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New Trends in Clinical Research: Increased Oversight and Transparency

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Issues for Today's Discussion

- Investigator-Industry Payments
  - Conflict of interest disclosure and management
- Safety of human subjects
  - Scrutiny on investigators and IRBs
- Expansion of public disclosure of study results and adverse events on clinicaltrials.gov

Scrutiny on Conflict of Interest

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 Act
- Institute of Medicine. April 2009. New report, "*Conflict of Interest in Medical Research, Education, and Practice.*"

FDA Requirements for Financial Disclosures by Clinical Investigators

- **Must disclose any compensation to the investigator whose value could be influenced by the outcome of the study:**
  - Any equity interest in the Sponsor whose value cannot be determined by reference to public prices;
  - Any equity interest in the Sponsor that is a publicly traded company that exceeds $50,000 during the study and for 1 year after completion;
  - Any proprietary interest in the tested product including, but not limited to, a patent, trademark, copyright, or licensing agreement;
  - Any significant payments of other sorts with a value of $25,000 or more (excluding costs of the study). 21 C.F.R. § 54.2, § 54.4

FDA Requirements for Financial Disclosures by Clinical Investigators

Certification and disclosure requirements – 21 C.F.R. § 54.4

The applicant of a marketing submission shall submit

- Certification (Form FDA 3454) attesting to absence of financial interests and arrangements for all investigators cited in the Certification
- Disclosure Statement (Form FDA 3455) disclosing financial interests for each investigator not cited in the Certification
  - Steps taken to minimize the potential for bias
- An application that does not contain required information shall include:
  - Certification that applicant acted with due diligence to obtain information but was unable to do so and stating the reason

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

Table 1: Disclosed Financial Interests

FDA Financial Disclosure Category	Number of Disclosed Financial Interests	Percentage of Total Disclosed Financial Interests
Payments from sponsors	165	77 percent
Equity interests	41	19 percent
Proprietary interests in tested product	5	2 percent
Financial arrangements that could influence the study outcome	3	1 percent
Total	214*	99 percent**

* Clinical investigators can disclose more than one financial interest. There were 206 clinical investigators with 214 disclosed financial interests.

** Total does not equal 100 percent because of rounding.

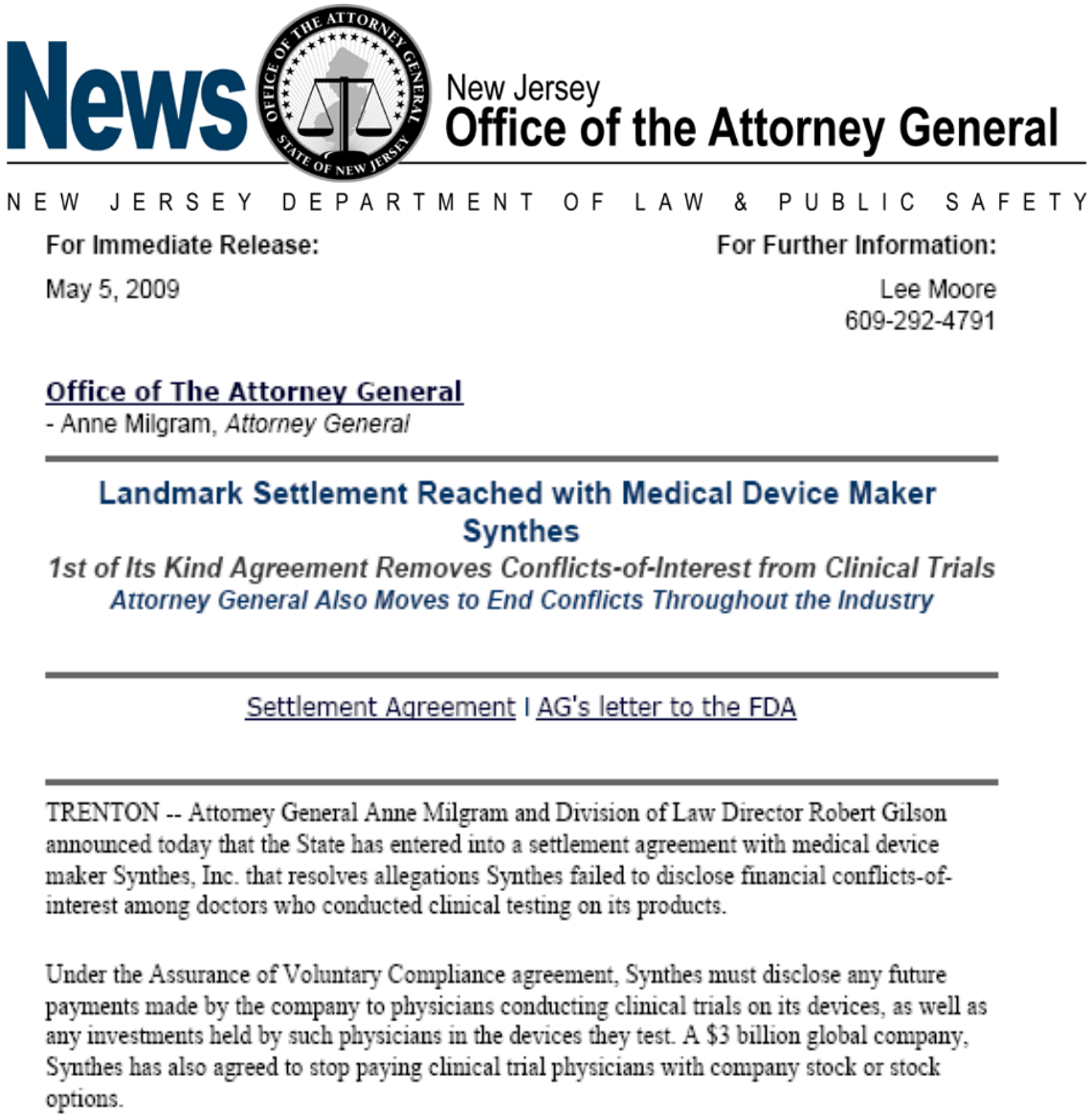
Source: OIG analysis of marketing applications, 2008.

