



U.S. Food and Drug Administration

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# Investigator Responsibilities – Regulation and Clinical Trials

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# Outline

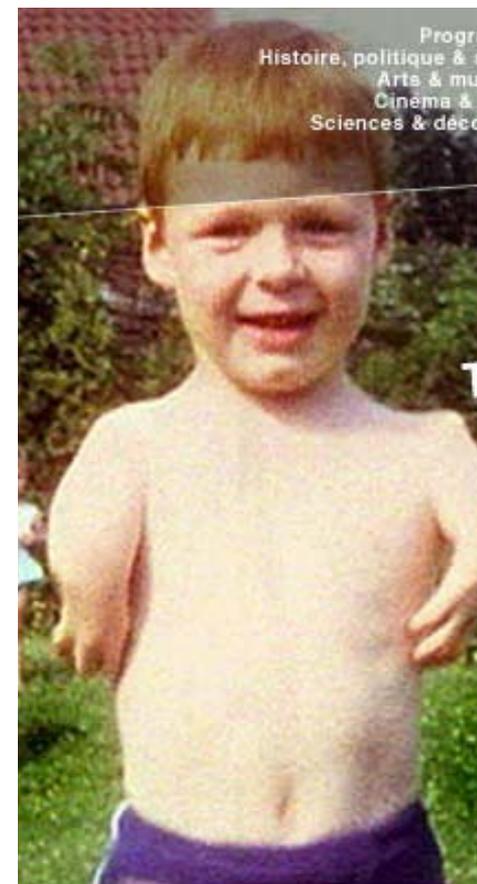
- Historical Perspective on FDA regulation of clinical trials
- Investigator responsibilities
- Case examples and suggestions

# Developing Safe and Effective Drugs

- Approvals are risk-benefit decisions
  - Relying on **data from clinical studies** that are properly designed, conducted, analyzed, and reported to the FDA
  - Relying on **public participation** and public confidence in the clinical trial enterprise
  - Based on FDA's **scientific review** of data collected by clinical investigators and submitted by sponsors

# Historical Perspective

- *1961-1962: Thalidomide tragedy*
  - Drug sold to public as a hypnotic in Europe, but investigational in U.S.
    - “West Germany’s Babysitter”
  - Epidemic of phocomelia
    - More than 10,000 children in 46 countries estimated to have been born with deformities as a consequence
    - 17 children born in America



# Historical Perspective (cont.)

- ***1961-1962: Thalidomide tragedy***

Exposed loopholes in Food, Drug and Cosmetic Act of 1938: Companies could distribute unapproved drugs for experimental purposes

- Did not require notification to patients of investigational status
- Did not require companies or doctors to keep track of distribution
- Did not require FDA to be notified of experimental use
- Did not require records to be kept
- Did not require demonstration of drug effectiveness

# Historical Perspective (cont.)

- ***1962: Kefauver-Harris Amendments***
  - Approval based on demonstration of efficacy as well as safety
  - Expanded inspectional authority - FDA can inspect company records regarding development and clinical testing
  - FDA must be notified before clinical trials could be conducted
  - Rulemaking authority over “Investigational New Drugs”
  - Expansive rulemaking authority over clinical trials
  - Gave FDA to power to halt clinical trials

# Historical Perspective (cont.)

- ***IND Regulations of 1963***
  - Created the current framework of clinical trials
  - Investigations must be “adequate” and “well-controlled”
  - Investigators qualified by scientific training and experience
  - Recordkeeping requirements
  - Informed Consent

# Legal Framework

- **Federal Food, Drug, and Cosmetic Act (FD&C Act)**
  - Section 505(i) is the statutory authority for FDA's oversight of clinical investigations to test safety and effectiveness
- **Code of Federal Regulations (CFR)**
  - Regulations promulgated under Section 505(i) describing FDA's authority over the conduct of clinical investigations including
    - Sponsor Responsibilities
    - Clinical Investigator Responsibilities
- **Guidance** – advisory only, to assist clinical investigators and sponsors in complying with the regulations
- **FDA Form 1572** – by signing this form, an investigator agrees to conduct a study in accordance with the protocol and applicable regulations and to provide adequate supervision of a study

