Beyond Pharmacovigilance: Overview of Biologics Inspections and Compliance

David Martin, M.D., M.P.H.
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

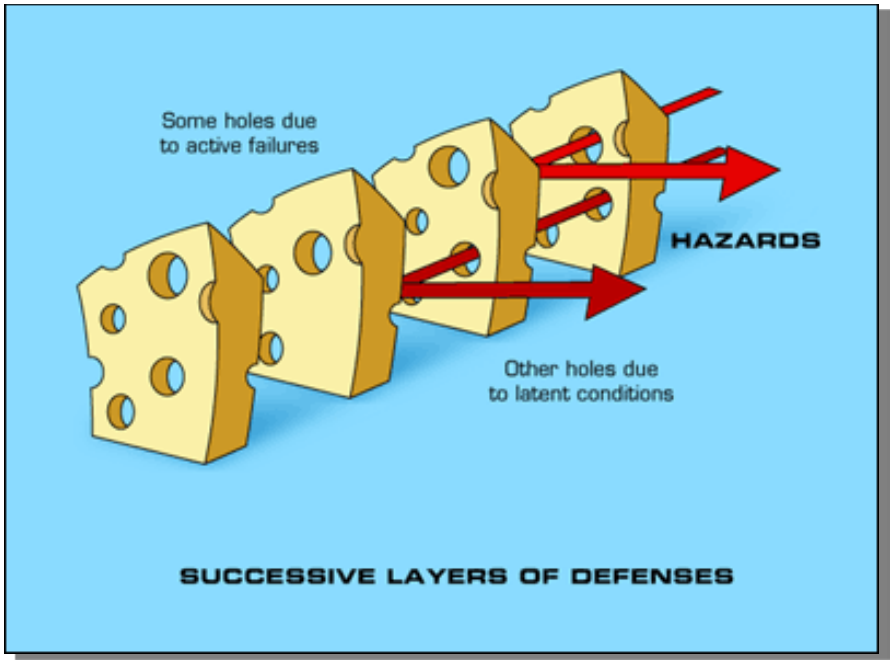
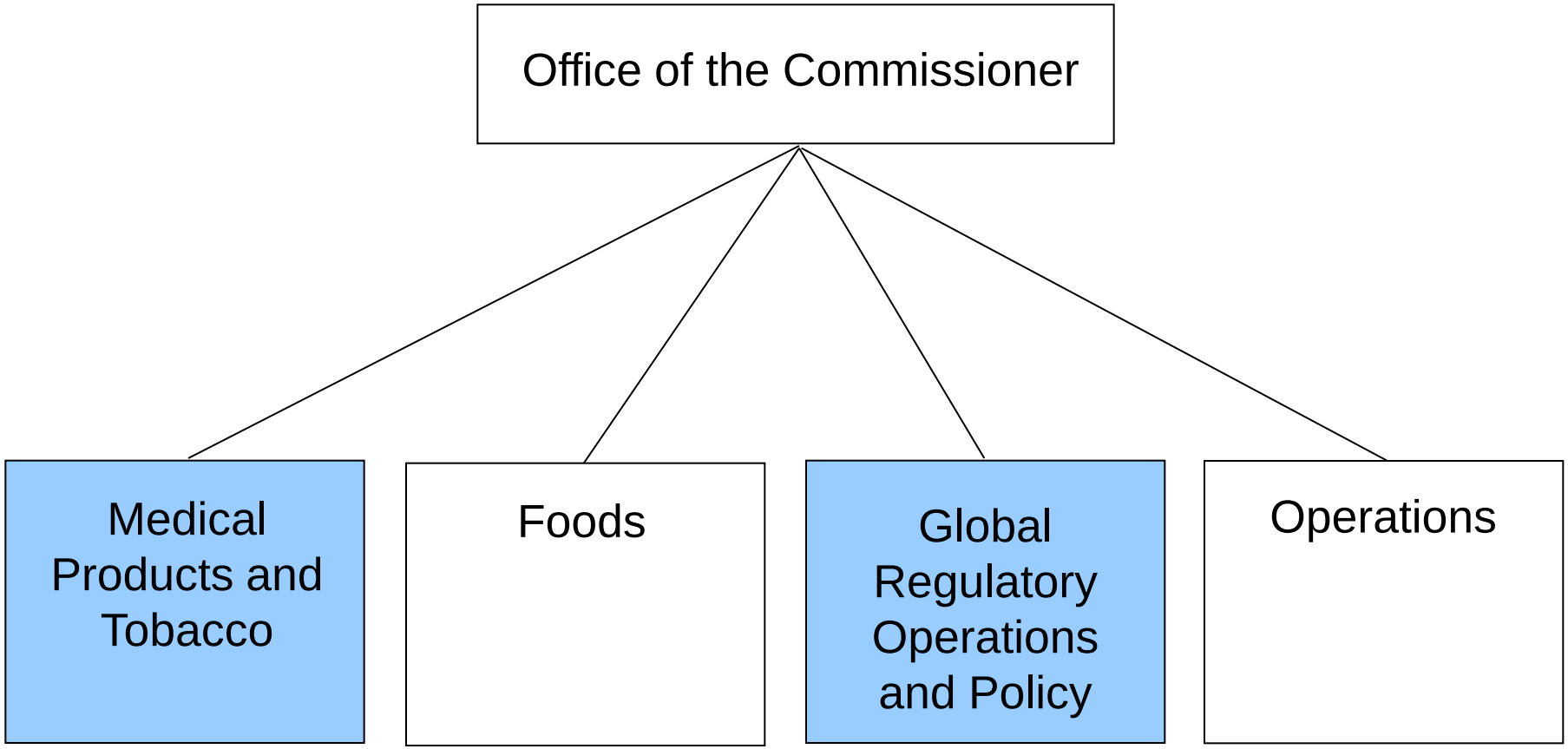