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

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:

Lee Moore
609-292-4791

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

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.

Enforcement Actions Related to Part 54

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

In a letter to the federal Food and Drug Administration (FDA) sent today, the Attorney General said she is hopeful the Synthes terms will become *"best practices"* for disclosure among medical device makers. Milgram's letter described the problem of undisclosed financial conflicts-of-interest among clinical investigators as *"rampant,"* and called on the FDA to more effectively address the problem by adopting rules that require full public disclosure. Copies of the Attorney General's FDA letter went to Senator Max Baucus, Chairman of the U.S. Senate Committee on Finance, and to Senator Charles E. Grassley, the ranking member of that committee.

In addition, Milgram said her office issued subpoenas today to five major medical device manufacturing companies seeking information about their business practices.

"Medical device makers have a duty to make certain that clinical trial results are accurate and unbiased," the Attorney General said. *"In creating these financial incentives for doctors, Synthes and the rest of the industry have done the exact opposite. Going forward, if the industry will not address this problem voluntarily, we most certainly will."*

Federal Physician Payments Sunshine Act Where We Are in 2009

- Originally introduced in 2007; reintroduced in 2009
- **January 23, 2009**: Senators Grassley and Kohl reintroduced a revised version of the *Physician Payments Sunshine Act,* as S. 301.
- **July 9, 2009**: Representative Baron Hill reintroduced the *Physician Payments Sunshine Act*, as H.R. 3138.
- **July 16, 2009**: Markup of H.R. 3200, *America's Affordable Health Choices Act*, included Physician Payments Sunshine Provisions in Section 1451.
- **September 8, 2009**: Draft outline of Senate Finance Committee health reform proposal released – includes (1) Sunshine Act and (2) Reporting Drug Samples to HHS (but not to public). Endorsed by PhRMA. Full bill not released yet.

