CDER's Role in FDA's Bioresearch Monitoring Program and Human Subject Protection

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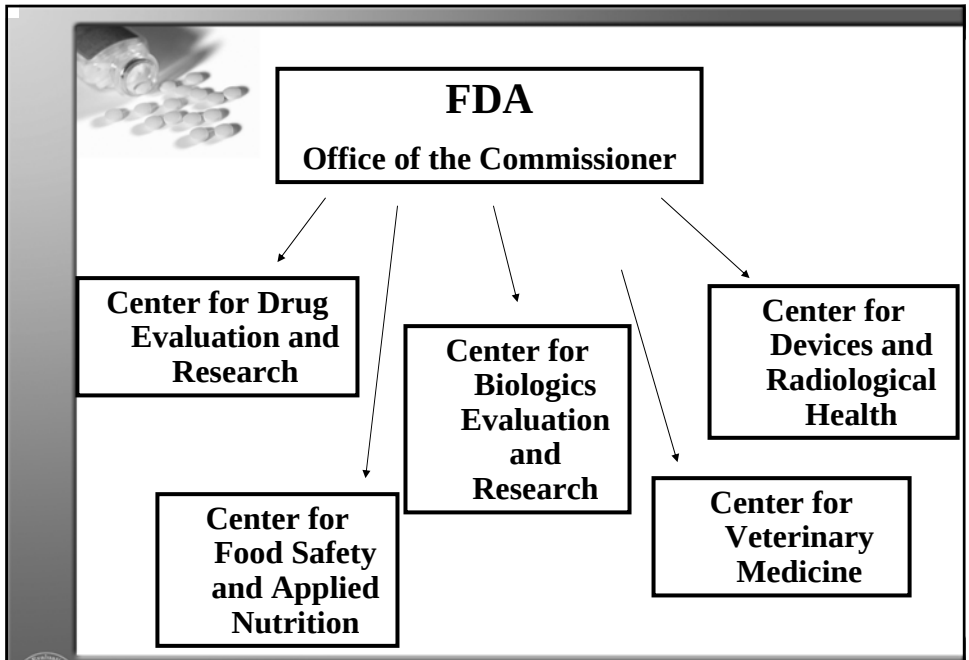
CDER's role in Bioresearch Monitoring and Human Subject Protections: Objectives

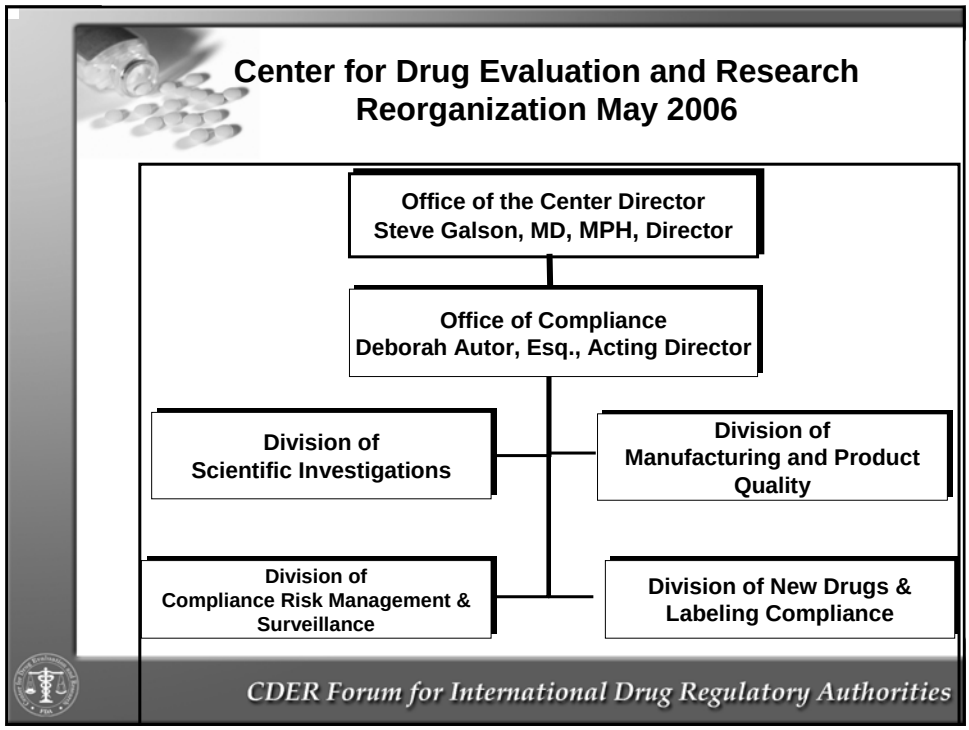
- What we do
  - Data Integrity
  - Compliance with Good Clinical Practice
  - Human Subject Protections
- Special issues in clinical studies conducted internationally
- What we find
  - Inspection metrics
  - Case studies