# Who is responsible for high quality research?

*Academic institution*

**Study Coordinator**

**Sponsor-investigator**

**Vendor**

**Bioequivalence study**

**CONTRACT  
RESEARCH  
ORGANIZATION**

*Regulators*

**Clinical Investigator**

*Study Subject*

**Contract Laboratory**

**Study nurse**

**SPONSOR**

**Sub-investigator**

**GLP Facility**

**Institutional Review Board**

# Which entities are directly regulated and inspected by FDA?

**Sponsor–investigator**

**Bioequivalence study**

**Clinical Investigator**

**SPONSOR**

**GLP Facility**

**CONTRACT  
RESEARCH  
ORGANIZATION**

**Institutional Review Board**

# Important Caveat for Clinical Investigators

Standards for clinical care of patients

≠

Standards for academic research

≠

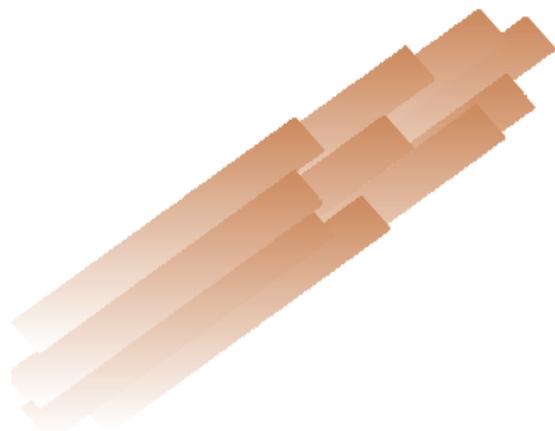
Standards for FDA regulated research

# Role of Clinical Investigators

- Good Clinical Practice (GCP) in FDA-regulated research is not the same as good clinical practice in caring for patients
  - For example, FDA regulations have very specific requirements for following the protocol, recordkeeping, and drug accountability
- Regulations are designed to
  - Ensure the **quality and integrity of data** collected in clinical trials
  - Ensure that the **rights, safety and welfare of research participants** are protected

## Guidance for Industry

### E6 Good Clinical Practice: Consolidated Guidance



ICH  
April 1996

## Good Clinical Practice

**(GCP):** A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>

# Who's in charge at the study site?

- **Good News:** Clinical investigators are in charge
- **Bad News:** Clinical investigators are in charge **and** held accountable
  - FDA regulations permit sponsors to delegate their responsibilities to Contract Research Organizations (CROs) but do **not** permit clinical investigators to delegate their general responsibilities to CROs or site management organizations, subinvestigators, or study staff
- **Penalties** for significant noncompliance
  - Warning Letters (posted on FDA website)
  - Disqualifications/Restrictions/Debarments (posted on FDA website)
  - Criminal prosecutions/prison/fines

# The Clinical Investigator

- An individual **who actually conducts a study** (i.e. under whose immediate direction the drug is dispensed to a subject.)
- In the event an investigation is conducted by a team of individuals, the investigator is **the responsible leader** of the team.

[21 CFR 312.3]

# Sponsor-Investigator

- An individual who **both initiates and conducts an investigation**, and under whose immediate direction the investigational drug is administered or dispensed.
- The term does not include any person other than an individual.
- The **requirements applicable to a sponsor-investigator** under this part include **both those applicable to an investigator and a sponsor.**

[21 CFR 312.3]

# Commitments on Form 1572

- Personally conduct or supervise investigation
- Follow protocol
- Ensure all persons assisting in study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64)
- Maintain adequate and accurate records and make them available for inspection in accordance with 21 CFR 312.68
- Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards
- Comply with other requirements in 21 CFR 312

# Investigator Responsibilities

- General responsibilities (312.60)
- Control of investigational drug (312.61)
- Record keeping and retention (312.62)
  - An investigator is responsible for:
    - Maintaining adequate records of the disposition of the drug
    - Accurate case histories that record all observations, and
    - Other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation
  - An investigator is required to maintain investigation records for:
    - 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated
    - 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not approved for such indication

# Investigator Responsibilities (cont.)

- Investigator reports (312.64)
  - Progress reports
  - Safety reports
    - Promptly report any adverse event that may reasonably be regarded as caused by, or probably caused by, the drug (err on the side of reporting)
    - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
  - Final report
  - Financial disclosure

# Investigator Disqualification

- 21 CFR 312.70
  - Repeated and deliberate failure to comply with the requirements
  - FDA provides notice of matter to investigator and provides opportunity to explain (informal hearing)
  - Opportunity for formal hearing
  - May result in ineligibility to receive investigational drugs

# Sponsor Responsibilities

- Sponsors are responsible for (312.50):
  - Selecting qualified investigators
  - Providing them with the information they need to conduct the investigation properly
  - Ensuring proper monitoring of the investigation
  - Ensuring that the investigation is conducted in accordance with the general investigational plan
  - Maintaining an effective IND
  - Ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks

# FDA Guidance on Investigator Responsibilities\*

- Outlines FDA expectations for study oversight
  - Appropriate **delegation** of study tasks
  - Appropriate **training** of study staff
  - Appropriate **supervision** of conduct of ongoing study
  - Appropriate **oversight of third parties** involved in the study (e.g. Site Management Organizations, outside labs specifically retained to conduct study assessments)

\*<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>

# FDA Guidance on Investigator Responsibilities (cont.)

- Outlines FDA expectations for protecting the rights, safety, and welfare of subjects
  - Provision of reasonable medical care for issues related to study participation (e.g. to manage an adverse event)
  - Facilitation of care for other health issues that might arise during the study
  - Avoiding exposure of subjects to unreasonable risks

# FDA Review Responsibilities

- FDA's primary objectives in reviewing an IND are:
  - In all phases of investigation, to ensure the safety and rights of participants
  - In phase 2 and 3, to help ensure that the quality of the scientific evaluation of the drug is adequate to permit an evaluation of the safety and effectiveness
- FDA will review:
  - The original IND submission (312.23)
  - Information amendments (312.31)
  - IND Safety Reports (312.32)
  - IND Annual Reports (312.33)

# FDA Clinical Hold (312.42)

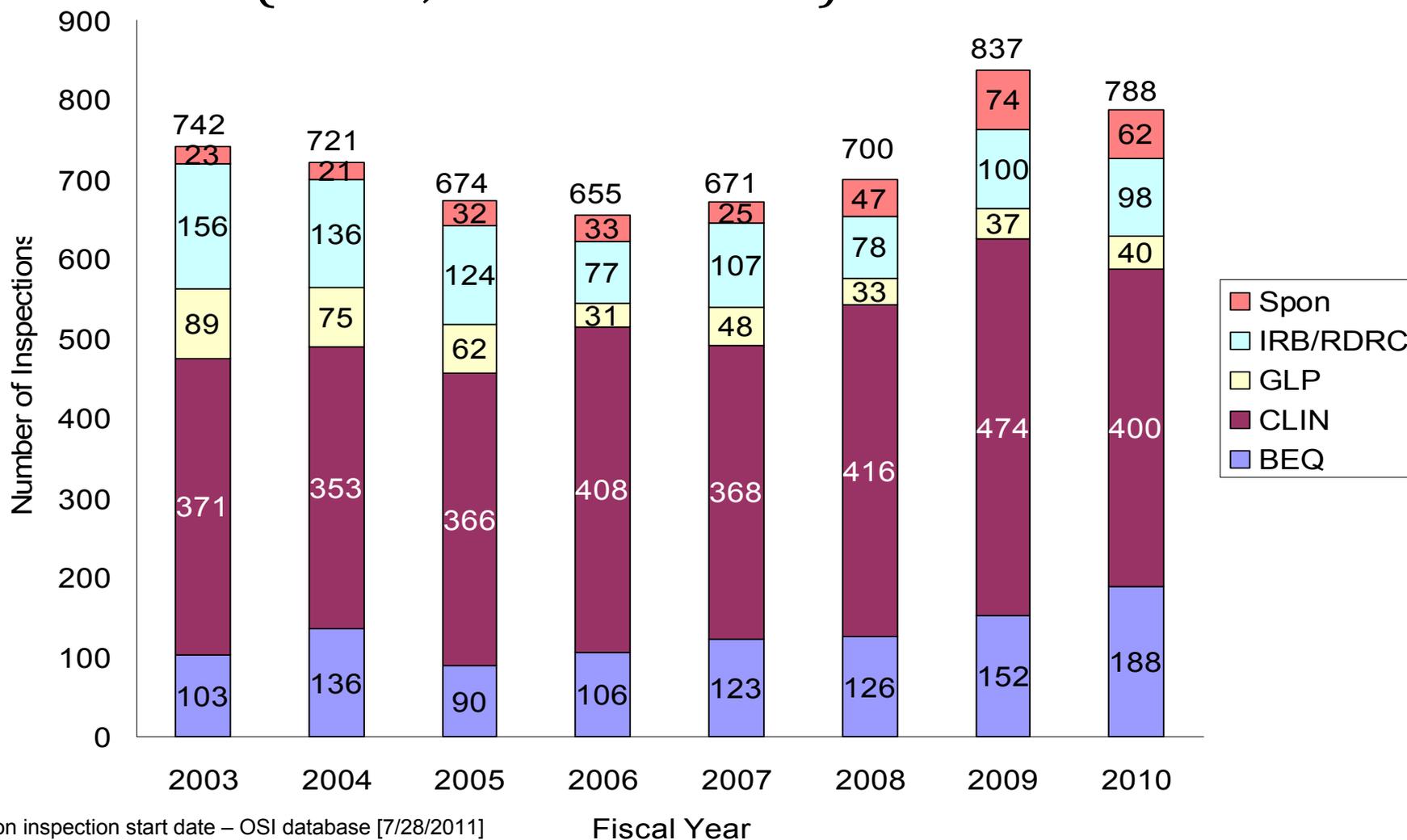
Situations that can prompt FDA to place a proposed or ongoing clinical trial on hold include:

- Unreasonable and significant risk of illness or injury (any phase)
- Clinical investigators are not qualified by scientific training or experience (any phase)
- Investigator brochure is misleading, erroneous, or materially incomplete (any phase)
- IND does not contain sufficient information to assess risks to subjects (any phase)
- Plan or protocol is clearly deficient to meet its stated objectives (phase 2 or 3)

# FDA Bioresearch Monitoring Program

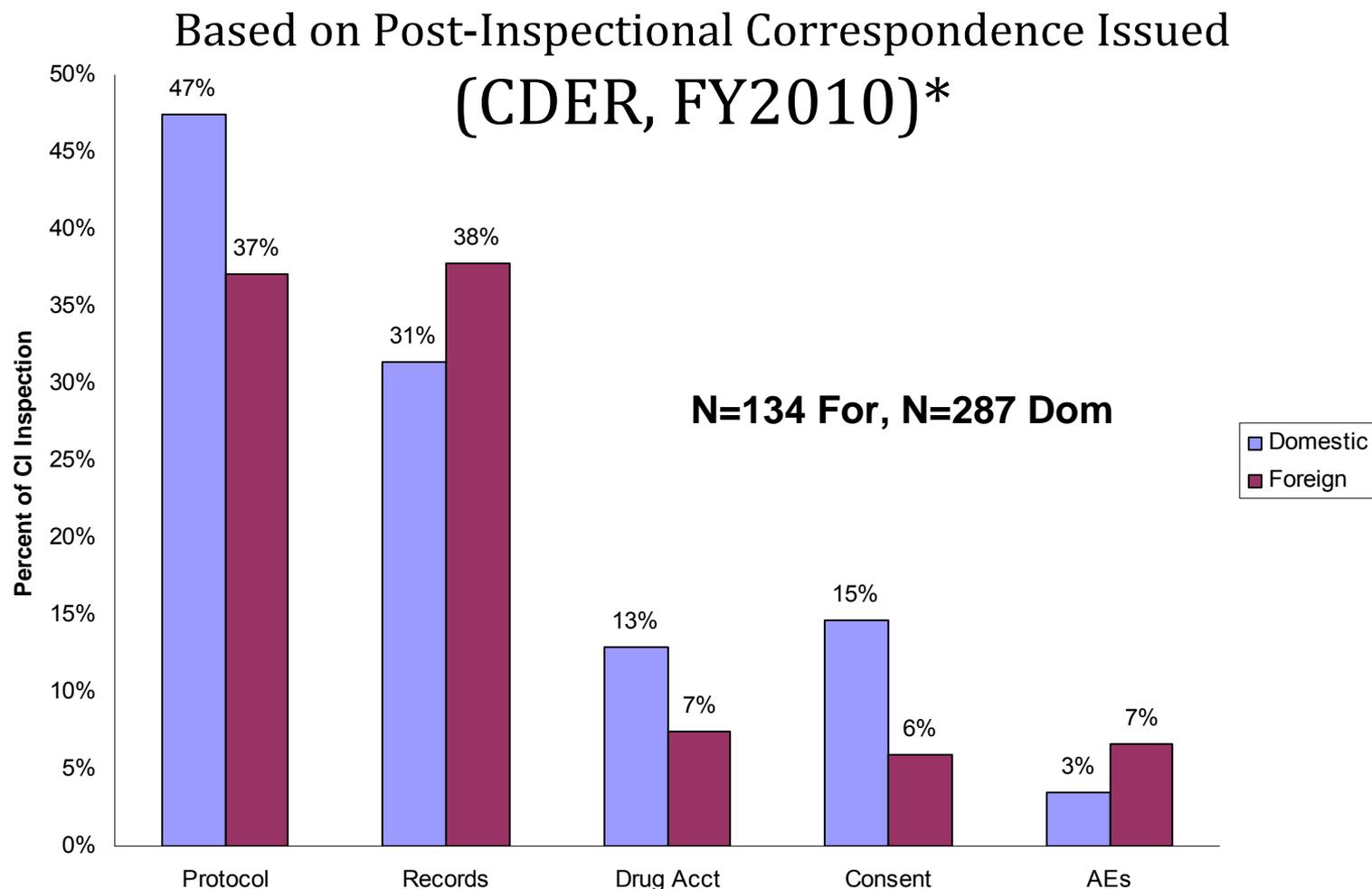
- Inspections of clinical investigators, sponsors, IRBs, GLP facilities and Bioequivalence studies
  - Investigator shall permit the FDA to have access to, and copy and verify any records or reports made by the investigator (312.68)
- Types of inspection
  - Data validation in support of new drug application
  - For cause (complaint)
  - Surveillance