Sunshine Act - Overview Relevant to Clinical Trials

- Requires submission of annual transparency reports**.** Applicable **drug** and **device** manufacturers must report:
  - (1) “payments or other transfers of value” to “covered recipients”
  - (2) aggregate amount of all “payments or other transfers of value”
  - (3) ownership or investment interests held by physicians in the applicable manufacturer
- **Covered recipient.** A physician, a physician medical practice, or a physician group practice with Medicare billing number (under Senate version; House version much broader.)
- **2009 bills add disclosure of payments for clinical trials.**
  - Provides for delayed reporting for payments made pursuant to product development agreements and clinical investigations
- Requires HHS to make reported information publicly available and submit reports to Congress and the states

IOM: Major New 2009 Report

- The Institute of Medicine states that financial conflict-of-interest in device and drug industry-sponsored clinical studies and the development of evidence reviews and practice guidelines:
  - "*raise concerns about the objectivity and trustworthiness of research conduct and publications, …and the commitment of health care professionals to the best interests of patients."*
  - *"contribute to questions about whether industry has undue influence in research and other activities*."
  - Report development, with hearings, began in 2007.
- Likely to have major legislative impact, similar to IOM Drug Safety Report

IOM: Major New 2009 Report

Recommendations relevant to manufacturers and the conduct and reporting of clinical trials:

- Congress should mandate public reporting of payments by industries and their foundations to physicians and other prescribers, biomedical researchers, health care institutions, professional societies, patient advocacy and disease-specific groups, providers of CME, and foundations created by any of these entities.
  - **Will this expanded list of recipients** be incorporated into Sunshine Act provisions of 2009?

IOM: Major New 2009 Report (cont'd.)

- Medical institutions engaged in clinical research should adopt and implement COI policies, via a formal COI committee
  - Including procedures for disclosure to patient subjects
- Physicians with COI should be restricted from participating in clinical investigation
  - Exception only if COI committee determines participation is critical; Must be publicly disclosed, including to patient subjects
- Companies should "not involve physicians and patients in marketing projects that are presented as clinical research"
- Physicians should "not make any presentations or publish articles that are controlled by industry or contain substantial portions written by someone who is not identified as an author or is not properly acknowledged"

New Actions by Medical Centers

As example, Cleveland Clinic COI Policy

- All Significant COIs must be disclosed to COI Committee
- If participation in research permitted, COI must be disclosed
  - in IRB consent forms to patient subjects
  - in or with manuscript for publication
  - in any substantive publication of research results
  - to other research personnel
- Public disclosure of payments
  - "Industry Relationships" web link to MD names
  - Speaking and consulting of $5,000 or more per year
  - Any equity, royalties, and fiduciary relationships in companies with which a physician collaborates

Financial Disclosures by Clinical Investigators

Challenges

- Companies must rely in part on accurate disclosure by investigators for certain Part 54 financial interests
  - No standardized tool for sponsor collection of data from physicians
- Tracking payment disclosures in multiple databases
- BiMo inspections and Warning Letters
  - Alleged deficiency in Part 54 compliance may occur in context of BiMo inspection that focuses on safety or data integrity issues
- Enforcement actions related to Part 54
  - May be triggered by malpractice and/or product liability issues related to an adverse outcome in a clinical trial

