

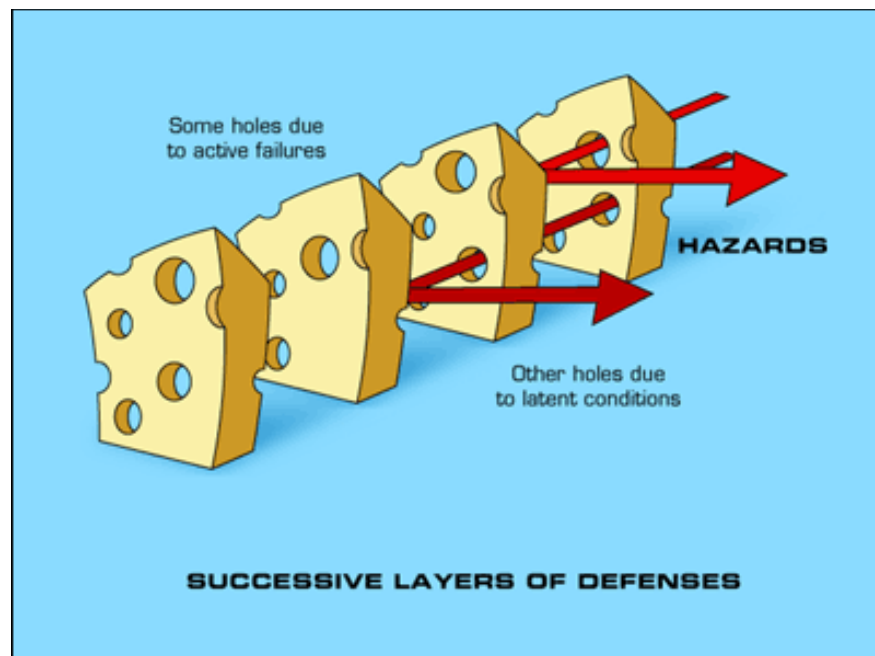


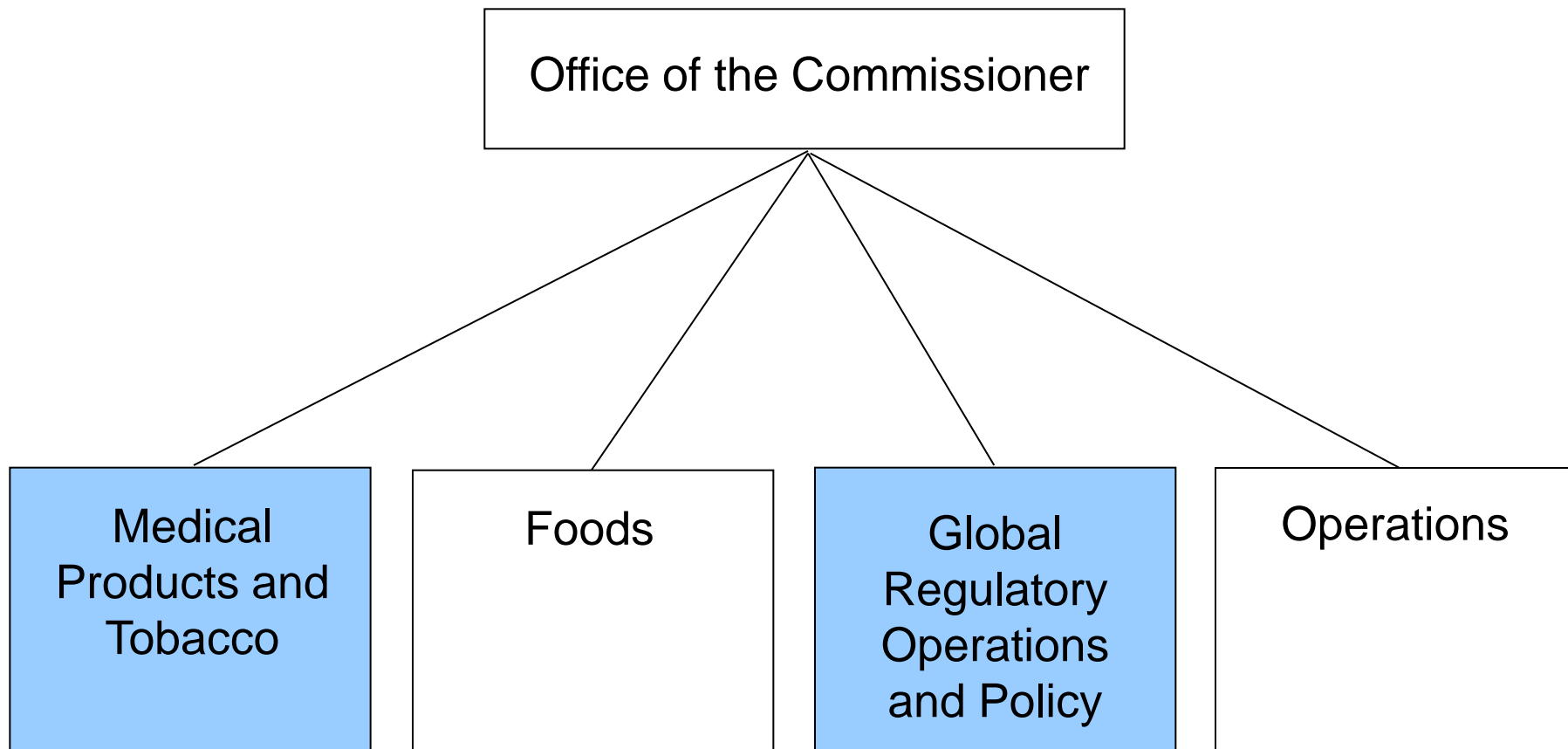
# **Beyond Pharmacovigilance: Overview of Biologics Inspections and Compliance**

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**Director, Division of Epidemiology**  
**Center for Biologics Evaluation and Research**

Application of Pharmacovigilance to  
U.S. FDA Regulatory Decisions for Vaccines  
June 3, 2012

# CBER pharmacovigilance is part of a layered defense system for biologics





Staff from both highlighted directorates are involved in vaccine inspections and compliance activities

# FDA Office of Regulatory Affairs



- Lead office for all FDA Field activities
  - Imports
  - Inspections
  - Enforcement
- Over 150 resident posts and border stations
- Liaison with state, local, tribal and territorial public health authorities

Director, Center for Biologics Evaluation and Research

Office of Vaccines Research and Review

Office of Cellular, Tissue, and Gene Therapies

Office of Blood Research and Review

Office of Biostatistics and Epidemiology

Office of Communication Outreach and Development

Office of Compliance and Biologics Quality

Office of Management

The highlighted offices execute CBER's inspections and compliance activities

# Inspections for vaccines

- Prelicense
  - New products or BLA supplements
- Preapproval
  - Prior approval supplements for biologics (e.g. new manufacturing facility or significant process changes)
- Biennial Good Manufacturing Practices
  - Production processes
  - Review of complaints, Biologic Product Deviation Reports, recalls, adverse event reporting, changes since last inspection
- Other
  - Bioresearch monitoring
  - Directed for cause

# Bioresearch Monitoring

- Assesses compliance with FDA regulations governing the conduct of clinical trials including those for informed consent and ethical review
- Evaluates the accuracy and reliability of clinical trial data submitted to CBER in support of research or marketing applications
- Clinical investigators, sponsors, contract research organizations, institutional review boards, and laboratories are subject to inspection
  - Pre-approval audit inspections
  - Surveillance inspections for ongoing studies
  - Investigation of complaints
  - Quality systems inspections for Institutional Review Boards and Labs (Good Laboratory Practices)



