Fourth Annual Medical Research Summit

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

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April 21, 2004

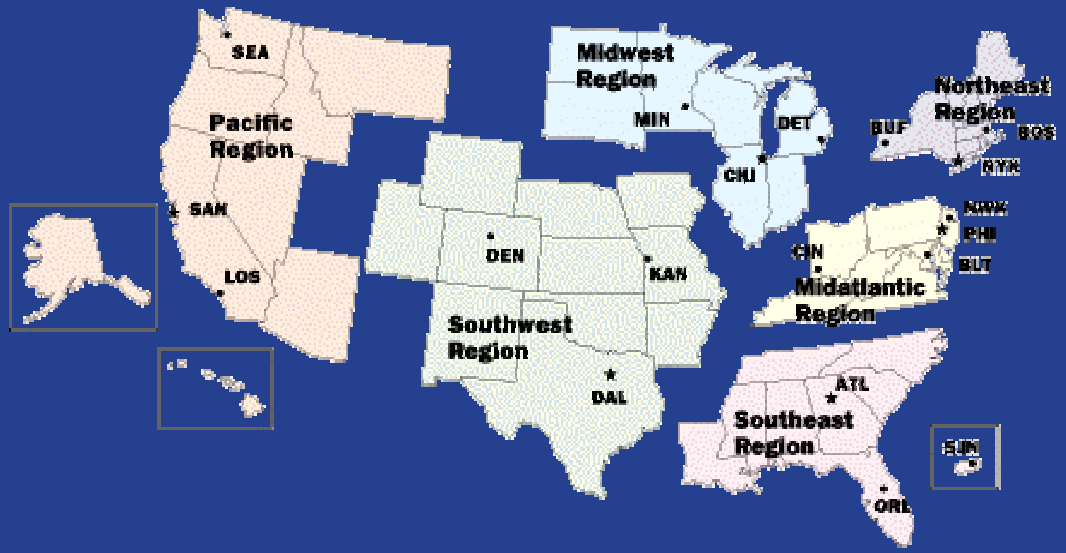
Agenda for Preconference II

- Introductions
- FDA Enforcement
  - FDA Bioresearch Monitoring Program
  - Pharmacovigilance
  - Financial Disclosures and Conflicts of Interest
  - CGMPs in Clinical Supply Production
  - FDA Inspection Readiness
- Fraud and Abuse in Clinical Trials
  - OIG Compliance Program Guidance for Pharmaceutical Manufacturers
  - PhRMA Industry Standards
- Break
- Enterprise Wide Risk Management in R&D
- Questions & Answers

FDA Enforcement

FDA Enforcement

FDA Regional Operations



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***

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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

Compliance Program 7348.811 - GCPs for Clinical Investigations

- Areas in scope for assessment of clinical investigators by FDA
  - Access to pertinent records (provided or refused)
  - Deviations from regulations affecting data validity or subject health and welfare
  - Control of the study by the investigator
  - Documentation (protocol, IRB approvals, informed consent, CRFs, source documents, sponsor communications)
  - Test article accountability

Pharmacovigilance

Pharmacovigilance

Improving patient and consumer safety is one of five critical initiatives established for the FDA

- 21 CFR Part 312.32 IND Safety Reports
- Recent observations and findings from compliance assessments and regulatory inspections related to safety reporting:
  - informal/unwritten procedures for handling of adverse event information
  - failure to meet required timeframes for reporting adverse events
  - failure to provide all participating investigators with written IND safety reports
  - no validation of computerized systems
  - failure to notify co-development partners of adverse events

Pharmacovigilance

Discussion Point

- How do you handle suspected adverse events occurring for comparator products used in clinical trials?

Financial Disclosures and Conflicts of Interest

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

Discussion Points

- How are pharmaceutical companies managing financial disclosure requirements?
- What about follow-up for changes in reporting of financial disclosures within one-year after the conclusion of a clinical trial?

CGMPs for Clinical Supplies

CGMPs for Clinical Supplies

Key Issue for the pharmaceutical industry – compliance with *Current Good Manufacturing Practices* in a research environment.