Scrutiny on Patient Subject Safety

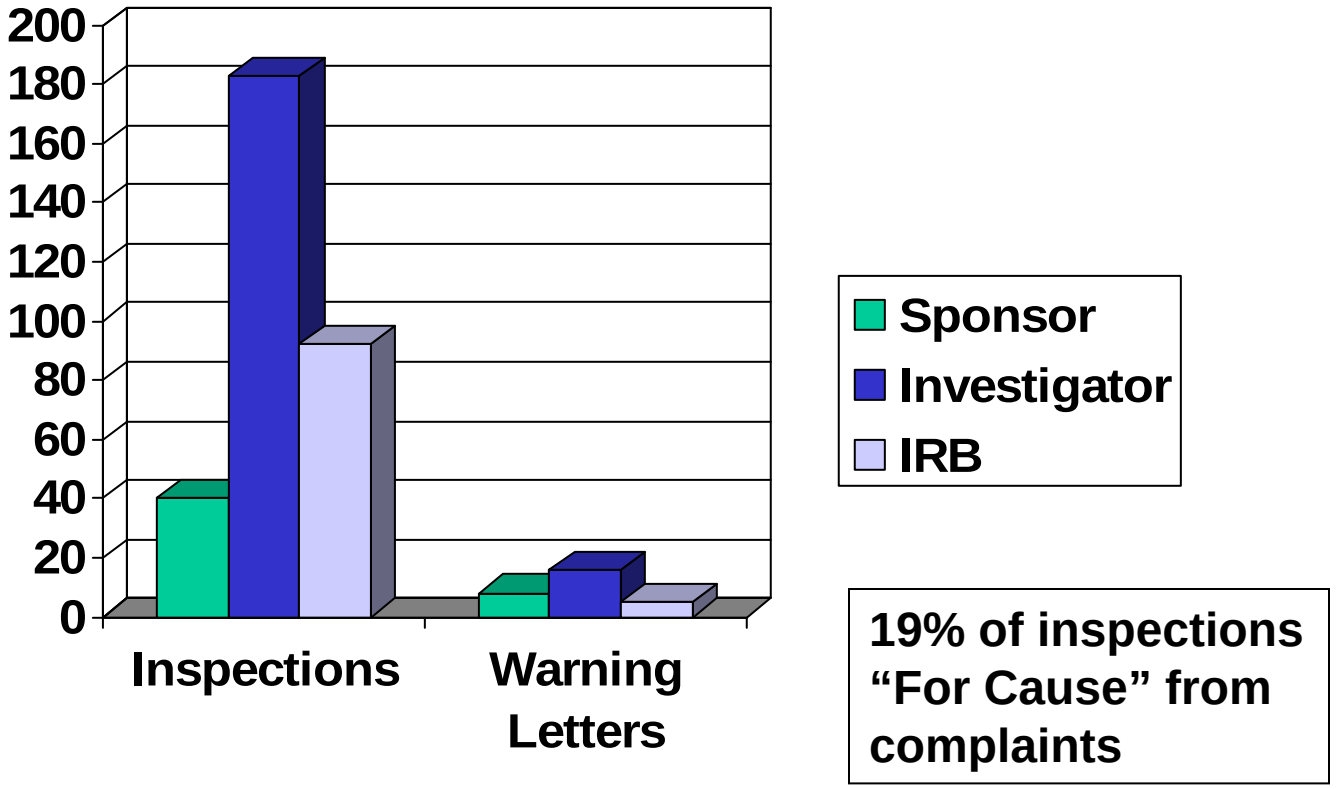
Major developments:

- September 2007. HHS Office of the Inspector General Report: "*The Food and Drug Administration's Oversight of Clinical Trials.*"
- 2009. Enforcement actions regarding IRBs and oversight of industry clinical studies

2007 OIG Report on Clinical Trials

- Inadequate on-site attention to patient safety protections compared with data integrity
  - FDA (Bioresearch Monitoring, BiMo)
  - IRBs
  - And, by extension, Sponsors and Investigators
- Excess reliance on voluntary compliance
- Incomplete data - no central registry of all IRBs
- Insufficient action to rapidly correct deficiencies
- Need for expansion of FDA oversight of Sponsors and their Investigators/subordinates