FDA's Jurisdiction

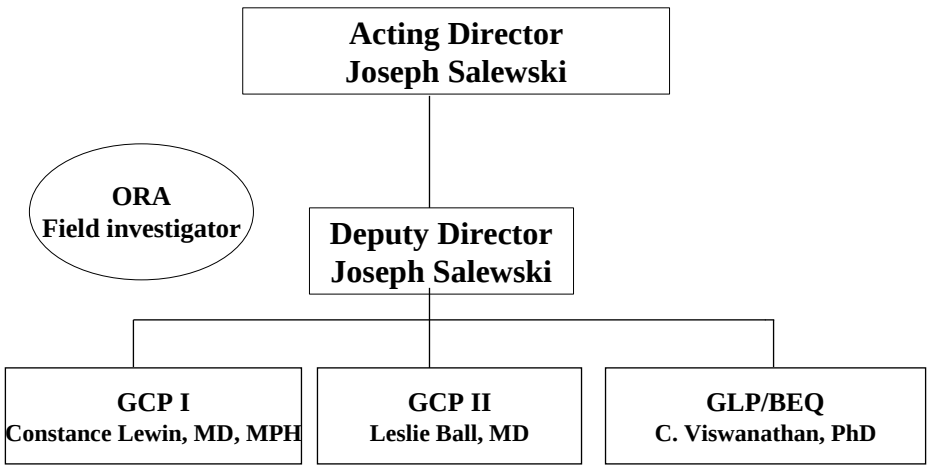
- Under Section 505 of the Federal FD&C Act
  - an FDA-approved marketing or research permit is required before new drugs, medical devices, food additives, etc. may move in interstate commerce
- FDA oversight on research studies conducted under an Investigational New Drug (IND) application, or studies that should be conducted under an IND
  - Clinical investigations of a marketed product may be exempt from an IND [21 CFR 312.2(b)]



CDER Forum for International Drug Regulatory Authorities



Division of Scientific Investigations (DSI)



Human Research Protections

- Apply at every stage of clinical research
  - Preclinical/laboratory studies
  - Development of protocol
  - Study review and oversight
  - Conduct of the clinical study
- Applies to all involved with clinical research, including the clinical investigator, sponsor/monitor, study staff, IRB, FDA, etc.

Good Clinical Practice

- Not specifically defined in FDA regulations
- ICH E6: Guideline for Good Clinical Practice (1.24)
  - *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.*

CDER's Bioresearch Monitoring (BIMO) Inspection Programs

- Clinical Investigators
- Sponsor/Monitor/CRO
- IRB/RDRC
- Bioequivalence/Good Laboratory Practice

Goals of BIMO

- Validity of data from studies in support of pending marketing applications
- Adherence to FDA GCP regulations
- Whether the rights and safety of subjects have been protected

FDA/CDER GCP Regulations

Applies to:	**Clinical research involving products regulated by FDA**
Regulatory oversight	**IRBs, Sponsors, CRO/Monitors, Clinical Investigators**
Relevant CFR include (but not limited to)	**21 CFR 50, 56** **■Part 50: Protection of Human Subjects** **■Part 56: IRBs** **21 CFR 312 (IND)** **21 CFR 314 (NDA)**
Penalties for non-compliance include (but not limited to)	**IRBs: 21 CFR 56.120, 56.121 (lesser administrative actions, Disqualification)** **Sponsors: Rejection of data; Clinical Holds; Termination of IND; Application Integrity Policy** **CI: Warning Letters, NIDPOE, Disqualification, Debarment**

What we do in CDER/DSI (cont.)