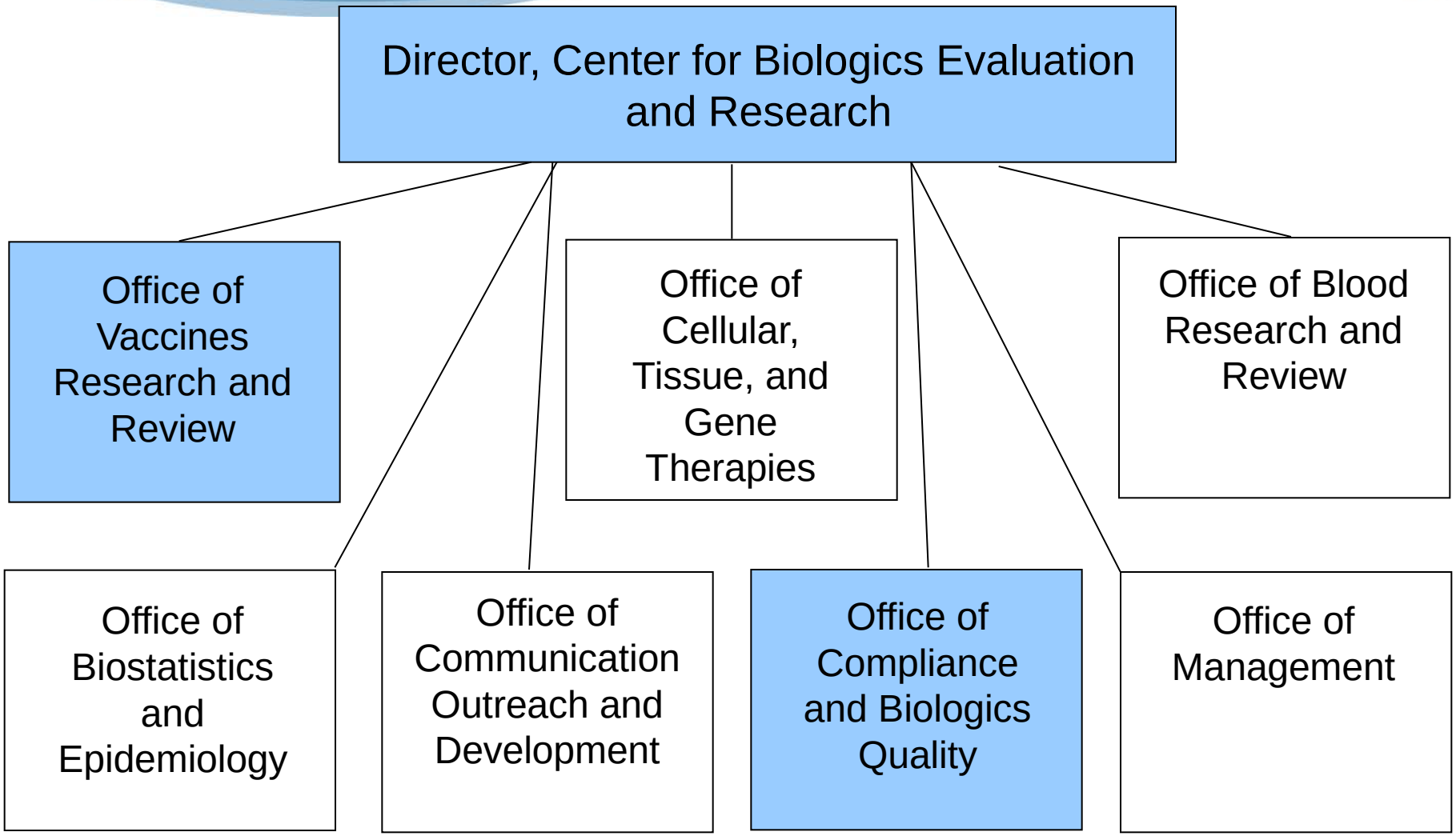
Figure source: Reason J, Human Error: Models and Management. *BMJ* 2000;320:768–70



