Third Annual Medical Research Summit

Preconference II – Workshop on FDA Enforcement, Fraud and Abuse, and Other Compliance Issues in the R&D Process

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Agenda for Preconference II

- Introductions
- Backgrounder on Key Statutes & Regulations
- Backgrounder on the OIG
- FDA Bioresearch Monitoring Program
- Break
- FDA Enforcement
- PhRMA Industry Standards
- Risk Assessments in R&D
- Questions & Answers

Backgrounder on Key Statutes & Regulations

Backgrounder on Key Statutes and Regulations

- Federal Food, Drug, and Cosmetic Act
- Anti-Kickback Statute
- False Claims Act
- Privacy/HIPAA
- State Laws
- Other Statutes

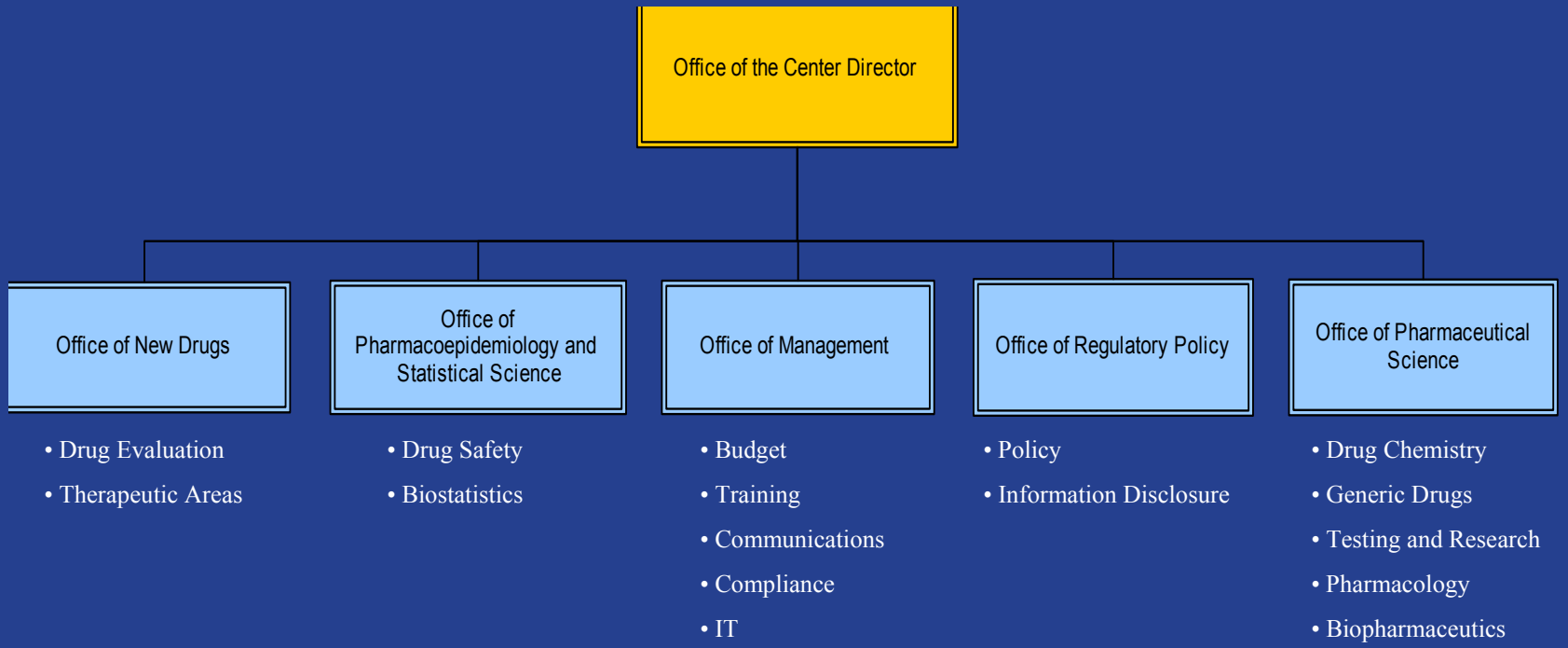
Federal Food, Drug, and Cosmetic Act

FFDCA:

- Adulteration
- Misbranding
- New Drug Approvals
- Investigational New Drug Exemptions
- Premarket Clearance for Safety and Effectiveness
- Labeling Claims
- Interstate Commerce

Food and Drug Administration

Center for Drug Evaluation and Research (CDER)



Federal Regulations Impacting R&D

21 CFR Part:

- 50 – Protection of Human Subjects
  - Informed Consent
  - Safeguards for Children in Clinical Investigations
- 54 – Financial Disclosures
- 56 – Institutional Review Boards
- 58 – Good Laboratory Practices
- 210, 211and 820 – Good Manufacturing Practices
- 312 – Investigational New Drug Applications
- 812 – Investigational Device Exemptions
- 814 – Premarket Approval of Medical Devices
- 310, 312 and 812 – Safety Reports

Anti-Kickback Statute

Prohibition

1. - offer or payment of remuneration(e.g., research funds), or

   - solicitation or receipt of remuneration in exchange for….