- Recent observations and findings from compliance assessments and regulatory inspections related to CGMPs:
  - Investigations management
  - Training tracking and record-keeping
  - Change management (product, process, test methods, documentation)
  - Process, equipment and method validation
  - Computer system validation
  - Vendor and supplier qualifications

FDA Inspection Readiness

FDA Inspections

- 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 Inspections

- 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 Inspections

Inspection Process

FDA Inspections

- Establishment Inspection 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 Inspections

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 Inspections

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 Inspections

Discussion point – Recent experience with inspections by regulatory agencies

FDA Inspections

Suggestions to enhance readiness for inspection by regulatory agencies (applicable to sponsors and clinical sites):

- Assign responsibility for managing an inspection to key individuals and identified designees
- Assign responsibilities for inspection tasks to individuals and designees (note-taking, retrieving documents, accompanying inspectors, etc.)
- Address logistics (meeting room, equipment, contact list, etc.)
- Review results of sponsor and CRO audits
- Prepare and train through mock inspections

Fraud and Abuse in Clinical Trials

Backgrounder on the OIG

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

Backgrounder on the OIG

OIG Work Plans – Recent Areas of Focus

- 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 Plans – Recent Areas of Focus (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

Compliance Program Guidance for Pharmaceutical Manufacturers

Compliance Program Guidance

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

Compliance Program Guidance

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
- Third Party medical billing companies
- Ambulance suppliers
- Pharmaceutical manufacturers (published April 28, 2003)

Compliance Program Guidance

Fundamental concerns about the pharmaceutical marketplace

- Is money – or anything of value – interfering with independent clinical/formulary decisions?
- Is misleading, inaccurate, or other inappropriate information influencing independent clinical/formulary decisions?
- Are inappropriate marketing practices leading to increased federal/state/private expenditures?
- Are these or any other practices placing patient safety and interests at risk?

Compliance Program Guidance

Compliance Program Guidance for Pharmaceutical Manufacturers

- Establish an effective corporate compliance program
  - Standards and Procedures
  - Oversight Responsibility
  - Education and Training
  - Lines of communication
  - Monitoring and auditing
  - Enforcement and Discipline
  - Response and Prevention

Compliance Program Guidance

Compliance Program Guidance for Pharmaceutical Manufacturers

- Three specific risk areas cited by the OIG
  1. Integrity of data used to establish government reimbursement
  2. Kickbacks and other illegal remuneration
  3. Drug samples

Enterprise Wide Risk Management in R&D

Evolution from "Traditional" Compliance Programs

- **Standards & Procedures**
- **Oversight Responsibility**
- **Education & Training**
- **Lines of Communication**
- **Monitoring & Auditing**
- **Enforcement & Discipline**
- **Response & Prevention**

QAU

Internal Audit

PricewaterhouseCoopers/EIU Survey

June 2003

- Overview
  - Global program of briefings to address key strategic issues
  - Focus on drawing conclusions about best practice and future trends
  - “Compliance: A gap at the heart of risk management”
- Research effort
  - 20 one-one-one interviews with executives at major companies, regulators and technology houses in US, UK, Europe and Asia
  - 160 executives from North America, Europe and Asia participated in a survey

PricewaterhouseCoopers/EIU Survey Results

- Only 15% feel their compliance procedures are effective in minimizing reputational risk
- Reputational Risk identified as #1 priority
- Only 25% believe they are in full compliance with regulations and laws
- Customers are viewed as second only to regulators as key drivers to adopt and implement best practices
- Compliance with internal risk control policies viewed as more effective at protecting against reputational damage than compliance with government and/or exchange rules

A New Strategy is Required

- Adopt an integrated view of enterprise wide risk management
- Embrace a new vision of compliance
- Develop a systemic approach to meeting requirements