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



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

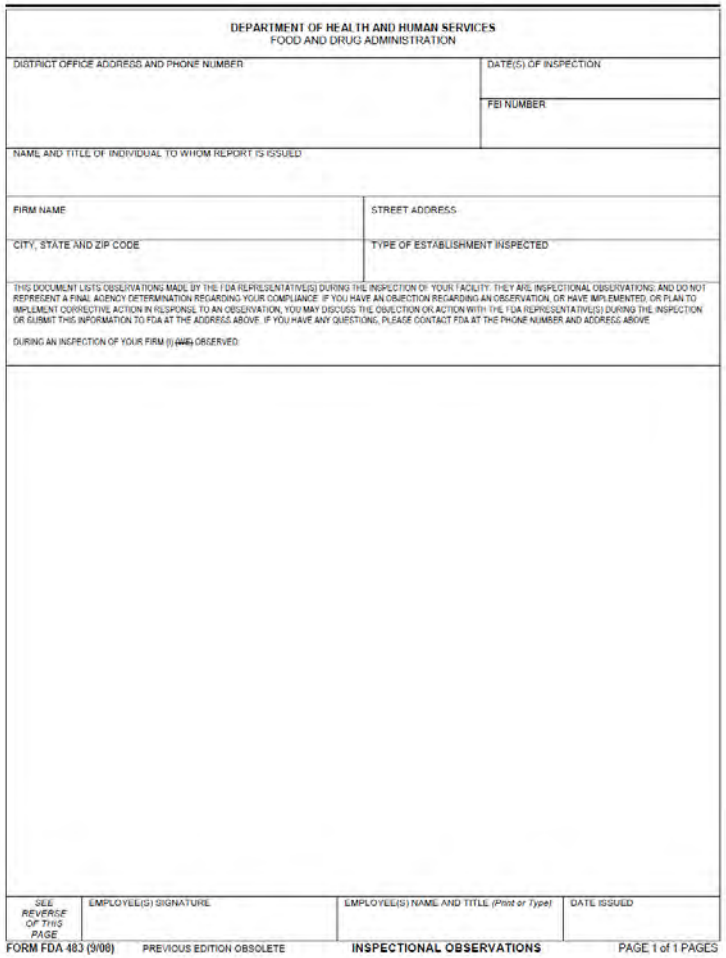
Bioresearch Monitoring

- 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



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

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.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