2. - purchase of goods or services,or
   - referral of beneficiaries

3. - where the goods/services are reimbursed by the federal health care programs

Exceptions and Safe Harbors

- consulting arrangements

False Claims Act

FCA:

- Prohibition against "knowing" submission of false or fraudulent claims to the federal government
- *Qui tam* actions
- Vehicle for attacking financial improprieties in the government reimbursement process

Privacy/HIPAA

- Growing number of privacy laws limit the collection, use, and disclosure of personal health information for research purposes
- Failure to address these requirements can result in significant disruptions in the R&D process -- delaying the discovery of promising new medicines
- HIPAA: Imposes strict limits on the collection, use, and disclosure of personal health information -- including in the research context
- General rule for research: "Covered entities" (e.g., clinical investigators, trial sites) may not disclose patient health information unless (1) patient provides written authorization, or (2) covered entity obtains waiver, which is available only in limited contexts

Privacy/HIPAA

- Most pharmaceutical manufacturers have clinical trials underway in Europe
- The EU Data Protection Directive prohibits transfers of personal information to other countries without adequate privacy protections
- Companies that fail to comply run the risk of potentially serious disruptions in data transfers to the US (e.g., disruption in clinical trial information that could be critical to gaining regulatory approval)
- EU has threatened increased scrutiny, particularly for sensitive (e.g., health) data.

Privacy/HIPAA

Discussion Points

- Authorizations or waivers
- Auditing Process
- Liability for Sponsor?

State Laws

- Numerous states have anti-kickback laws
  - Scopes/clarity vary substantially
- Minnesota and Vermont
  - Pharmaceutical manufacturer reporting requirements

Backgrounder on OIG

Backgrounder on the OIG

- Agency – Office of Inspector General (OIG), Health and Human Services
- Mission – To improve HHS programs and operations and protect them against fraud, waste, and abuse. By conducting independent and objective audits, evaluations, and investigations, we provide timely, useful, and reliable information and advice to department officials, the administration, the Congress, and the public.
- http://oig.hhs.gov

Backgrounder on the OIG

OIG Work Plan for 2003

- Human Subject Protections for Children
  - Evaluation of the role of IRBs in overseeing clinical research in children
- FDA's NDA Process
  - Examination of the FDA process for reviewing NDAs under PDUFA
- Commitment of Principal Investigators' Effort in Grant Applications
  - Determine whether major research universities committed more than 100% of principal investigators' effort in applications for NIH training grants

Backgrounder on the OIG

OIG Work Plan for 2003 (Continued)

- Management and Oversight of Research Grants
  - Assessment of the NIH's postaward financial and programmatic review of research grants at university, hospital, and other research facilities
- Funding of General Clinical Research Centers
  - Assessment of NIH procedures for awarding funds to general research centers that provide a research infrastructure for clinical investigators receiving primary support from NIH and other federal agencies

Backgrounder on the OIG

OIG Work Plan for 2003 (Continued)

- Monitoring Adverse Events in Clinical Research
  - Assessment of the adequacy of NIH practices to ensure that grantees comply with federal regulations on reporting and monitoring adverse events in clinical trials

Backgrounder on the OIG

Office of Counsel to the Inspector General Work Plan for 2003

- Advisory Opinions – responses for formal opinions on the application of the anti-kickback statute and other fraud and abuse statutes
- Fraud Alerts – inform the health care industry about practices that are suspect
- Anti-Kickback Safe Harbors
- Compliance Program Guidance to the Health Care Industry

Backgrounder on the OIG

Goals of the Compliance Program Guidance Initiative at OIG

- Effort to engage the health care community in preventing and reducing fraud and abuse in federal health care programs
- Assist health care industry in establishing voluntary corporate compliance programs
- Enhance health care provider operations
- Improve the quality of health care services
- Reduce the cost of health care
- Encourage use of internal controls to efficiently monitor adherence to statutes, regulations and program requirements