# Bioresearch Monitoring Program Inspections\* (CDER, FY 2003-2010)



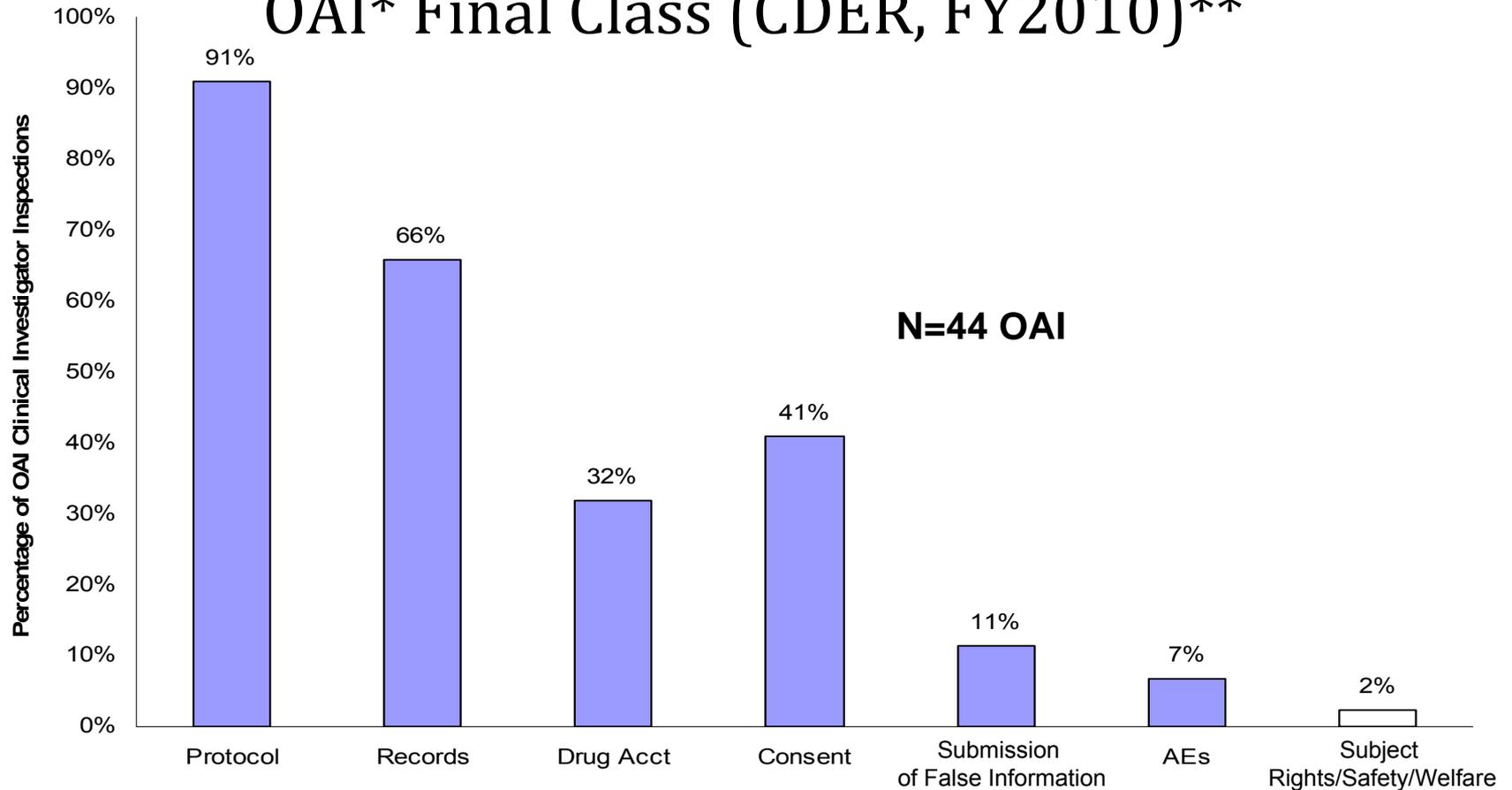
\*Based on inspection start date – OSI database [7/28/2011]