SEE REVERSE OF THIS PAGE | EMPLOYEE(S) SIGNATURE | EMPLOYEE(S) NAME AND TITLE (Print or Type) | DATE ISSUED

FORM FDA 483 (9/08) PREVIOUS EDITION OBSOLETE INSPECTIONAL OBSERVATIONS PAGE 1 of 1 PAGES

- 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

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

Most testing consolidated under the Division of Biological Standards and Quality Control - CBER has met ISO 17025 standards

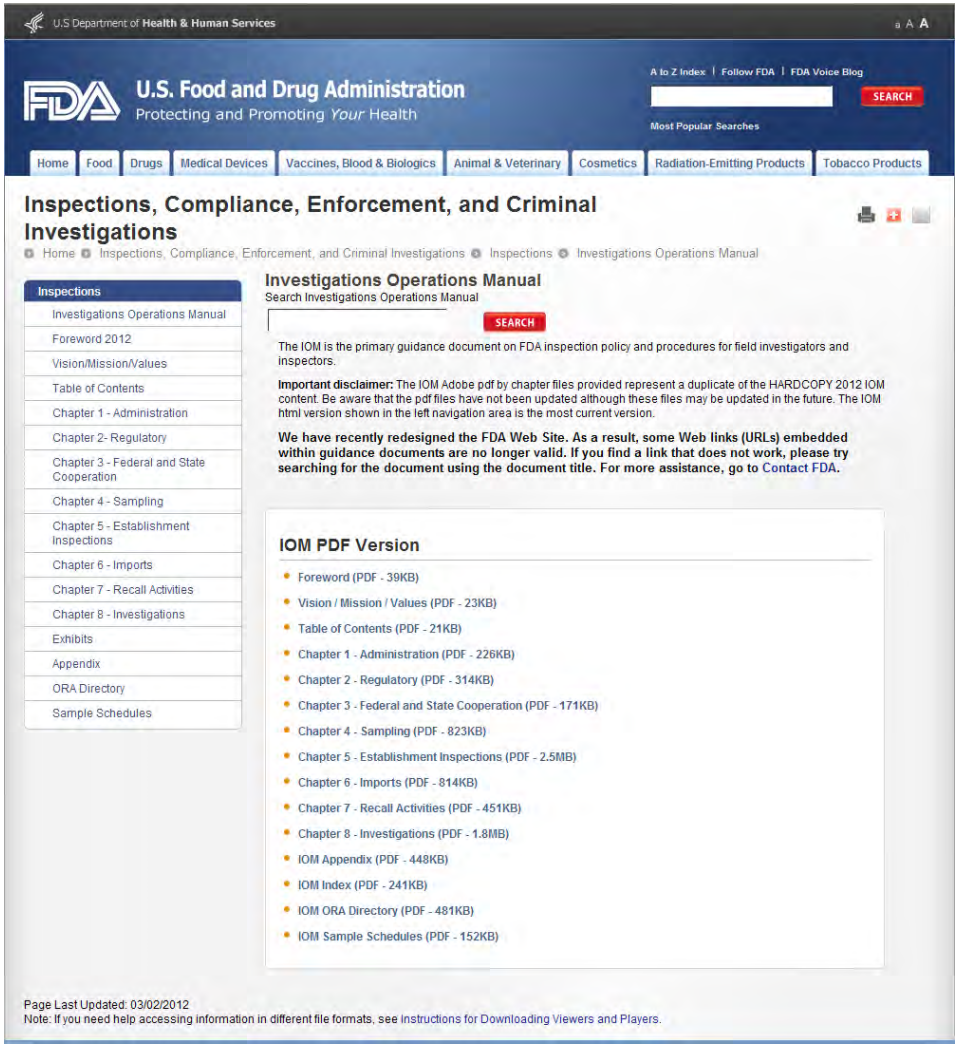
Summary

- 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



The **FDA Investigations Operations Manual** is available at:

http://www.fda.gov/ICECI/Inspections/IOM/default.htm