# FDA-483

- Establishment Inspection Report
  - Narrative description of findings
  - Response from industry is reviewed
  - Complete evidentiary review is undertaken by ORA and CBER to determine if action is indicated
  - Examples available at:  
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/default.htm>

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION			
DISTRICT OFFICE ADDRESS AND PHONE NUMBER		DATE(S) OF INSPECTION	
		FEI NUMBER	
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED			
FIRM NAME		STREET ADDRESS	
CITY, STATE AND ZIP CODE		TYPE OF ESTABLISHMENT INSPECTED	
<small>THIS DOCUMENT LETS 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.</small>			
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SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED



# Regulatory actions

- Regulatory meetings
- Advisory Actions
  - Untitled letters
  - Warning letters
    - Require a response from industry within a specific timeframe
    - Posted on FDA website
    - Not required, but usually serves as FDA's last attempt to seek compliance without resorting to enforcement action
- Enforcement Actions
  - Administrative: license suspension or revocation
  - Legal: seizure, injunction, consent decree, prosecution

# Bioresearch Monitoring: potential consequences if action is indicated

- For the study:
  - Clinical hold
  - Data might be rejected
  - Another study might be required
- For the investigator:
  - Advisory actions such as warning letters
  - Investigator disqualification
  - Potential criminal conduct may be referred to the Office of Criminal Investigations

# Seizure

- “Warrant for arrest of property” from a U.S. Federal court
- FDA establishes probable cause for a violation of federal law (e.g., the Food, Drug, and Cosmetic Act)
- Product seized by U.S. Marshals with FDA investigators – usually with no notice
- Product cannot be released without a court order

# Injunction

- Commands a company to do something or to stop doing something
- Filed by the U.S. Department of Justice
- Grants FDA the right to inspect facilities, shut down operations, and dispose of goods at the firm's expense
- Company receives advance notice
- Violation of terms can result in civil or criminal contempt

# Consent decree

- Approved by court and agreeable to FDA and the other party
- May be permanent or limited
- May be precise or broad
- May allow continued production and distribution if certain conditions are met

# Recalls

- Voluntary action by firm in lieu of FDA initiated enforcement action (addressed under 21 CFR Part 7 Subpart C)
- Mandatory recall authority for vaccines (and certain other biologics) under the Public Health Service Act



# Lot Release



- Products licensed under the Public Health Service Act are subject to lot release
- Goals:
  - Prevent substandard lots from reaching the public
  - Real time monitoring of manufacturer's quality control testing
  - Assessment of the impact of manufacturing supplements
- Process:
  - CBER reviews information (protocols) for lots that will be distributed commercially
  - CBER receives samples and may perform testing in addition to protocol review

# Summary

- Pharmacovigilance is the last defense in a layered system designed to ensure biologic product quality
- Inspections for vaccine products are carried out by field staff from the Office of Regulatory Affairs and Division of Manufacturing and Product Quality staff from the Center for Biologics
- FDA may take advisory or enforcement actions to ensure compliance
- FDA works to ensure research subject protection and data integrity through Bioresearch Monitoring inspections
- CBER reviews vaccine lots before granting manufacturers permission to distribute them



# Acknowledgements

- This presentation was adapted from content originally drafted by the members of the FDA CBER Office of Compliance and Biologics Quality

# Appendix

U.S. Department of Health & Human Services

U.S. Food and Drug Administration  
Protecting and Promoting Your Health

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## Inspections, Compliance, Enforcement, and Criminal Investigations

Home | Inspections, Compliance, Enforcement, and Criminal Investigations | Inspections | Investigations Operations Manual

### Inspections

- Investigations Operations Manual
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- Vision/Mission/Values
- Table of Contents
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- ORA Directory
- Sample Schedules

### Investigations Operations Manual

Search Investigations Operations Manual

SEARCH

The IOM is the primary guidance document on FDA inspection policy and procedures for field investigators and inspectors.

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