# Frequency of Clinical Investigator Related Deficiencies



\*Based on letter issue date; Inspections may have multiple deficiencies, [7/28/2011]

# Frequency of Clinical Investigator Related Deficiencies Based on Post-Inspectional Correspondence Issued: OAI\* Final Class (CDER, FY2010)\*\*



\*OAI: Denotes Official Action Indicated (significant deficiencies found)

\*\*Based on letter issue date; Inspections may have multiple deficiencies, Includes OAI untitled letters, [7/28/2011]

# Common mistakes – Risk factors for non-compliance

- Poor supervision and training of study staff
- Insufficient investigator involvement in study conduct
- Inappropriate delegation of study tasks to unqualified persons
- Failure to adequately protect study subjects
- Overworked investigator and study staff (e.g. too many subjects, complex study with large data collection, too many concurrent studies)

# Case #1 G

# The New York Times

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SUNDAY, FEBRUARY 6, 2005

## Abuses Endangered Veterans In Cancer Drug Experiments

By DEBORAH SONTAG

ALBANY — Carl M. Steubing, a decorated Battle of the Bulge veteran whose experience of war made him a pacifist but also instilled in him a zest for living life at full tilt, took his diagnosis of gastroesophageal cancer in 2001 as a challenge.

With a thatch of white hair and a rich baritone voice, Mr. Steubing, at 78, was not ready to succumb to illness. A retired music educator and wedding photographer, he remained active as a church choir director, expert cook, painter, golfer and fisherman. He was married to a woman 24 years his junior, and they had seven children and three grandchildren between them.

Mr. Steubing jumped at the chance to participate in an experimental drug study at the Stratton Veterans Affairs Medical Center in Albany, believing it offered him the hope of surviving longer. The research coordinator, Paul H. Kornak, told Mr. Steubing that he was "just a perfect specimen," with the body of a man half his age, according to Jayne Steubing, Mr. Steubing's widow.

He was not, though. Because of a previous cancer and poor kidney function, Mr. Steubing was not even eligible to participate in the experiment, according to government documents. Mr. Kornak, however, brushed that obstacle aside. He altered Mr. Steubing's



Paul H. Kornak, who posed as a doctor for veterans, in 1999.

### IN HARM'S WAY

Research, Fraud and the V.A.

medical records, according to prosecutors, and enrolled him in the study. He also posed as a doctor.

In 2001, Mr. Steubing endured about six periodic treatments with an aggressive three-drug chemotherapy combination. Each infusion made him violently ill and forced his hospitalization. He died in March 2002.

Last month, at the federal courthouse in Albany, Mrs. Steubing glared at Mr. Kornak, 53, as he pleaded guilty to fraud, making false statements and criminally negligent homicide in the death of an Air Force veteran, James DiGeorgio. When Mr. Kornak admitted to falsifying the medical data of "subject initials CMS" — Carl M. Steubing — Mrs. Steubing's face crumpled.

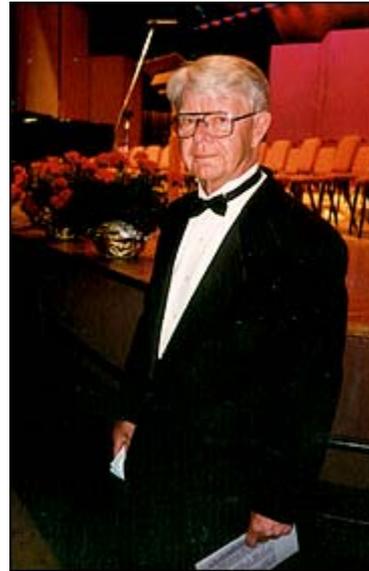
Mr. Kornak, who is scheduled to be sentenced in May, also agreed to cooperate in a widening investigation of the hospital's cancer research program. From 1999 to 2003, when he worked there, scores of veterans were, at the least, put at risk. But allegations of carelessness, fraud and patient abuse in the hospital's cancer research program predated Mr. Kornak, and employees say that administrators not only dismissed their concerns, but harassed them for standing up for the veterans.

"Research violations were a way of life at Stratton for 10 years," said Jeffrey Fudin, a pharmacist at the hospital. "Stratton officials turned a blind eye to unethical cancer research practices and punished those who spoke out against them. The whole Kornak episode could have been prevented."

According to Mr. Kornak's lawyer, E. Stewart Jones, there was a "clear systems failure," permitting a research culture where "rules weren't followed, protocols weren't applied and supervision was nonexistent."