- **For the Review Divisions**
  - DSI will arrange for routine data audit GCP inspections to determine data integrity and safety of subjects in pivotal clinical trials, and provide the inspection reports to the review division prior to the Division Action Goal Date
- **For the Public**
  - DSI will investigate complaints related to the conduct of clinical trials, including arranging for directed or "for cause" inspections, and take appropriate regulatory action
  - DSI will arrange for routine surveillance inspections of IRBs to determine if rights, safety, and welfare of human subjects are protected

What we do in CDER/DSI/GCP

- Issue assignments to Office of Regulatory Affairs (ORA) field investigators and participating on inspection when scientific or medical expertise is required
- Evaluate the results of inspections from a scientific and regulatory perspective.

What we do in CDER/DSI/GCP (cont.)

- Recommend scientific follow-up
- Recommend and implement regulatory actions
- Provide expert advice on program design, policy issues and guidance
- Educate and informing program constituents

How Does CDER Assess Compliance with GCP?

Specific Responsibilities of Sponsors, IRB's and Clinical Investigators

Sponsor Responsibilities (21 CFR 312.50-312.58)

- General and Specific Responsibilities of Sponsors include:
  - Select qualified investigators
  - Provide information with the information they need to conduct an investigation properly
  - Ensure that the investigation(s) is conducted in accordance with the protocol(s)
  - Maintain an effective IND for the investigations
  - Ensure that FDA and participating investigators are promptly informed of significant new adverse events or risks with the drug

Protection of Human Subjects (21 CFR Part 50)

Part 50: Informed consent and research involving children

- Informed consent is a responsibility of Clinical Investigators under 21 CFR 312.60
- General requirements for IC (21 CFR 50.20)
  - Must have consent (exceptions specified)
  - Seek consent only when subject has the opportunity to decide
  - Must be in understandable language, no waiver of legal rights
- Exceptions specified (21 CFR 50.23 and 50.24)
  - Life threatening situation
  - Presidential waiver related to particular military operation
  - 50.24 Emergency Research

IRB Responsibilities (21 CFR Part 56)

- Standards for composition, operation, and responsibilities of IRB that reviews clinical investigations regulated by FDA
- Note: CI responsibilities relevant to IRBs:
  - CI's required to meet requirements of Part 56 (21 CFR 312.60)
  - Assurance of IRB review (21 CFR 312.66)

IRB Responsibilities (21 CFR Part 56 - cont.)

- IRB membership (21 CFR 56.107)
- IRB functions (21 CFR 56.108, 56.115)
  - Written procedures
  - Reporting to IRB and FDA of unanticipated problems, non-compliance
  - Determine risks to subjects are minimized an reasonable in relation to benefits to subjects (if any) and knowledge gained
  - Equitable subject selection
  - Keep records, minutes, correspondence available for inspection by FDA
- FDA may refuse to consider an investigation in research or marketing application if the IRB refuses the inspection

Clinical Investigator Responsibilities (21 CFR 312.60)

- Ensure research is conducted according to protocol
- Protect the rights, safety and welfare of subjects under the investigator's care
- Ensure control of drugs under investigation (21 CFR 312.61, 62, 63)
- Obtain consent of each human subject to whom drug is administered under Part 50 (exceptions at 50.23 and 50.24)

Clinical Investigator Responsibilities (21 CFR 312.60 - cont.)

