls

- Reagents
  - Loss of potency
  - Contamination
- Blood collection bags
- Blood Bank computer software
- Viral Marker Test Kits

FYI

- All non-blood, biological product recalls are posted on CBER's website at www.fda.gov/cber
- All product recalls are posted weekly in FDA's enforcement report, www.fda.gov

Fatalities associated with blood collection or transfusion

Where is the fatality reporting requirement?

- Title 21 Code of Federal Regulations, Subchapter F - Biologics
  - Part 606 – CGMP for Blood and Blood Components
    - 606.170 – Adverse Reaction File
  - Part 640 – Additional Standards for Blood & Blood Products
    - 640.73 – Reporting of Fatal Donor Reactions

Adverse Reactions

21 CFR 606.170(a)

- Records shall be maintained of any reports of complaints or adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion.
  - Written report of an investigation
    - with conclusions & follow-up
  - When product at fault, forward reports to manufacturer/collection facility

Adverse Reactions

21 CFR 606.170(b)

- ASAP notification of CBER when a complication of blood collection or transfusion is confirmed to be fatal
  - Written report of investigation submitted within 7 days
    - From collecting facility for donor reaction
    - From facility that performed compatibility test for transfusion reaction
- Every facility (registered or not) is required to report

Adverse Reactions – Source Plasma

- 21 CFR 640.73 in Subpart G – Source Plasma
  - Must report if a donor has a fatal reaction which, in any way, may be associated with plasmapheresis

How do I report a fatality?

- See http://www.fda.gov/cber/transfusion.htm
  - Phone: 301-827-6220
  - Email: fatalities2@fda.hhs.gov
  - Fax: 301-827-6748

- Send 7-day written report to:
  - Center for Biologics Evaluation and Research (CBER)
    Office of Compliance and Biologics Quality
    Attn: Fatality Program Manager (HFM-650)
    1401 Rockville Pike
    Rockville, MD 20852-1448

Emergencies

If the situation is an emergency
that requires immediate action,
such as a case of food-borne illness
or a drug product that has been tampered with,
call the agency's main emergency number,
staffed 24 hours a day,

301-443-1240.

After we report, then what does FDA do?

It depends…

- If no larger safety risk & you provide sufficient information, FDA will review, track, and trend…
- ORA field investigator may follow up – immediately or on your next inspection
  - Response is proportionate to the risk