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How to Conduct a Clinical Research Compliance Assessment

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Overview

- Examples of Clinical Research-Related Enforcement Actions
- What Laws and Other Rules Apply to R&D/Clinical Compliance?
- Key Risk Areas for R&D/Clinical Research Activities
- Practical Advice on How to Conduct a R&D Compliance Assessment

A Few Preliminary Notes

- This presentation and the accompanying discussion provide general information on recent legal and regulatory developments. They are not intended to be, and should not be relied upon, as legal advice.
- Any views expressed during this presentation are those of the individual speakers and not of their employers.

A Few Preliminary Notes (cont'd.)

- All of the information discussed regarding the recent settlements is based on publicly available information
- None of the information we share today about identifiable companies reflects non-public or "inside" information
- Some of the information discussed today is based on settlement documents, complaints, DOJ statements and related materials
    - Caution is appropriate with respect to whether these documents provide a complete, accurate, and/or fair depiction of the conduct of any company or individual

Clinical Research-Related Enforcement

- Government Prosecutions:
  - *United States v. InterMune, Inc.*, Deferred Prosecution Agreement (Dec. 4, 2006)
    - patient registry
  - *United States v. Serono Laboratories, Inc.*, Government's Sentencing Memorandum (December 14, 2005)
    - observational study
  - *United States v. Cell Therapeutics*, *Inc.,* Settlement Agreement (April 17, 2007)
    - clinical studies
  - *United States v. Pfizer/Parke Davis,* Sentencing Memorandum (May 2004)
    - medical science liaisons

InterMune

- Settlement Date: October 24, 2006
- Date of Alleged Conduct: August 2002-January 2003
- Product(s):
  - Actimmune (approved for treatment of chronic granulomatous disease and severe, malignant osteopetrosis)

Intermune (cont'd.)

- **Alleged Misconduct Related to Research:**
  - **ASAP Registry:** Actimmune Safe and Appropriate Use Program (ASAP) Registry to collect information about IPF patients
  - Stated purpose to make information available to physicians and InterMune for research/analysis, support publications
  - Actually operated mainly by InterMune sales and marketing
  - Sales reps received incentives for each patient enrolled in ASAP Registry
  - Numerous GCP issues with Registry raised by a third party administrator-- including reps involvement with operation

Intermune (cont'd.)

- **Source of Allegations:**
  - *Qui tam* lawsuit filed by former sales rep who claimed she was fired for refusing to promote Actimmune for unapproved uses
- Criminal Resolution: 2-year Deferred Prosecution Agreement (DPA)
- Civil Provisions:
  - $36.9 million fine
  - Five-year CIA

Serono

- Settlement date: December 14, 2005
- Alleged Misconduct Related to Research:
  - Paying excessive reimbursement to physicians for participating in two studies run by SeronoLabs: SeronAIDS and SALSA
    - SeronAIDS was an “observational study” used to examine efficacy, dosage, and side effects of Serotism. Doctors (thought leaders/high prescribers) were paid $75 per patient/per quarter for data collected on a one page form. Data was not used in any study and Serono did not give feedback on data submitted.
    - SALSA was also an observational study consisting of a questionnaire completed by doctors and patients about the patients perception of change in their body shape. Doctors were paid $200 for each patient and $75 for each form returned to Serono. Serono reps used questionnaire to talk about lipodystrophy to doctors.

Cell Therapeutics

- Date of Settlement: April 13, 2007
- Alleged Misconduct Related to Research:
  - In CTI-funded off-label studies for Trisenox, CTI "knowingly and willfully" did not provide free study drug or provide drug at cost, and required investigators to purchase from commercial sources and directed them to submit claims for Medicare reimbursement
- Civil Provisions:
  - Company agreed to pay $10,500,000 to resolve allegations that company violated FCA through off-label promotion
  - Must enter into a CIA if they begin to manufacture and sell a commercial product before May 2012
- Criminal Provisions: None

Parke-Davis: Neurontin

- Whistleblower case initiated by Regional Medical Liaison ("RML"); settled in 2004
  - Pfizer, which acquired Parke-Davis, agreed to pay $430M to settle criminal and civil claims. Pfizer also entered into a CIA monitored by the OIG.
- Alleged Misconduct Related to Research:
  - Parke-Davis RMLs improperly "pushed" to discuss off-label
    - Worked closely with sales representatives to directly sell Neurontin to physicians for off-label uses with little supervision from headquarters
    - "Cold-called" doctors without prior appointment or inquiry regarding off-label uses
    - Discussed off-label uses during scheduled appointments with multiple doctors over lunches or dinners
    - Falsely represented themselves as neutral scientific experts