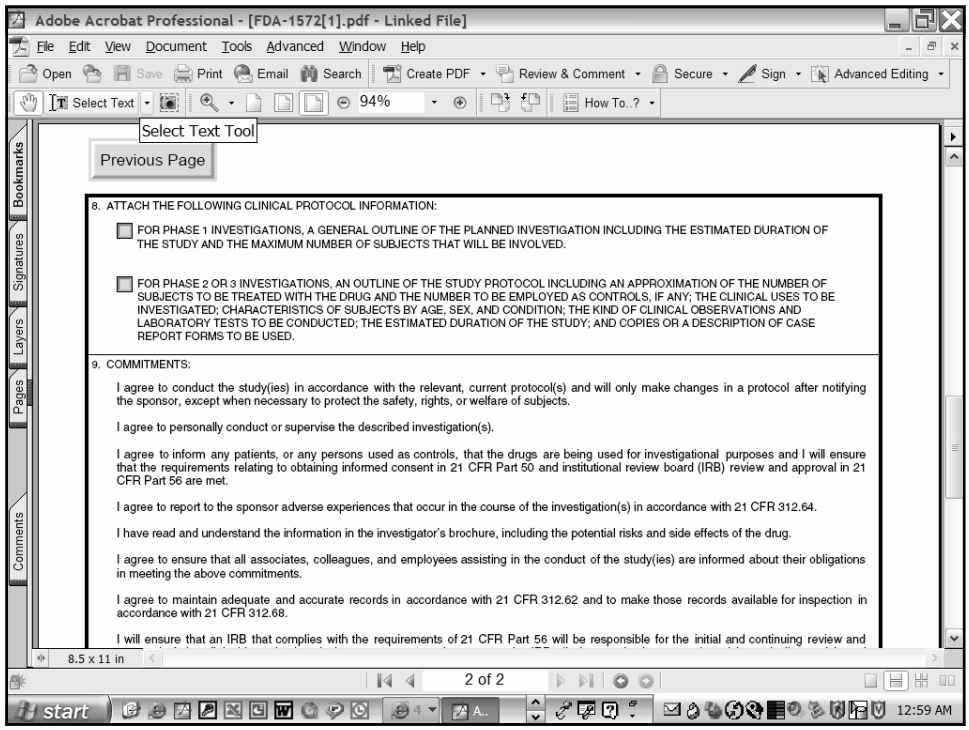
- 21 CFR 312.61 (Control of investigational drug)
- 21 CFR 312.62 (Investigator record keeping and retention)
- 21 CFR 312.64 (Investigator reports)
- 21 CFR 312.66 (IRB review)
- 21 CFR 312.68 (Inspection of records)
- 21 CFR 312.69 (Handling of controlled substances)
- 21 CFR 312.70 (Disqualification of clinical investigators)

Clinical Investigator Responsibilities: Form FDA 1572

- Names of sub-investigators who will be assisting in the conduct of investigation
- **Commitment to:**
  - Follow current protocol
  - Personally conduct or supervise investigation
  - Ensure all persons assisting in study are informed of obligations
  - Inform subjects of investigational drugs and 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)

Clinical Investigator Responsibilities Form 1572 (cont.)

- **Commitment to:**
  - Inform associates in conduct of study
  - Maintain adequate and accurate records and make available for inspection (21 CFR 312.68)
  - Ensure initial and continuing review by IRB, report all changes to research and unanticipated problems involving risks to subjects, and not make changes without IRB approval except where necessary to eliminate immediate hazards to subjects
  - Comply with other requirements in 21 CFR 312



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FDA Regulations Regarding Foreign Clinical Trial Data

- Contribution of non-U.S. data to FDA applications continues to increase
- FDA sets conditions under which such data can be used in support of research or marketing in U.S.
  - Foreign studies conducted under IND
  - Not conducted under an IND, but meeting criteria specified in FDA regulations.

FDA Regulations Regarding Foreign Clinical Trial Data (2)

- Conducted under U.S. IND
  - Must meet same requirements of 21 CFR 312
- FDA may accept foreign studies NOT conducted under IND if the studies are:
  - Well designed
  - Well conducted
  - Performed by qualified investigators
  - Conducted in accordance with ethical principles acceptable to the world community (Declaration of Helsinki [DOH] or laws and regulations of country where research is conducted--whichever represents greater protection)

[21 CFR 312.2120(a)]

FDA Regulations Regarding Foreign Clinical Trial Data (3)

21 CFR 312(b): Data Submissions

- Sponsor who wishes to rely on a foreign clinical study to support IND or application for marketing approval shall submit to FDA
  - Description of investigator's qualifications
  - Description of research facilities
  - Detailed summary of protocol and results of study, and should FDA request, case records maintained by the investigator
  - Description drug product, including components, formulation, specifications and bioavailability, if available
  - If study intended to support effectiveness, information showing study is adequate and well controlled under 21 CFR 314.26

FDA Regulations Regarding Foreign Clinical Trial Data (4)

- Proposed Rule: Human Subject Protection; Foreign Clinical Studies Not Conducted Under IND; published June 10, 2004
  - http://www.fda.gov/OHRMS/DOCKETS/98fr/04-13063.pdf
  - Comment period closed September 8, 2004
  - GCP principles underlie new criteria
    - Protection of study participants
    - Quality and integrity of data
  - Reflects FDA interest to achieve GCP globally

FDA Regulations Regarding Foreign Clinical Trial Data (5)

- Proposed Rule (cont.)
  - Proposes to replace requirement that such studies be conducted in accordance with DOH with requirement that the studies be conducted in accordance with GCP, including review and approval by an independent ethics committee (EIC).