Integrity-Driven Performance

ERM Defined

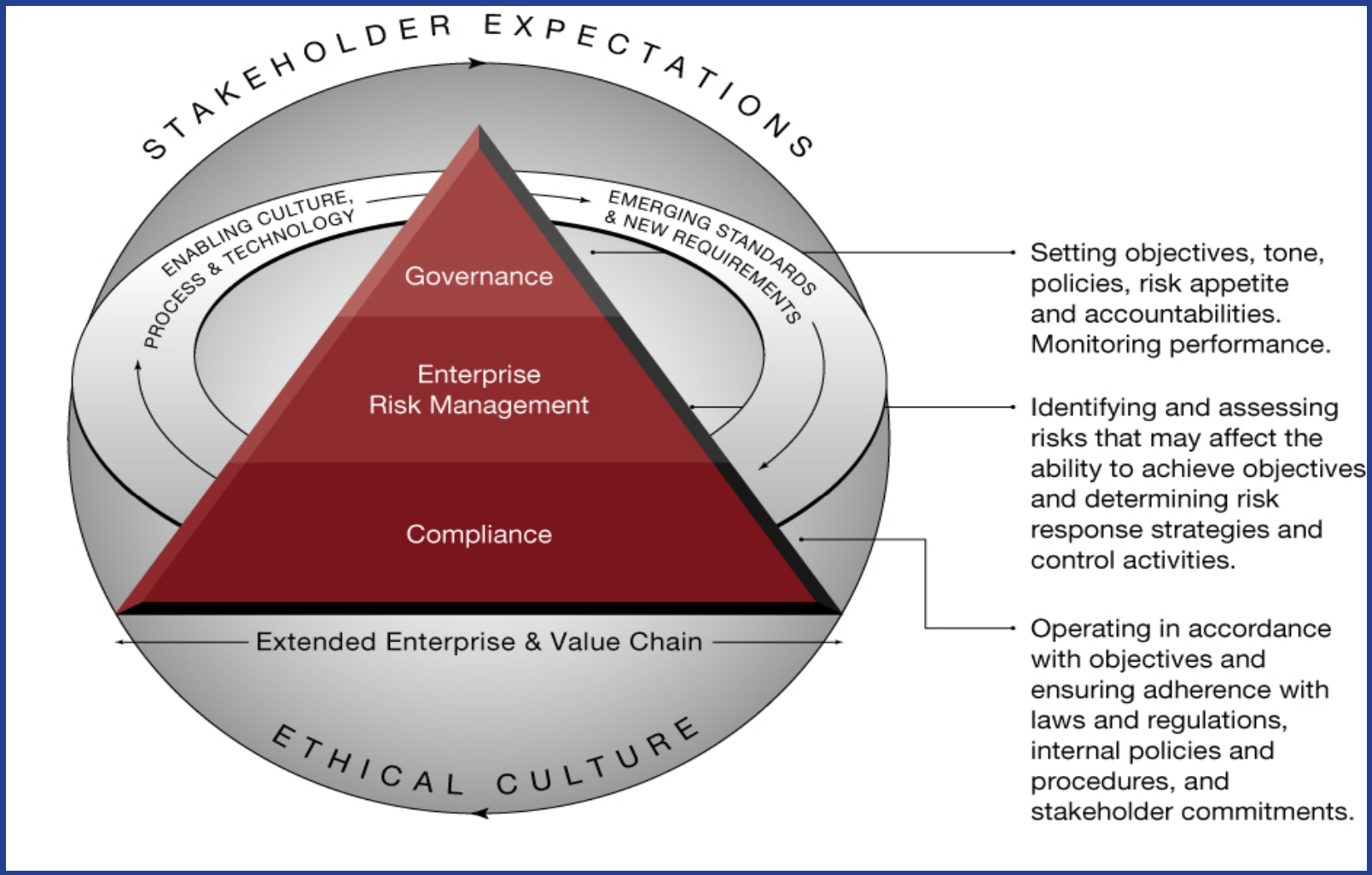
- Evolution from compliance as “seven elements” and “insurance policy” to enterprise wide risk management as an “enabler” of good business
- Compliance transitions from a reactive, process intensive activity to a dynamic program enabling the organization to manage a broad range of changes that can impact its performance
- Enterprise Risk Management is a process that includes:
  - Identification of potential events that may impact objectives
  - Risk assessment and response
  - Consideration of risks in formulation of strategy
  - Application across the entity
  - Managing risk is to be within the entity’s risk appetite
  - A portfolio view of risks at the entity-level is taken
  - Monitoring the performance of EWRM