Backgrounder on the OIG

Compliance Program Guidance Issued by the OIG

- Hospitals, nursing facilities, home health, and hospice programs
- Clinical laboratories
- Durable medical equipment suppliers
- Medicare+Choice organizations
- Individual and small group physician practices
- Ambulance suppliers
- Pharmaceutical manufacturers (draft published October 3, 2002)

Backgrounder on the OIG

Draft Compliance Program Guidance for Pharmaceutical Manufacturers

- Seven elements of an effective compliance program
- Three specific risk areas
- Integrity of data used to establish government reimbursement
  - Liability under the False Claims Act and Anti-Kickback statute
- Kickbacks and other illegal remuneration
  - CME, grants, consulting fees, other remuneration
- Drug samples

Backgrounder on the OIG

Special Advisory Bulletin – Offering Gifts and other Inducements to Medicare and Medicaid Beneficiaries

- Published in August 2002
- Prohibits offers or transfers of any remuneration that the person knows or should know is likely to influence the beneficiary's selection of a particular provider, practitioner, or supplier of Medicare or Medicaid payable items or services
- Gifts or free services should not exceed $10 per item and $50 annual limits
- Implications for clinical research

FDA Bioresearch Monitoring Program

FDA Bioresearch Monitoring (BIMO) Program

- Comprehensive program of on-site inspections and data audits to monitor the conduct and reporting of FDA regulated research
- To assure the quality and integrity of data submitted to the agency in support of new product approvals
- To provide for protection of the rights and welfare of human subjects involved in FDA regulated research
- Scope includes new medicines, medical devices, color additives, and veterinary products
- Domestic and international research

FDA Bioresearch Monitoring (BIMO) Program

- GLPs for non-clinical testing laboratories
  - Compliance Program 7348.808
- GCPs for clinical investigations
  - Compliance Program 7348.811
- Sponsors, contractors, and monitors of clinical investigations
  - Compliance Program 7348.810
- Institutional Review Boards (IRBs)
  - Compliance Program 7348.809
- http://www.fda.gov

FDA Bioresearch Monitoring (BIMO) Program

Compliance Program 7348.810 - Sponsors, Contractors, and Monitors of Clinical Investigations

- Responsibilities of sponsors:
  - Obtain agency approval for clinical studies
  - Manufacture and label investigational drug
  - Initiate, withhold, discontinue clinical trials
  - Select qualified investigators and monitors
  - Evaluate and report adverse experiences
  - Maintain records
  - Submit progress reports and the final results of studies

FDA Bioresearch Monitoring (BIMO) Program

Compliance Program 7348.810 - Sponsors, Contractors, and Monitors of Clinical Investigations

- Sponsors may transfer responsibilities to a Contract Research Organization (CRO):
  - Written agreement specifying transferred responsibilities
  - CROs are subject to same regulatory actions as sponsor

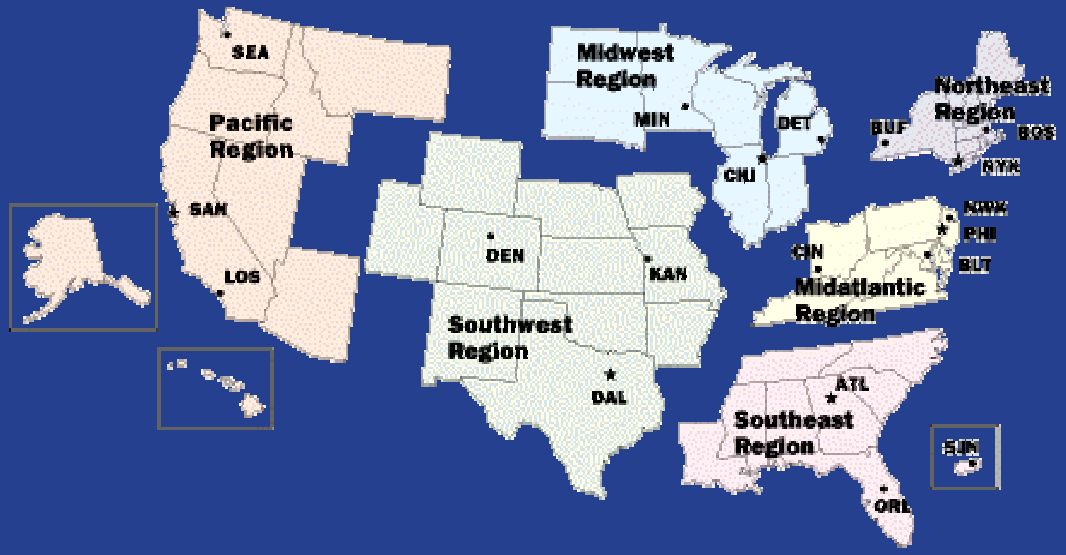
FDA Bioresearch Monitoring (BIMO) Program