FDA Regulations Regarding Foreign Clinical Trial Data (6)

- Proposed rule (cont.)
  - Why is FDA proposing to replace DOH as basis for assessing foreign studies?
    - FDA determined that it cannot require adherence to an external statement that could be changed in ways that would be incompatible with our regulations and policies
    - GCP provides broader and more detailed attention to quality of study conduct as well as ethical principles
    - ICH GCP document explicitly notes that the principles it articulates “have their origin in DOH.”

FDA Regulations Regarding Foreign Clinical Trial Data (7)

- Proposed rule (cont.)
  - Required documentation under proposed regulation
    - Same items as 312.120 (b) (1) thru (5), AND
    - Names and qualifications of IEC members
    - Summary of IEC decision
    - Description of informed consent procedure
    - Description of incentives, if any
    - Description of study monitoring
    - Description of investigator training in GCP
  - Encourages sponsors to obtain written commitments by investigators to comply with GCP; if obtain copies of such commitments would be required
  - Sponsor may submit a request to waive requirements, with justification

FDA Regulations Regarding Foreign Clinical Trial Data (8)

- Foreign data as sole basis to support marketing approval from FDA [21 CFR 314.106(b)]
  - Data is applicable to US population and medical practice
  - Studies are performed by investigators of recognized competence
  - Data is considered valid without an on-site FDA inspection
  - FDA is able to validate the data through an on-site inspection

  (FDA policy is flexible depending on nature of product.)

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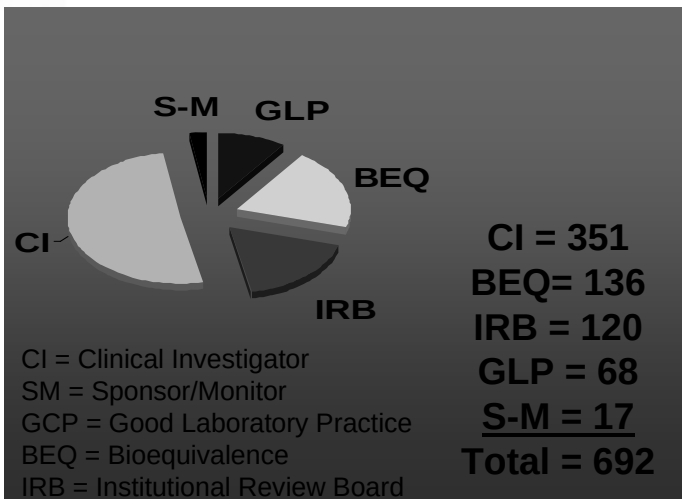
CDER BIMO Inspections (FY 2004)



CI = Clinical Investigator
SM = Sponsor/Monitor
GCP = Good Laboratory Practice
BEQ = Bioequivalence
IRB = Institutional Review Board

CI = 351
BEQ= 136
IRB = 120
GLP = 68
S-M = 17
Total = 692

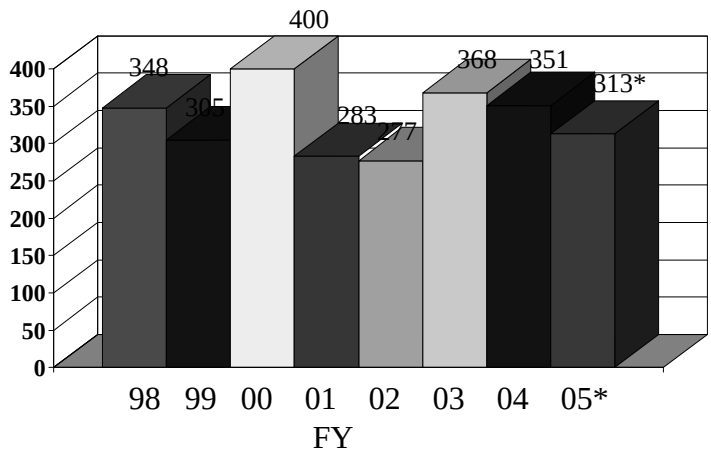
Clinical Investigator Inspections, all Centers, 2004