It was also a culture whose de-

Continued on Page 18



### Routine Visit Leads to an Inquiry

In December 2001, a clinical research associate for Ilex Oncology made a routine visit to the Albany veterans' hospital, where Ilex was sponsoring a bladder cancer study.

Ilex, a cancer drug company, was offering the Albany research program \$2,500 for each study subject. Such payments are a standard practice, and many researchers say that they barely cover the cost of conducting the studies. Critics of drug-testing practices, however, consider the payments a threat to scientific integrity.

Ilex's research associate discovered some paperwork that raised suspicions, according to Caren Arnstein, a spokeswoman for the Genzyme Corporation, which bought Ilex at the end of last year.

"Things about the dates didn't look right," Ms. Arnstein said. "If the results of a pathology report for a biopsy are dated prior to the biopsy being taken — something seemed off."

The discrepancies led to an audit by Ilex. In the spring of 2002, the Albany hospital began an internal review of the cancer research program, eventually referring the matter to the inspector general, according to The Times Union.

Ilex shut down the Albany study and alerted the F.D.A. The agency had also received another complaint, an F.D.A. official said.

In September, however, the Food and Drug Administration started proceedings to disqualify Dr. Holland from conducting further clinical research because he had "failed to protect" subjects under his care in Albany.

According to the F.D.A., patients' medical records were altered in at least five experimental drug studies, enabling veterans like Mr. Steubing to be enrolled in studies for which they were either too sick or too healthy to qualify. A patient with coronary disease, for instance, was enrolled in a study that excluded heart patients because of a risk of hemorrhages. A patient with impaired renal function was administered a drug toxic to kidneys that probably contributed to his death, the agency said.

# Case #1: Lax Supervision

- Study coordinator enrolled ineligible subjects in oncology trials
- Coordinator altered source records and created fraudulent CRFs to make subjects appear eligible
- Data manipulations should have been apparent to attentive clinician
- Subject who was ineligible due to poor renal and liver function was enrolled, dosed, and died as a result
- Study coordinator sentence to 71 months in prison and debarred from many future involvement in FDA regulated research
- Dr. Holland – 5 years probation, \$500k restitution to defrauded drug companies, disqualified

# Case#2

The United States Attorney's Office  
Eastern District of Louisiana

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**JAILED PSYCHIATRIST PLEADS GUILTY AND IS SENTENCED ON CHARGES OF FALSIFIED RECORDS OF CLINICAL TRIALS INVOLVING CHILDREN**

August 19, 2010

**FOR IMMEDIATE RELEASE**

**DR. MARIA CARMEN PALAZZO**, age 58, pled guilty in federal court today before U. S. District Judge Mary Ann Vial Lemmon to fifteen (15) counts of failing to prepare and maintain records, with intent to defraud and mislead, in connection with clinical trials to evaluate the efficacy and safety of Paxil in children and adolescents with Obsessive-Compulsive Disorder (OCD), announced U. S. Attorney Jim Letten.

According to court documents, **PALAZZO**, who specialized in psychiatry, was a clinical investigator for SmithKline Beecham d/b/a GlaxoSmithKline, who was involved in two clinical trials evaluating Paxil's safety and effectiveness in children and adolescents. One of the clinical trials included 150 children and adolescents with OCD. Palazzo prepared multiple psychiatric evaluations on study patients which contained different diagnoses and treatment plans; reported symptoms of OCD when **PALAZZO** knew that the study subject did not demonstrate such symptoms; and reported that Paxil was effective in treating OCD when it was not.

**PALAZZO** is currently serving an 87 month prison sentence after being convicted of 39 counts of health care fraud following a 2008 conviction. In addition, she was sentenced to 18 months of imprisonment and 3 years of supervised release under federal supervision and risk additional imprisonment should she violate any rules of the release. Additionally, she was ordered to pay restitution to SmithKline in the amount of \$25,000 and to forfeit her personal assets.

U.S. Attorney's Office  
Eastern District of Louisiana  
500 Poydras St  
Suite 210-B  
New Orleans, Louisiana 70130  
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**DR. P, age 58, pled guilty in federal court today before U. S. District Judge to fifteen (15) counts of failing to prepare and maintain records, with intent to defraud and mislead, in connection with clinical trials to evaluate the efficacy and safety of Paxil in children and adolescents with Obsessive-Compulsive Disorder (OCD)...**

## Case #2 (cont.)

- “The defendant agreed to conduct Studies 704 and 716 **in accordance with the protocol** and to only make changes in the protocol after notifying the sponsor or, if necessary, for the safety of a study subject.
- The defendant also agreed to **personally conduct or supervise the investigation and to maintain adequate and accurate records** in accordance with 21 CFR §312.62, and to comply with all other obligations of clinical investigators found in 21 CFR §312.
- At the bottom of each **Form 1572** was a warning that statements on the form had to be truthful and if found not to be, could result in a prosecution for false statements to a government agency.”