Parke-Davis: Neurontin

- Alleged Misconduct Related to Research (cont'd):
  - In addition, Parke-Davis improperly:
    - developed slide kits for RMLs to promote off-label
    - engaged in "ghostwriting" of off-label publications
    - sponsored CME to promote off-label
    - funded research with limited scientific support
    - misused consulting programs and advisory boards

Recent CIA Provisions Related to Research

- Code of Conduct must set forth company's commitment to engage in research in accordance with all Federal health care program and FDA requirements
- Must develop policies and procedures that address sponsorship or funding of research activities (including clinical trials, market research, or authorship of articles or other publications) in a manner that is designed to ensure compliance with all applicable Federal health care program and FDA requirements
- Policies and procedures must ensure that sales and marketing activities are separate from clinical trial enrollment.

Recent CIA Provisions Related to Research (cont'd.)

- Training programs for all applicable employees must explain proper method of conducting research (including clinical trials) in accordance with Federal health care programs and FDA requirements.
- IRO shall review and prepare a report regarding company systems, policies, processes, and procedures relating to funding or sponsorship of research agreements, grants, and/or research collaborations (including clinical trials and independent research).

What Laws and Rules Apply?

- Laws and Regulations
  - Federal Food, Drug & Cosmetic Act
  - Federal and State Fraud/Abuse Laws
    - Anti-Kickback Statute (42 U.S.C. § 1320a-7b) and state laws
    - False Claims Act (31 USC § 3729-33) and state laws
  - FDA Clinical Investigator Disclosure Regulations (21 C.F.R. Part 54)
  - False Statements Act (18 U.S.C. §1001)

What Laws and Rules Apply? (cont'd.)

- **Regulatory Guidance**
  - HHS-OIG Compliance Program Guidance for Pharmaceutical Manufacturers (68 Fed. Reg. 23731)
    - Pursuant to HHS OIG Healthcare Compliance Program Guidance, payments to HCPs for research services:
      - Should be provided under a written contractual agreement on a fee-for-service basis
      - Should be fair market value
      - Should be for "legitimate, reasonable, and necessary" services
    - Educational/research grants provided by a manufacturer to a physician:
      - Must not be based "in any way, expressly or implicitly" on the physician's referral of the manufacturer's product
      - Must be for a *bona fide* educational or research program
    - Manufacturers should develop procedures that clearly separate research contracts from product marketing/promotion

What Laws and Rules Apply? (cont'd.)

- Regulatory Guidance (cont'd.)
  - FDA Guidance on Financial Disclosure by Clinical Investigators (March 20, 2001)
  - Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection (Office of Public Health and Science, HHS) (May 12, 2004)
  - Bioresearch Monitoring Compliance Program 7348.810, Sponsors, Contract Research Organizations and Monitors

What Laws and Rules Apply? (cont'd.)

- Pharmaceutical Industry Standards
  - PhRMA Principles for Conduct of Clinical Trials and Communication of Clinical Trial Results
  - PhRMA Code on Interactions with Healthcare Professionals
- Medical Society Standards
  - AMA Guidelines
- ICMJE Guidelines for Publication in Scientific Journals

R&D Compliance Key Risk Areas

- Payments to HCPs for company-sponsored clinical research
- Payments for additional patient recruiting/enrollment ("time and effort" payments)
- Gifts, meals, "bonuses" to HCPs related to clinical research activities
- Clinical investigator selection
- Clinical investigator meetings
- Payments to HCPs for R&D advisory boards, other consulting activities

R&D Compliance Key Risk Areas (cont'd.)

- Investigator Sponsored Studies (ISS or ISTs)
- Clinical study publications (disclosure, ghostwriting)
- Investigator conflict of interest/financial disclosure
- Activities of Medical Science Liaisons
- Charitable donations to physician organizations, patient groups
- Educational grants/CME activity
- Human subject protection (informed consent, IRB approval, payments/incentives to trial subjects)

Risk Area -- Example for Assessment: Clinical Investigator Compensation

- Potential issues:
  - Making payment or any other type of compensation tied to the outcome of the study
  - Providing compensation/equipment/services/support not linked directly to study research/medical procedures
  - Reimbursing travel/lodging for investigator's spouse to accompany investigator at meetings
  - Holding investigator meetings at lavish resorts or entertainment destinations
  - Compensating investigators in company stock or stock options (or selecting an investigator with proprietary or equity interest)
  - Paying "bonus" payments or providing gifts to investigators or their staff for delivering results or enrolling additional patients; payments for additional patient recruiting/enrollment activities