Enterprise Wide Risk Management

Key Enterprise Business Issues

- Continued business and compliance failures
- Increased stakeholder scrutiny and expectations
- Meeting new expectations and myriad of requirements within existing operations
- Managing enterprise-wide compliance processes in a cost effective manner

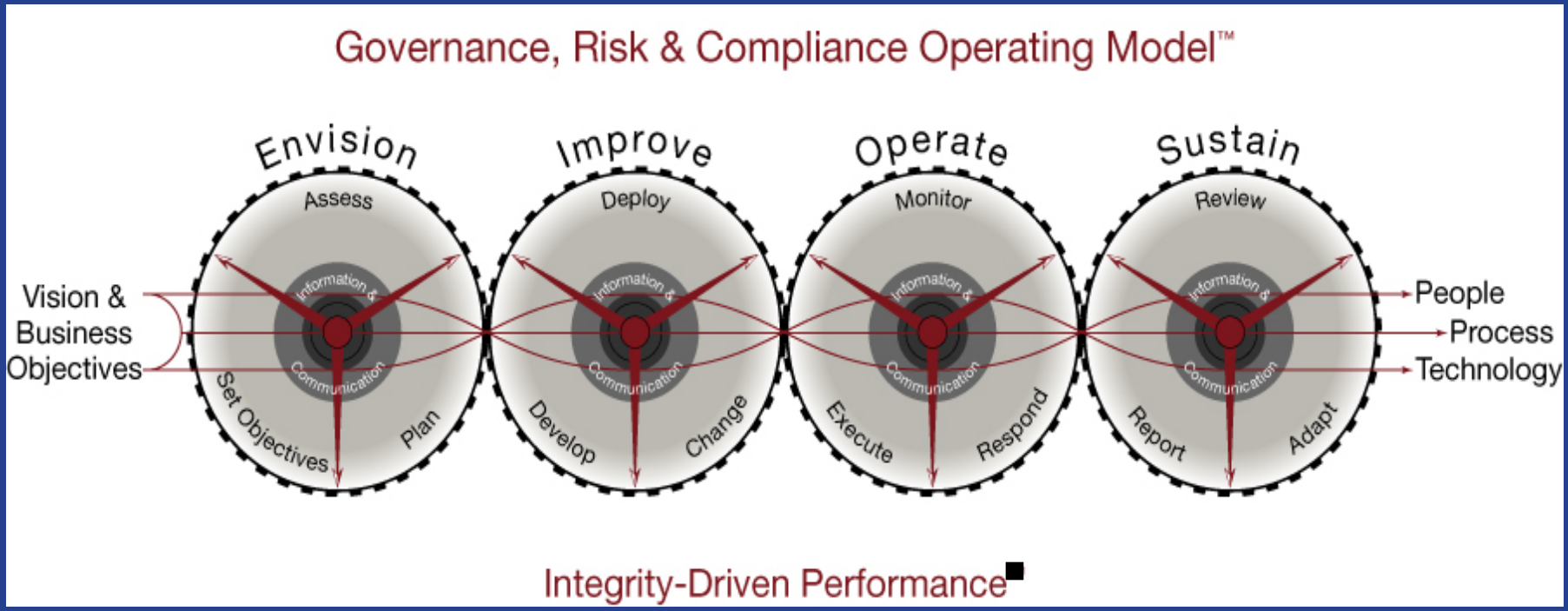
Integrated View of Governance, Risk Management & Compliance



“Before & After” - A New Vision of Compliance

- Compliance as an *outcome*, not as a function
- Compliance as a *value driver* (e.g., customer service, operational efficiency, etc.)

