KING & SPALDING

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*Track III*
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# Advanced Issues in Clinical Compliance

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# Overview

- Key Risk Areas for R&D/Clinical Research Activities
- Examples of Clinical Research-Related Enforcement Actions and CIA Provisions
- Payments to Investigators and Disclosure of Financial Interest
- Key Takeaways

# Preliminary Notes

- All of the information discussed regarding the settlements is based on publicly available information
- None of the information shared 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

# Medical/Research 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

# Medical/Research Risk Areas (cont'd)

- Investigator Sponsored Studies (ISS, IST, IIR)
- Clinical study publications (disclosure, ghostwriting)
- Disclosure of study results (cherry-picking data, etc.)
- Investigator conflict of interest/financial disclosure
- Activities of Medical Science Liaisons
- Charitable donations to physician organizations, patient groups
- Educational grants/CME activity

# 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. Forest Labs,* Settlement Agreement (April 2009)
    - failure to disclose study results
  - *United States v. Pfizer,* Settlement Agreement (September 2, 2009)
    - clinical studies

# 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)
- **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

# Intermune (cont'd)

- **Alleged Misconduct Related to Research:**
  - **ASAP Registry:** Actimmune Safe and Appropriate Use Program (ASAP) Registry to collect information about idiopathic pulmonary fibrosis (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

# 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
- Criminal Provisions: None

# Forest Laboratories

- Date of Settlement: April 2009
- Alleged Misconduct Related to Clinical Research:
  - **Failure to disclose negative clinical trial results.** Forest Laboratories failed to disclose the negative results of a clinical study for Celexa. The large, placebo-controlled study found Celexa to be no more effective than a placebo for pediatric use and in which more patients taking Celexa attempted suicide or reported suicidal ideation than those patients taking only the placebo.
  - The negative data that Forest failed to disclose was among the data later considered by the FDA when mandating that Forest add a "black box" warning to both the Celexa and Lexapro product labels for pediatric use.
- Settlement Amount: $170 million

# Pfizer

- **Date of Settlement:** September 2, 2009
- **Alleged Misconduct Related to Research:**
  - **Pfizer-funded Scientific Studies Misrepresented Safety Evidence for Geodon®:** Pfizer funded scientific studies that misrepresented the evidence supporting the safety profile for Geodon®. The misrepresented evidence was used in Pfizer-supported CME seminars, round table discussions, promotional advertisements, journal supplements, and Pfizer-created slides used by physicians who were paid to promote Geodon® to other physicians.
- **Criminal Fine:** Total of $1.3 billion
- **Civil Settlement**: $1 billion

# CIA Provisions: Medical/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.
- Controls for dissemination of product information, systems and oversight of Medical Information process
- Policies and procedures that address sponsorship or funding of research activities (including clinical trials, market research, or authorship of articles or other publications)
- Policies and procedures must ensure that sales and marketing activities are separate from clinical trial enrollment.
- 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.

# CIA Provisions: Medical/Research (cont'd)

- Disclosure on company website of payments made directly to physicians related to clinical research or education (subject to any confidentiality provisions in clinical research agreements with HCP entered into prior to CIA).
- Registry of clinical trials and disclosure of results on www.clinicaltrials.gov for company-sponsored studies.
- Establish a Publication Monitoring Program, including audits of at least 30 Publication Activities, i.e., engagement of HCPs by company to product articles, during each reporting period.
- 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).

# HHS OIG Guidance on Payments for Research

- 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

# Risk Area -- 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

# Scrutiny on Conflict of Interest/Disclosure of Investigator Payments

Major 2009 developments

- January 2009. HHS Office of the Inspector General. "*The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information.*"
  - 21 CFR Part 54
- Federal Physician Payments Sunshine legislation
- Institute of Medicine. April 2009. New report, "*Conflict of Interest in Medical Research, Education, and Practice.*"

# 2009 OIG Report on Financial Disclosure

January 2009. HHS Office of Inspector General.
"*The Food and Drug Administration's Oversight of Clinical Investigators' Financial Information*."

- Incomplete **financial disclosure** by investigators
  - Only 1% of investigators disclosed at least one financial interest.
- FDA-approved marketing applications lack financial disclosures by sponsors
  - 42% were missing required certification or disclosures
- FDA and sponsors failed to take action to minimize bias in 20% of applications with disclosed financial interests