FDA Inspection Process

FDA Enforcement

FDA Enforcement

FDA Regional Operations



FDA Bioresearch Monitoring (BIMO) Program

Compliance Program 7348.810 - Sponsors, Contractors, and Monitors of Clinical Investigations

- Establishment Inspections:
  - Organization and Personnel
    - Organization charts
    - Outside services and contractors
    - List of monitors for studies being inspected
  - Selection, Monitoring and Documentation of Clinical Investigators
  - Monitoring Procedures and Activities
    - Process, procedures, frequency, scope of activities
    - Review of records

FDA Bioresearch Monitoring (BIMO) Program

Compliance Program 7348.810 - Sponsors, Contractors, and Monitors of Clinical Investigations

- Establishment Inspections (continued):
  - Quality Assurance Unit (not required by regulation)
  - Adverse experience/effects reporting
  - Data collection and handling (21 CFR Part 11)
  - Test material and packaging/labeling (samples)

FDA Bioresearch Monitoring (BIMO) Program

Compliance Program 7348.810 - Sponsors, Contractors, and Monitors of Clinical Investigations

- Establishment Inspections Reports:
  - NAI – No objectionable conditions or practices were found during an inspection or the objectionable conditions found do not justify further regulatory action
  - VAI – Objectionable conditions or practices were found, but the agency is not prepared to take or recommend any administrative or regulatory action
  - OAI – Regulatory and/or administrative actions will be recommended

FDA Enforcement

Examples of FDA Enforcement Activity

- FD-483
- Warning and untitled letters
- Reinspection
- Termination of exemption
- Withdrawal of approvals
- Seizure of test articles
- Injunction
- Prosecution under FFDCA and other federal statutes

FDA Enforcement

Examples of Warning Letters

- Study kick-off without IRB approval and informed consent from patients
- Protocol and investigational plan violations
- Expired drugs and shipping errors (wrong drug/wrong investigator)
- Lack of drug accountability and failure to maintain adequate records
- Failure to complete adverse experience forms and reports to IRB
- Failure to adequately supervise a study

FDA Enforcement

Other Areas of Enforcement Related to R&D

- Data Integrity – Obligations of Sponsors
- Investigator Fraud
- Financial Disclosures and Conflicts of Interest
- Disqualification of Clinical Investigators

Data Integrity – Obligations of Sponsors

General:

- Ensuring that information submitted in support of regulatory approvals is complete and accurate.

Specific:

- Monitoring investigators' compliance with protocol/regulations
- Assuring that all source records exist and that CRFs accurately reflect underlying records
- Assuring transcription of data for analysis is accurate
- Reporting data to FDA with proper quality control and traceability
- Maintaining data security

Data Integrity – Scrutiny

- Both FDA and OIG/HHS have identified this is an area of enforcement priority.
  - FDA ramping up inspections of clinical investigators
  - FDA acting against clinical investigator violations
  - FDA also examining why sponsors, IRBs fail to detect violations

Clinical Investigator Fraud

The Pharmaceutical Development Environment

- Increasing number and complexity of NCEs in development
- Average number of clinical trials required for each potential new medicine is increasing
- Competition for clinical investigators and study sites
- Gaining access to patients
- Increased testing of drugs in developing countries
- Outsourcing of key clinical development functions

Clinical Investigator Fraud

Signs of Fraud

- Subject registered or examined on holiday or weekend
- Subject seen when investigator is not in the office
- Consent form irregularities
- Lab results repeating or rounding
- Lack of study drug accountability

Clinical Investigator Fraud

Applications and Sponsors Associated with Violative Clinical Investigators

Clinical Investigator	Applications	Sponsors
A	91	47
B	49	25
C	43	21
D	21	17
E	12	6
F	6	6
G	92	48

Source: Stan W. Woollen, FDA Associate Director for Bioresearch Monitoring, October 2001

Clinical Investigator Fraud

Discussion Points

- Roles of clinical monitors, QA, compliance officers, and others
- What keeps you awake at night?