Systematic Approach to Meeting Requirements



- Aligns EWRM processes with business strategy
- Aligns and leverages people, process and technology
- Applies at an enterprise, business unit or topical level

EWRM Key Enablers

- Instilling a culture of business integrity and ethical values
- Integrating EWRM into core, day-to-day business processes
- Achieving effectiveness through EWRM technology architecture
- Measuring performance and calculating value

EWRM – A “Horizontal” Review

Assess and Evaluate Business Policies

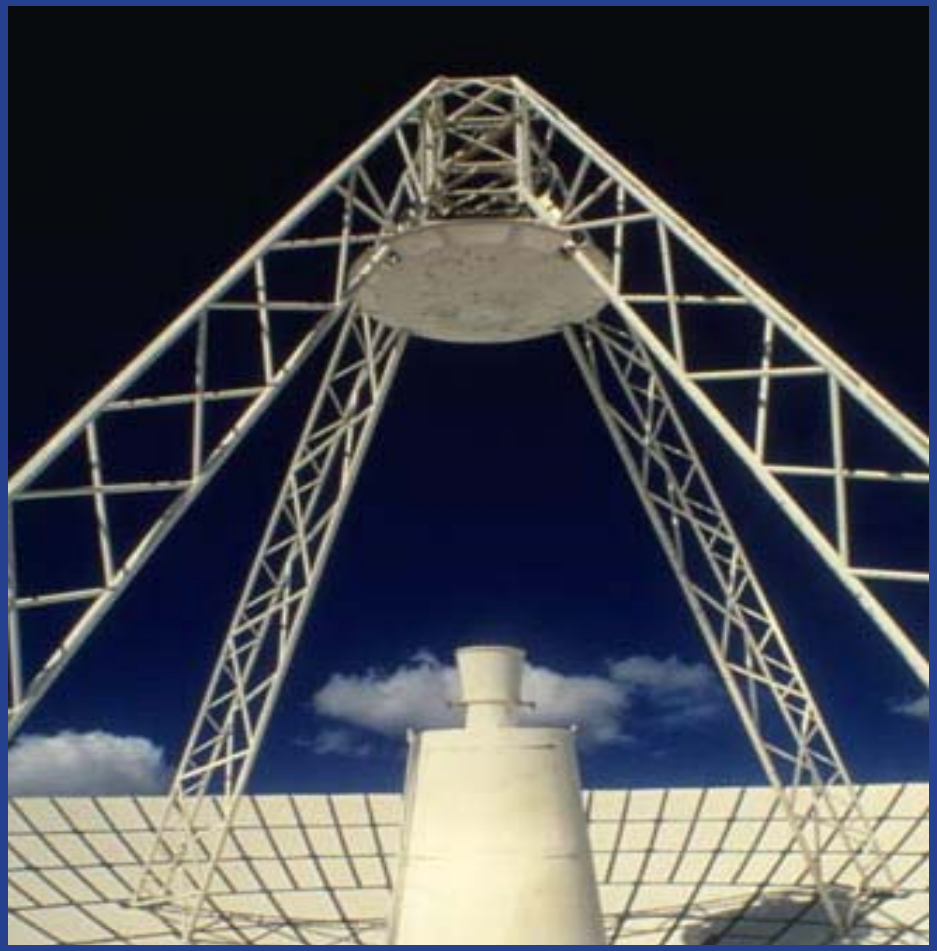
- Review the objectives, structure, policies
- Review implementation of policies
- Test/assess effectiveness across the organization
  - Baseline
  - Ongoing

The review activity should evaluate the design, implementation and effectiveness of the business unit's compliance-related objectives, programs and activities.