Recent Major Developments



FDA BiMo Device Clinical Trial Inspections

The Gray Sheet. Jan 7, 2008

FDA Warning Letters - Common Issues

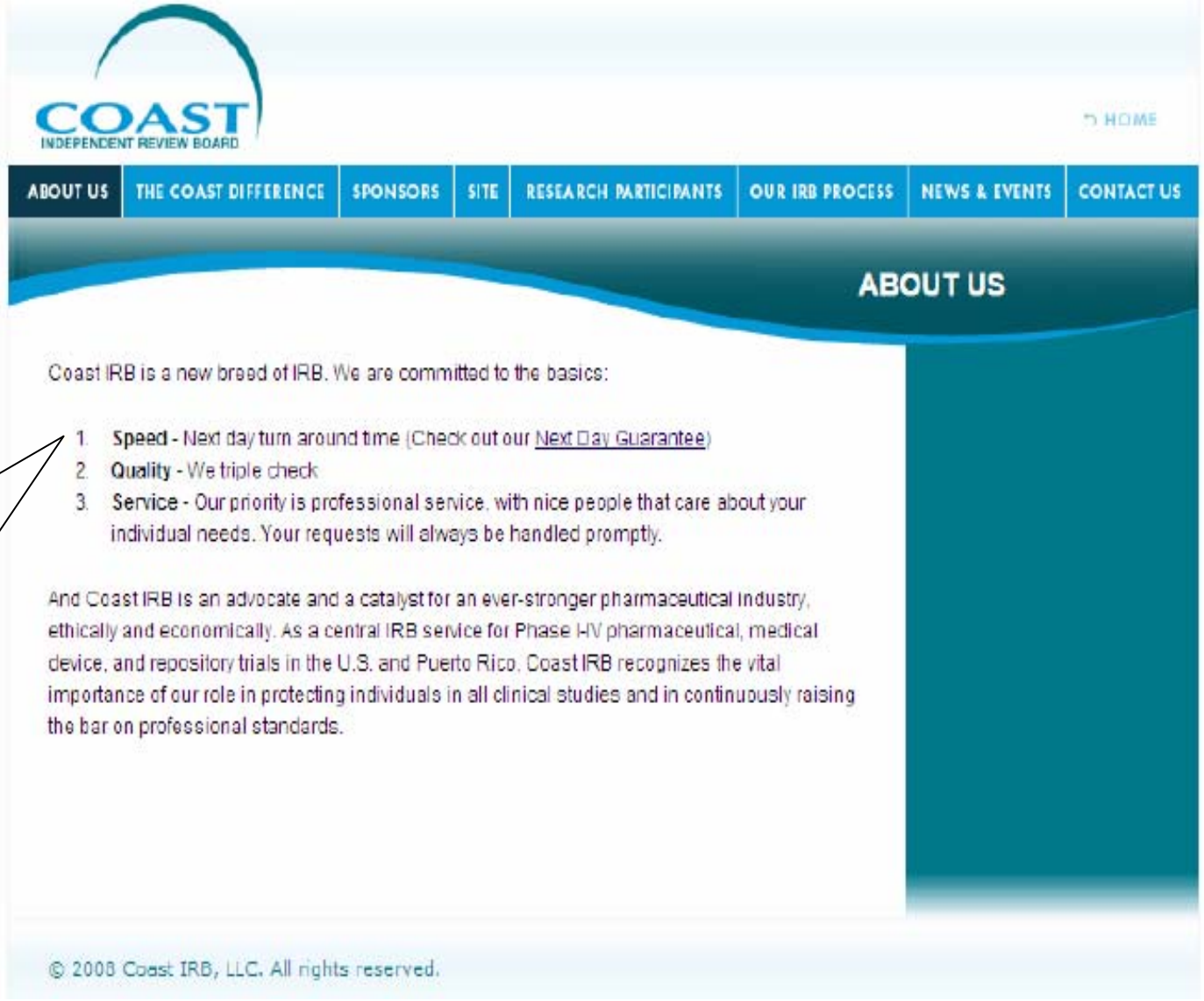
- Investigator deficiencies commonly cited by FDA
  - Failing to obtain consent (beginning research before consent)
  - Failing to ensure continuing review - lapsed IRB approval
  - Failing to follow research plan
    - Inclusion of patients that should be excluded
    - Omissions, modifications, errors
  - Failing to ensure direct oversight over research and safety in human subjects [this has become a focus of recent FDA letters]
  - In responses to FDA, failing to identify changes in specific processes to ensure all ongoing and future studies will be in compliance. FDA will not find sufficient:
    - Promises of more staff and team meetings
    - Too busy with excess reliance on others in “research team”

FDA Warning Letters – Recent Trends

- From Jan. 2002 – Dec. 2006, CDER's Div. of Scientific Investigations (DSI) issued only 12 Warning Letters to clinical investigators (out of 1800 inspections)
- Since Jan. 2007, DSI issued 32 Warning Letters to clinical investigators – including 12 in the first few months of 2009
- DSI has significantly decreased the time it takes to issue WLs to investigators following an inspection (currently an average of 11 months)
- CDER now ranks inadequate supervision of study staff as one of the primary deficiencies of investigators

FDA IRB Enforcement Trends

- FDA Warning Letter to Coast IRB: example
  - (March 11, 2008, Division of Scientific Investigations)
    - Purpose - determine whether IRB was in compliance with regulations governing IRBs and human subjects
    - Investigation focused on expedited review of a human subject recruitment advertisement
    - FDA found that an inexperienced board member conducted expedited reviews and reviewed research under expedited review that did not meet criteria
      - Failed to notify other IRB members of action approved via expedited review
      - Failed to maintain meeting minutes in sufficient detail to indicate action taken by IRB



Note focus on speed

FDA IRB Enforcement Trends, with a Sting

FDA News

FOR IMMEDIATE RELEASE

April 14, 2009

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Imposes Restrictions on Coast IRB due to Violations

The U.S Food and Drug Administration today announced that Coast IRB, LLC of Colorado Springs, Colo., has agreed to voluntarily halt some aspects of its clinical trial oversight operations due to serious concerns about the company's ability to protect human subjects participating in clinical trials.