Financial Disclosure

Objectives of the Financial Disclosure Rules for Clinical Investigators (21 CFR 54)

- Alert the IND/NDA sponsor to any potentially problematic financial interest
- Minimize the potential for study bias
- Facilitate collection of accurate data that may be submitted years later

Financial Disclosure

Disclosable Financial Arrangements with Clinical Investigators

- Compensation that could be affected by study outcome
- Proprietary interest in the product under study
- Equity interest in the sponsor where the value cannot readily be determined
- Equity interest in a publicly held company (i.e., sponsor) that exceeds $50,000
- Significant payments unrelated to the study with cumulative value of $25,000 or more (e.g., honoraria, grants, retainers, equipment)

Financial Disclosure

Key Definition of a Clinical Investigator

- Listed/identified investigator or subinvestigator directly involved in the treatment or evaluation of research subjects
- Includes a spouse and dependent children

Financial Disclosure

Discussion Points

- Obligations of sponsors
- Obligations of applicants
- FDA published guidance *Financial Disclosure by Clinical Investigators*

PhRMA Industry Standards

PhRMA – Industry Standards

- Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results
- Code on Interactions with Healthcare Professionals

PhRMA – Industry Standards

Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results

- Clinical trials are conducted in accordance with all applicable laws and regulations, recognized principles of GCP, worldwide
- Independence of clinical investigators and others involved in clinical research is respected:
  - Exercise decision-making to protect research participants
  - Compensation to clinical investigators will be reasonable and based on their work
  - Compensation will not be paid in stock
- IRBs or Ethics Committees review trials before initiation

PhRMA – Industry Standards

Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results (continued)

- Participation in clinical trials is based on informed consent, freely given without coercion
- Timely communication of study results, regardless of the outcome of the study. Results must be:
  - Objective
  - Accurate
  - Balanced
  - Complete
- Sponsors will not suppress or veto publications

PhRMA – Industry Standards

Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results (continued)

- Investigators will be able to review relevant data, figures, and reports for the entire study (no limitation to individual investigator's data)
- Only substantial contributors to a publication may be acknowledged as authors or contributors to a publication

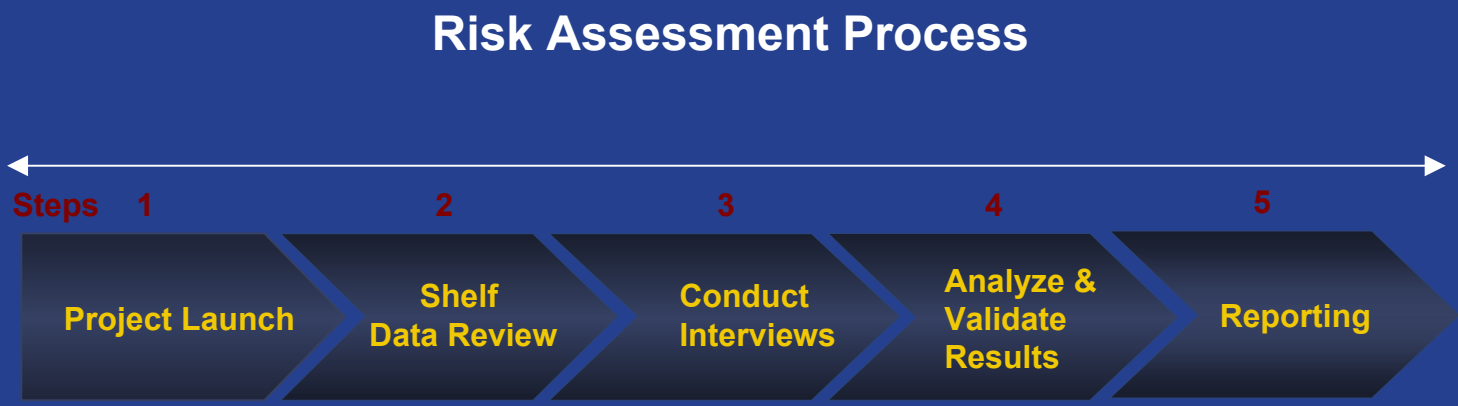
PhRMA – Industry Standards

Code on Interactions with Healthcare Professionals

- Informational presentations by or on behalf of a pharmaceutical company
- Third-party educational or professional meetings
- HCPs as consultants
- Speaker training
- Scholarships and educational funds
- Educational and practice related items

Risk Assessments in Medical Products R&D

Risk Assessments in Medical Products R&D



Risk Assessments in Medical Products R&D

Risk Assessment Ratings

- **Potential Impact of Risk**
- **Probability**
- **Primary Exposure**
- **Control Mechanisms**
- **Accountability**

Other Issues

Questions & Answers

For More Information

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