Review Process for Addressing Fraud/Risk Exposure

- Anti-Fraud programs
- Training
- Fraud specific risk assessment
- Detection processes
  - Use of models and technology
- Whistle-blower/hotline programs
- Incidence reporting and tracking

Treat as a process review, not a fraud detection exercise



Building the R&D Risk Profile

1.4 Research & Development:

Risk Area – Research & Development	Primary Business Impact	Industry Risk Rating (High/Medium/Low)
Good Laboratory Practices	Government fines, loss of license to operate	**High**
Good Clinical Practices	Government fines, loss of license to operate	**High**
Good Manufacturing Practices	Government fines, loss of license to operate	**High**
Human subject protection requirements	Government fines, loss of license to operate, legal exposure	**High**
International laws and regulations for research and development	Government fines, loss of license to operate	**High**
Federal animal rights legislation: ▪ Animal welfare regulations ▪ Public Health Service policy on humane care and use of laboratory animals	Government fines, legal exposure	**Medium**
PhRMA code (e.g., clinical investigations and publications)	Government fines	**Low**
Clinical investigator fraud	Government fines, legal exposure	**Medium**
Subject recruitment and enrollment requirements	Government fines, legal exposure	**Medium**
Adverse event reporting requirements	Government fines, legal exposure	**High**
Privacy and data protection laws and regulations	Government fines, legal exposure	**High**
Compliance controls for partnerships and outsourced services/functions (e.g., CRO, SMO)	Government fines	**Medium**

Industry Risk Rating

High – Major industry issue: high - potential impact, degree of focus, level of enforcement activity

Medium – Moderate industry issue: moderate - potential impact, degree of focus, level of enforcement activity

Low – Minor industry issue: no/little potential impact, no focus, no/little enforcement activity

Building the R&D Compliance Profile

1.4 Research & Development

Risk Area – Research & Development	Policies & Procedures	Learning Management	Auditing & Monitoring (Does not address corrective action taken by company as a result of auditing findings)	Accountable Manager(s)	Management Systems & Processes
Good Clinical Practices	Refer to Business Conduct Policy Clinical Operations SOP Committee established. ***Procedure Name:*** Monitoring (SOP 1) ***Responsible Unit:*** Research, Clinical Operations ***Procedure Name:*** Monitoring Plans (SOP 20) ***Responsible Unit:*** RESESARCH, Clinical Operations ***Procedure Name:*** Audits and Inspections (SOP 5) ***Responsible Unit:*** Research, Clinical Operations Refer to Policy on Corporate Quality Audits and Compliance Audit Program ***Policy Name:*** Requisitioning Formulated Material for Investigational Use ***Description:*** Guidelines for requisitioning formulated material for investigational use. This included proper authorization and compliance, domestic and international regulatory requirements ***Responsible Unit:*** Headquarters, Laboratories, International Regions and Subsidiaries, Research ***Latest Update:*** 09/30/01 ***Policy Name:*** Recovery or Quarantine of Investigational Drugs ***Description:*** Responsibilities and actions to be taken in cases of potential or actual recovery or quarantine of any of the company's investigational drugs distributed to outside investigators ***Responsible Unit:*** Headquarters, International, Research ***Latest Update:*** 07/31/02	***Course:*** Annual Compliance Training ***Audience:*** Clinical Research ***Media:*** Classroom ***Content:*** on-line ***Course:*** Good Monitoring Principles & Practices ***Audience:*** Clinical Research ***Media:*** Classroom ***Content:*** on-line ***Course:*** Verification and Monitoring Plans Audience: Clinical Research ***Media:*** Classroom ***Content:*** on-line 15 Courses related to Information Systems, Databases, etc. ***Audience:*** Admin, CRAs, Monitors ***Content:*** Clinical Application Training Team	WRQA GCP unit audits compliance with regulations and GCP training in Research. CQC unit in Clinical Development audits Phase I – Phase III clinical studies. **Corporate Audit Report 2002** ***Country:*** USA ***Last Audit:*** 2002 ***Issues:*** ? Payments made for clinical studies performed by state-employed HCPs not properly reviewed ? Obtaining/maintaining patient information within the study files not in compliance with GCP ? No specific guidelines regarding inspection/investigation by the FDA/other government agencies Corporate Quality Audits and Compliance (CQAC) audited WRQA procedures related to the requirements of its new charter. **Corporate Audit Report 2002** ***Country:*** Italy ***Last Audit:*** 2002 ***Issue:*** ? Draft SOP for conducting observational studies not reviewed/approved ? Inadequate Medical and Scientific Affairs SOP No written procedures on handling of free drugs provided to investigators CQC unit in Clinical Development audits Phase I – Phase III clinical studies.		Clinical project management system. Electronic data capture (EDC) tool for collecting clinical data. Reporting web–site to obtain global view of data to plan, organize and manage clinical trials. Application in clinical project management system to manage grants and payments for clinical investigations.