Risk Area -- Example for Assessment: Clinical Investigator Compensation

- Benchmarking:
  - OIG Compliance Program Guidance for Pharma Manufacturers
    - Payments to HCPs for research services:
      - Should be provided under a written contractual agreement on a fee-for-service basis
      - Should be fair market value
      - Should be for "legitimate, reasonable, and necessary" services
  - "Studies of Rx drugs when the studies are of questionable scientific value and require little or no scientific pursuit, [and] nonetheless offer substantial benefits based on, or related to, use of the product" are considered improper under the anti-kickback law. *OIG Special Fraud Alert, 59 Fed. Reg. 65372, 65376 (Dec. 19, 1994)*

Risk Area -- Example for Assessment: Clinical Investigator Compensation

- Benchmarking (cont'd.):
  - PhRMA Principles:
    - Payment to clinical investigators/institutions should be reasonable and based on work performed by the investigator and his/her staff, not on any other considerations.
      - A written contract or budgetary agreement should be in place detailing the nature of the research services to be provided and the basis for payment for those services
    - When investigators/staff are required to travel to meetings related to the trial, they may be offered reimbursement for reasonable travel, lodging, and meal expenses. Venue and circumstances should be appropriate for meeting purpose.
    - When enrollment is *particularly challenging*, reasonable additional payments may be made to compensate the investigator/institution for time and effort spent on extra recruiting efforts to enroll appropriate participants.

Risk Area -- Example for Assessment: Clinical Investigator Compensation

- Benchmarking (cont'd.):
  - FDA Investigator Financial Disclosure:
    - Sponsors must disclose to FDA whether clinical investigators have financial interests that could affect reliability of data submitted in an application
    - FDA may refuse to accept for filing an application that does not include certification and/or disclosure
    - FDA will evaluate information to determine impact on reliability of study
    - If investigator compensation/payment arrangements calls reliability of study into question, FDA may require data audits, request additional data analyses or studies, or refuse to rely on data

How to Conduct an R&D Compliance Assessment

- Research Compliance Assessments: Framework
  - Leadership and Accountability -- someone responsible for R&D compliance
  - Policies - *e.g.*, ISS, MSLs, physician consulting
  - Training
  - Communication and Reporting
  - Monitoring and Auditing
  - Performance and Disciplinary Standards
  - Process for Follow-Up and Remediation
- Similar to sales and marketing compliance assessment, but focus is on R&D risk areas
- May focus on aspects of this or all elements -- can vary in scope depending on needs

How to Conduct an R&D Compliance Assessment (cont'd.)

- How to Conduct a CR Risk Assessment
  - Determine what areas to review
    - Areas of greatest risk? Amount of activity (spending -- e.g., payments to HCPs, consultants, investigators), consequences of non-compliance, likelihood of discovery, relationship to other risks (PL, Gov't Investigation, etc.)
    - Ability to assess against objective standards
    - Areas where remediation most likely to take hold
  - Determine what to assess
    - Activities
    - Controls
    - Recognize limits -- without email, review will paint a limited picture

How to Conduct an R&D Compliance Assessment (cont'd.)

- CR Risk Assessment -- Documents
  - Compliance policies
  - Clinical trial agreements
  - Consultant agreements
  - Grant and funding requests
- CR Risk Assessment -- Interviews
  - Legal (start here -- in-house lawyers know the issues)
  - Finance (money flows, amounts, documentation)
  - CR Operations (know how things really work)
  - CR Personnel
  - MSLs
  - Medical affairs
  - Scientific Communications
  - Marketing (Phase IV)

Recommended Documents to Review

- Organizational Charts
- Standard Operating Procedures (“SOPs”) e.g.,:
  - Investigator Selection
  - Financial Disclosure Procedure
  - Terminating a Clinical Investigator as a Corrective Action for Non-Compliance/Debarment
  - Concept Approval Process for Investigator-Sponsored Studies
- Chart of Active Clinical Trial Sites
- Template Agreement for Clinical Services
- Sample Master Clinical Trial Agreements
- Chart of Investigator-Initiated Trials by Indication
- Financial Information

Recommended Employees to Interview

- Executive Vice President, Medical & Regulatory Operations
- Senior Vice President, Clinical Research
- Vice President, [e.g., Oncology or other therapeutic area]
- Clinical Research Associate(s)
- Medical Science Liaison(s) (Mid Atlantic, Central, other geographic regions or therapeutic areas)
- Senior Director, Medical Science Liaisons
- Vice President/Director, Scientific Communication/Medical Affairs
- Senior Director, Medical Affairs

Recommended Employees to Interview

- Associate Director, Finance (Supporting Clinical Research Function)
- Associate Director, Clinical Operations
- Senior Manager(s), Clinical Operations
- Consultant/Regulatory Counsel