- CDER: 351
- CBER: 71
- CDRH: 178

- Total: 600

Clinical Investigator Inspections

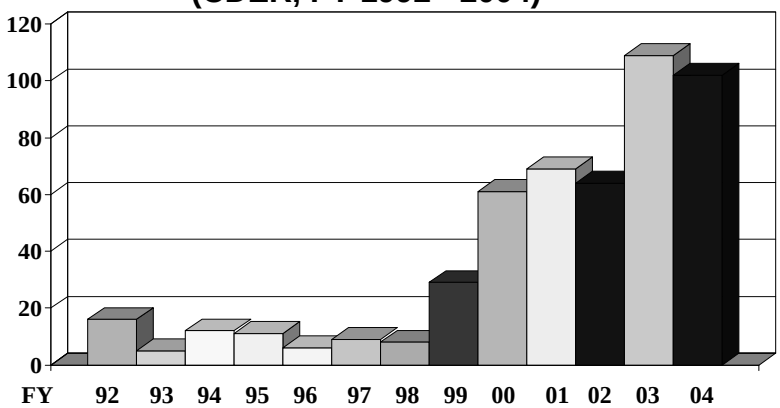
Center for Drug Evaluation & Research
FY 97-04



*FY 2005 as of 9/2005, pending receipt of info from field

*As of 9/05

CI "For Cause" Inspection Assignments
(CDER, FY 1992 - 2004)



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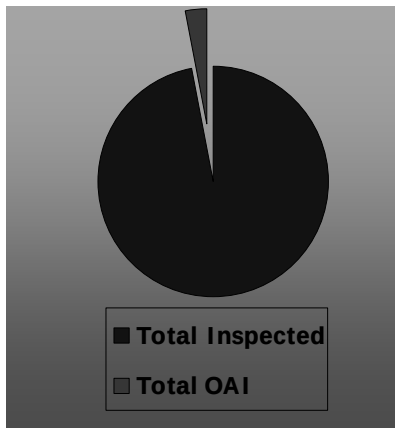
Prevalence of OAI Inspections (DSI Data)

Total number of FDA inspections
(1/77-9/2004): = 7,483

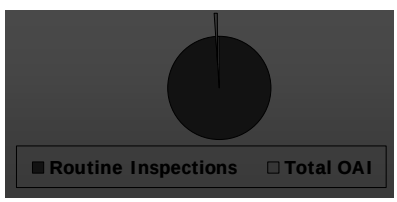
Total OAI cases = 237

Percent OAI = 3.2%

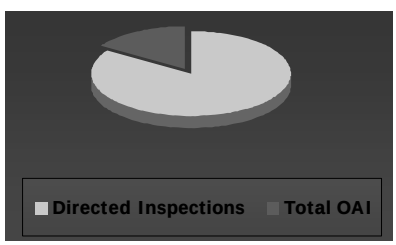


Prevalence of OAI Inspections (DSI data)

Routine FDA inspections (1/77-9/2004): = 6,730
Total OAI cases = 84
Percent OAI = 1.25%



Directed FDA inspections (1/77-9/2004) = 818
Total OAI cases = 153
Percent OAI = 18.7%