Building the R&D Compliance Performance Scorecard

	Adequacy of Controls				Effectiveness		Risk		Efficiency
Risk Area – Research & Development	**Policies & Procedures**	**Learning Management**	**Monitoring**	**Auditing**	**Management Systems & Processes**	**Total Control and Effectiveness Score**	**Industry Risk Rating (High/Medium/Low)**	**Priority Index**	**Burden to the Business**
International laws and regulations for research and development.	2	1	1	1	1	**6**	High	2.00	Low
Human subject protection requirements	3	2	1	1	1	**8**	High	2.67	Medium
Adverse event reporting requirements	3	1	1	2	1	**8**	High	2.67	Medium
Privacy and data protection laws and regulations	2	2	2	3	2	**11**	High	3.67	Medium
Good Laboratory Practices	3	3	2	2	2	**12**	High	4.00	Medium
Good Manufacturing Practices	3	2	2	3	2	**12**	High	4.00	High
Good Clinical Practices	2	3	2	3	3	**13**	High	4.33	Medium
Subject recruitment and enrollment requirements	2	1	1	1	1	**6**	Medium	4.00	Low
Compliance controls for partnerships and outsourced services/functions (e.g., CRO, SMO)	2	1	2	1	1	**7**	Medium	4.67	Low
Clinical investigator fraud	3	2	1	1	1	**8**	Medium	16.00	Medium
PhRMA code (e.g., clinical investigations and publications)	3	2	1	1	2	**9**	Low	9.00	Low

Building the R&D Compliance Performance Scorecard

Key Attributes Tested

Assessed the following key attributes when analyzing the information compiled in the Compliance Profile:

- The *Adequacy* of the compliance program controls in each risk category. Outlined the extent to which the following four activities existed for a particular risk category:
  - Policies and Procedures
  - Learning Management
  - Monitoring
  - Auditing
- The *Effectiveness* of the Compliance Management Systems and Processes in administering the program.
- The *Efficiency* of the compliance control environment by assessing the burden of the compliance program on the business for each risk category.
- The *Industry Risk Rating* for each risk category.

EWRM – A “Vertical” Review

Conducting an Investigator Site Audit

- Establish the objectives
  - Ensure rights & safety of study subjects
  - Ensure integrity of data
  - Verify compliance with regulatory requirements
  - Verify compliance with protocol requirements
- Criteria for Selecting the Audit
  - Study drug, protocol or project
  - Study complexity
  - Number of patients
  - Investigator experience
  - Historical performance (identified through audits)
  - Experience of the site monitor or CRO
  - Specific concerns

Conducting an Investigator Site Audit

- Workplan Steps
  - Interview key site personnel
    - Document involvement of the investigator and other delegated responsibilities
    - Document informed consent process
  - Review regulatory study file
    - Regulatory documents – (FD1572, CVs, IRB composition, financial disclosure statement)
    - Most recent consent form (all versions)
    - IRB approval/re-approvals
    - Current protocol and all amendments
    - Monitor log and correspondence
    - Financial payments usually not reviewed
  - Compare CRF entries to source documentation
  - Confirm any deviations with management
  - Assess any special requirements (e.g., diagnostic equipment)

Conducting an Investigator Site Audit

- Workplan Steps (continued)
  - Compare CRF entries to source documentation
    - Document investigator involvement
    - Document functional responsibilities (e.g., consent, randomize, exams, dose adjustments)
    - Confirm that source records support dates and data in CRF
    - Confirm all sources for records identified
  - Confirm any deviations with management
  - Assess any special requirements (e.g., diagnostic equipment)

Questions & Answers

For More Information…

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