## Case #2 (cont.)

- Study records indicated that Dr. P
  - **included psychiatric diagnoses inconsistent with patients' psychiatric histories;**
  - **prepared multiple psychiatric evaluations on study patients which contained different diagnoses and treatment plans;**
  - **reported symptoms of OCD when the study subject did not demonstrate such symptoms; and**
  - **examined study subjects when she had not.**
- Sentenced **to thirteen (13) months in prison** to run concurrent to the previous sentence for health care fraud, as well as serve one (1) year of supervised release
- Ordered to pay restitution to sponsor in the amount of \$91,824 and \$1,500 in special assessments.

# How can clinical investigators ensure high quality data and subject safety?

- Build quality into conduct of the study
  - Create systems that limit opportunity for errors
  - Simplify protocol and outcomes assessments
  - Standardize systems and formats where possible, use validated instruments and definitions
  - Keep protocol amendments to a minimum and check CRFs and consent forms against each change
  - Insist on training and then test it, do beta tests/dry runs
  - Have a disaster plan, e.g. back ups if key study staff leave or site experiences flood or disaster

# How can clinical investigators ensure high quality data and subject safety? (cont.)

- Select qualified staff and ensure adequate training and supervision
  - Ensure staff are not performing tasks they are not qualified to do (e.g. assessing eligibility, performing physical exams, assessing AEs)
  - Ensure oversight of subinvestigators and study staff

# How can clinical investigators ensure high quality data and subject safety? (cont.)

- Fully understand scope of responsibilities
  - Ensure protocol is consistent with best interests of patients and allows adequate monitoring for subject safety
  - Assess ability to comply with protocol visits; laboratory testing; electronic systems for data capture, archiving and transmission to sponsor; maintaining records, drug accountability, inspections by FDA

## How can clinical investigators ensure high quality data and subject safety? (cont.)

- Implement system to detect and correct errors in real time
  - Pay attention to monitoring queries and respond promptly
  - Audit trail of changes should make clear what was changed, who changed it, and why it was changed
  - Evaluate need for system wide corrections and training

# Key Messages

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practices (GCP) in research
  - Ensure that all staff have a clear understanding of responsibilities under FDA regulations
- At stake is public confidence and participation in the clinical trials and ultimately the availability of safe and effective products

# Contacts

- FDA—Running Clinical Trials

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>

- Good Clinical Practice Contacts

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134476.htm#bio>

- IND/IDE Contacts

<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134493.htm>

- Office of Scientific Investigations

<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm>

- Office of Critical Path Programs

<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>

- Office of Human Research Protections

<http://www.hhs.gov/ohrp/>

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## Office of Scientific Investigations

### The goals of OSI are to:

- To verify the integrity of efficacy and safety data submitted to the FDA in support of new drug applications.
- To assure that the rights and welfare of human research subjects are protected.

### OSI Accomplishes this by:

- Auditing and verifying clinical trial data submitted to the FDA in support of applications to demonstrate the safety and efficacy, or bioequivalence, of drugs for human use;
- Directing inspections of Institutional Review Boards (IRBs) for compliance with standards and regulations designed to protect the rights and welfare of human research subjects; and
- Ensuring that investigators, sponsors, and contract research organizations who conduct nonclinical and clinical studies on investigational new drugs comply with United States laws and regulations covering good clinical practice and good laboratory practice.

### In the News

- [FDA, international counterparts report progress on drug inspection collaboration \(August 2, 2011\)](#)
- [FDA Notifies Pharmaceutical Companies that Contract Testing Conducted by Cetero Research May Require Reevaluation \(July 26, 2011\)](#)
- [OSI Warning Letters \(May 26, 2011\)](#)
- [OSI Metrics Overview \(May 26, 2011\)](#)
- [Important Notice to IRBs Reviewing FDA-Regulated Research \(January 27, 2011\)](#)
- [FDA proposes changes to the informed consent elements \(December 29, 2009\)](#)
- [FDA, European Medicines Agency Launch Good Clinical Practices Initiative \(August 3, 2009\)](#)
- [Previous OSI News](#)

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- [Bioresearch Monitoring Program \(BIMO\)](#)
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