Beyond Pharmacovigilance: Overview of Biologics Inspections and Compliance

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Application of Pharmacovigilance to U.S. FDA Regulatory Decisions for Vaccines
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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

- 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

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Appendix

The FDA Investigations Operations Manual is available at:

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