According to the company's records, these actions may involve approximately 300 active human research studies conducted by some 3,000 clinical investigators.

Until further notice, Coast IRB has agreed to stop reviewing new FDA-regulated studies. Also, Coast IRB will direct clinical investigators in on-going FDA-regulated studies approved by Coast IRB to halt new subject enrollment. FDA has issued a Warning Letter to Coast IRB outlining its concerns and FDA will continue to actively monitor the company and take appropriate action as necessary. These restrictions will remain in effect until the FDA is satisfied that Coast IRB has taken necessary corrective actions that bring it into compliance with FDA regulations designed to protect human research subjects.

Today's actions follow a recent undercover operation by the U.S. Government Accountability Office (GAO). The GAO submitted to Coast IRB for review a fictitious research study involving a purportedly FDA-cleared medical device. Although no human subjects were involved, the GAO operation heightened FDA's concerns about Coast IRB's ability to protect the rights and welfare of human research subjects.

In evaluating the information provided by the GAO investigators, FDA determined that Coast IRB committed several violations of the laws and regulations intended to protect the rights and welfare of human research subjects in clinical trials and that the company failed to perform the robust review needed to approve a study.

FDA Amendments Act of 2007

PUBLIC LAW 110–85–SEPT. 27,2007

Title VIII. Clinical Trial Registry and Results Databases.

A four stage process using the NIH clinicaltrials.gov registry

- Expansion of Registry Data Bank. **Dec 26, 2007**
  - Sponsor must submit data for applicable clinical trials initiated after, or ongoing, on Dec 26, 2007.
- Linking the Registry to Existing Results. **Dec 26, 2007**
- Registry and Results Data Bank. **Sept 27, 2008**
  - Submission of "Basic Results."
  - Existence of agreements with investigators
  - Adverse events. **Sept 27, 2009**
- Expanded Registry and Results Data Bank. **Sept 27, 2010**
  - Expansion by rule making of the results to be disclosed

Clinical Trial Registry and Results Databases

Expanded Registry and Results Databank – Sept. 27, 1010

In preparation for rule making,

- Public meeting held April 20, 2009
  - Federal Register announcement at, http://edocket.access.gpo.gov/2009/E9-6198.htm
  - Transcript at, http://prsinfo.clinicaltrials.gov/public-meeting-april09.html
- Written comments were required to be submitted to the docket by June 22, 2009
  - Docket No. NIH-2009-0002 at http://www.regulations.gov

Clinical Trial Registry and Results Databases

Adverse events disclosure

- If HHS secretary fails to issue regulation by March 2009, default provisions in the Act take effect **September 2009**
- Serious adverse events
  - Table of anticipated and unanticipated SAEs
  - Organ system grouping
  - Number and frequency in each trial arm
- Frequent adverse events
  - Table of anticipated and unanticipated AEs
  - Table of AEs that exceed frequency of 5% in any trial arm
  - Organ system grouping
  - Number and frequency in each trial arm

Clinical Trial Registry and Results Databases

- New public disclosure of adverse events
  - A standardized format that may lead to misuse of comparisons with competitors
- More extensive results disclosure, and possibly full protocol
- Timing of disclosures to media, analysts and market (SEC)
- Contracts with investigators and clinical sites
  - “Who owns the data?” Access to data and restrictions on publication and discussion

Implications of Recent Developments for Manufacturers

Review of internal risks and enhance processes related to:

- Part 54. Disclosure of Payments to investigators
- Federally-mandated disclosure of payments to physicians and many other parties
  - Disclosure risks include accuracy of data and characterization of payments
- Increased scrutiny on patient safety
  - Including selection of and interaction with IRBs
- Much broader disclosure of adverse events as well as study results

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