# 2009 OIG Report on Financial Disclosure

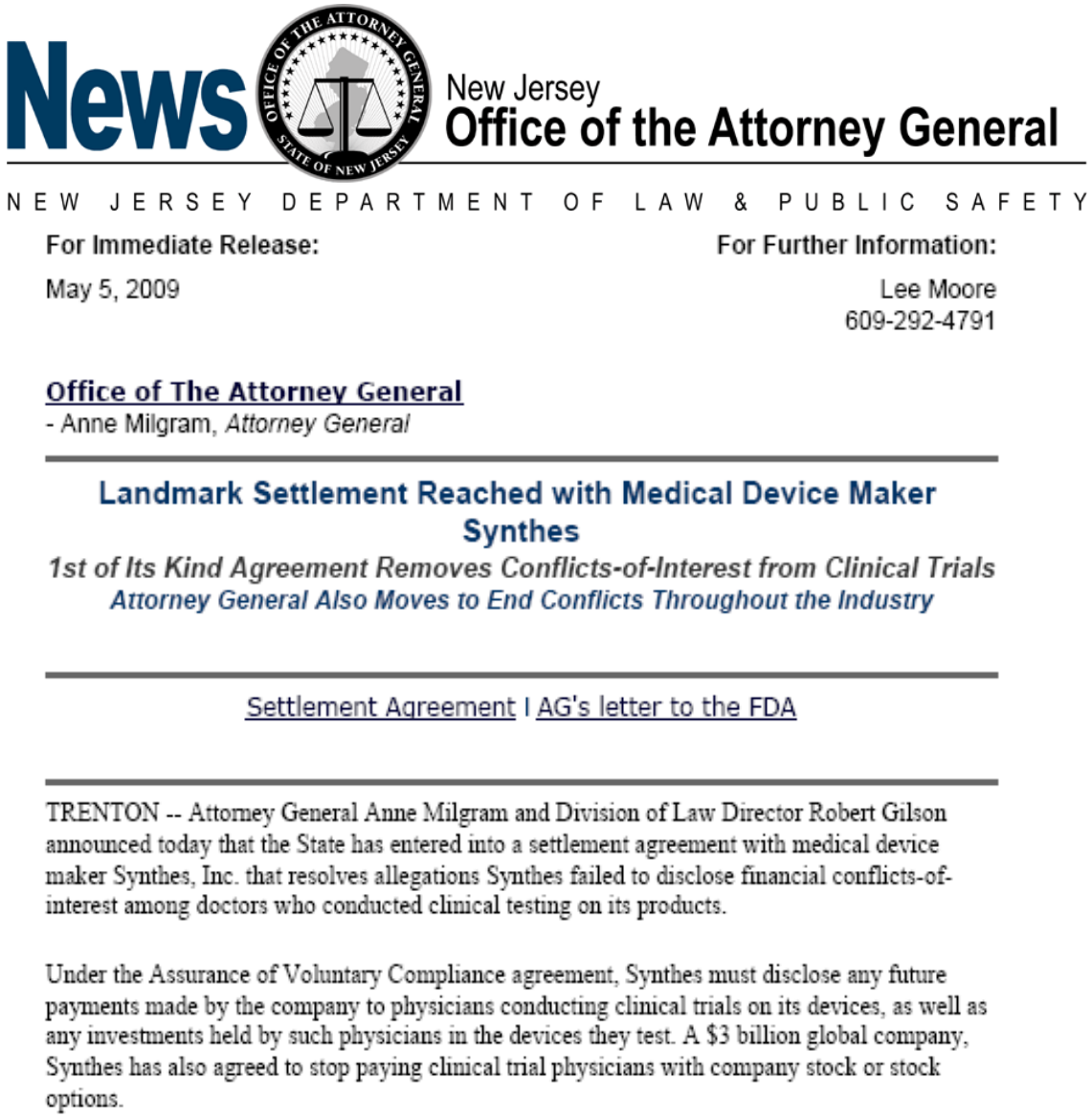
OIG recommended that FDA should ensure:

- Sponsors submit complete financial information for all investigators
  - On site inspections by FDA
  - Issuance of new FDA guidance and higher threshold for use of “due diligence exemption” by sponsors
- Sponsors submit financial information for FDA review during pre-clinical trial (IND/IDE) application process
- FDA reviewers of marketing applications consistently examine financial interests and take action in response

# FDA Financial Disclosure Requirements: Investigator Interests

- 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

# Enforcement Actions Related to Part 54



News

New Jersey
Office of the Attorney General

NEW JERSEY DEPARTMENT OF LAW & PUBLIC SAFETY

For Immediate Release:

May 5, 2009

For Further Information:

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**Office of The Attorney General**
- Anne Milgram, *Attorney General*

**Landmark Settlement Reached with Medical Device Maker Synthes**

***1st of Its Kind Agreement Removes Conflicts-of-Interest from Clinical Trials***

***Attorney General Also Moves to End Conflicts Throughout the Industry***

Settlement Agreement I AG's letter to the FDA

TRENTON -- Attorney General Anne Milgram and Division of Law Director Robert Gilson announced today that the State has entered into a settlement agreement with medical device maker Synthes, Inc. that resolves allegations Synthes failed to disclose financial conflicts-of-interest among doctors who conducted clinical testing on its products.

Under the Assurance of Voluntary Compliance agreement, Synthes must disclose any future payments made by the company to physicians conducting clinical trials on its devices, as well as any investments held by such physicians in the devices they test. A $3 billion global company, Synthes has also agreed to stop paying clinical trial physicians with company stock or stock options.

# Enforcement Actions Related to Part 54

News
New Jersey
Office of the Attorney General
NEW JERSEY DEPARTMENT OF LAW & PUBLIC SAFETY

Under terms of the settlement Synthes, Inc. has agreed to:

- Prohibit compensation of clinical investigators tied to the outcome of the clinical trial
- Pay clinical investigators "fair market value compensation" for their clinical trial work, as well any other consulting services they provide to the company
- Collect information on financial interests from clinical investigators
- Create a Financial Interest Information Database that will record all relevant financial interests related to clinical investigators
- Disclose all financial interests of all clinical investigators on the company's Web site
- Provide complete disclosure of financial interests to the FDA and conduct reasonable due diligence to insure that the disclosures are complete and accurate
- Disclose all financial interests directly to health care facilities serving as clinical trial sites
- Provide Financial Interest and Disclosure training to employees.

# Key Takeaways

- Medical Affairs and Research/Development activities often involve (1) interactions with customers; (2) product information
- These types of activities raise standard healthcare compliance issues:
  - Kickback/inducement
  - FDA promotion
- These healthcare compliance risks are in addition to array of other regulatory/ethical requirements for the conduct of clinical research
- Same healthcare compliance concepts are important
  - No buying business
  - Compliance with FDA promotional rules
  - Commercial compliance policies should apply
- Emphasis on disclosure of trial results and clinical investigator payments