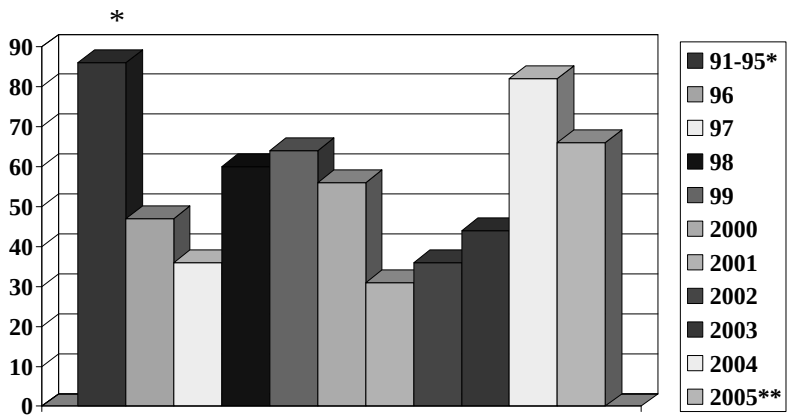


Criteria for Assigning International Inspections

International sites may be audited

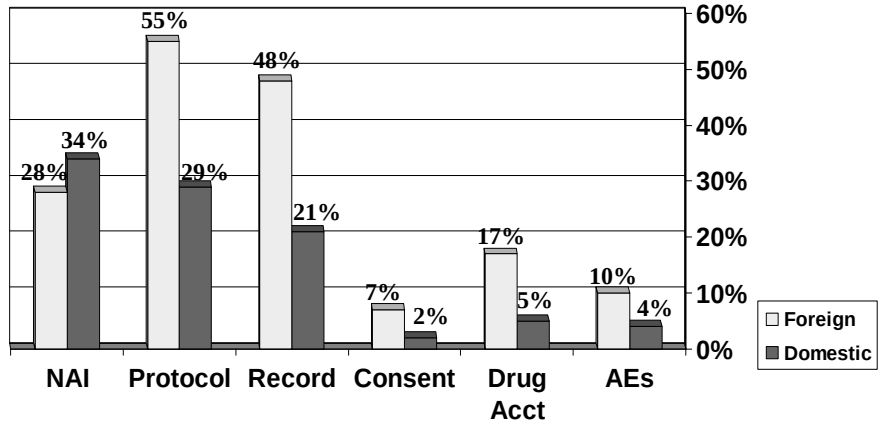
- if there are insufficient domestic data;
- only foreign data are submitted to support an application;
- domestic and foreign data show conflicting results pertinent to decision-making; or
- there is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

Clinical Inspections - International
(CDER, FY 1992 - 2005)



**FY 2005 as of 9/05, pending receipt of info from field

Clinical Investigator Deficiencies
CDER Inspections - FY 2004



Foreign n = 71*
Domestic n = 243*

*% does not include Biologic inspections

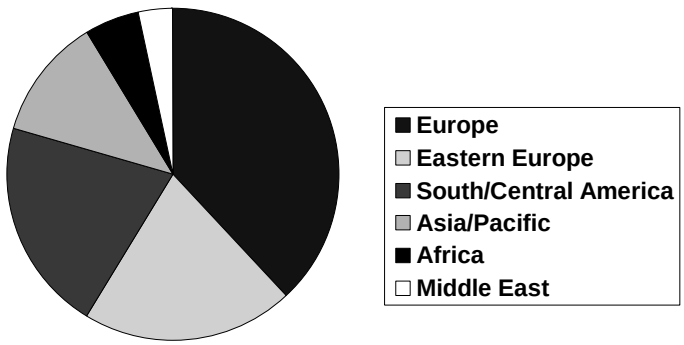
Sites of International Inspections 1980 - 2004*

Algeria**	1	**Germany**	45	**Norway**	4
Argentina	9	**Greece**	2	**Panama**	2
Australia	8	**Guatemala**	2	**Peru**	5
Austria	4	**Hong Kong**	4	**Philippines**	1
Bahamas	1	**Hungary**	8	**Poland**	9
Belgium	20	**Ireland**	1	**Portugal**	2
Brazil	8	**Israel**	4	**Romania**	1
Canada	122	**Italy**	27	**Russia**	19
Chile	2	**Japan**	3	**Slovenia**	1
China	1	**Kenya**	1	**South Africa**	20
Columbia	1	**Latvia**	3	**Spain**	14
Costa Rica	7	**Lithuania**	1	**Sweden**	26
Croatia	2	**Malawi**	1	**Switzerland**	1
Czechoslovakia	5	**Mexico**	7	**Taiwan**	1
Denmark	8	**Netherlands**	20	**Thailand**	1
Dominican Rep.	1	**New Zealand**	3	**U. K.**	82
Estonia	1	**Nigeria****	1	**Venezuela**	2
Egypt	1			**Zambia**	1
Finland	14				
France	41				
Gabon	1				

***through 9/30/2004 (55 countries; N=582; 82 in FY 2004)

**data reviewed in U.S.

International Clinical Inspections CDER FY 2005*



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Case Study #1: Impact of Inspection

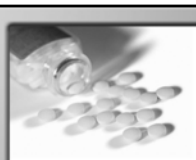
Drug X in Long-Term Treatment of Condition Y

- Objective of the study to test the efficacy of drug X in outpatients when compare to placebo, as measured by the number of days until relapse
- Basis for site selection: site Eastern Europe showed a significant treatment response
- FDA inspectional findings: there were in-patient hospitalizations for 24 subjects out of 35 subjects enrolled.
- DSI recommended to review division to reject data from this site

Case Study #2: Impact of Inspection

Study of Drug Y in Treatment of Condition Z

- Study efficacy endpoint was based on rating scale
- Site in Europe had identical sets of scale scores in study subjects
- Inspectional findings: ratings were not conducted according to the protocol for all subjects (32 randomized)
- Impact: influences significance on outcome (p=0.06 without this site data)
- DSI participation in site inspection
- Site copied the individual scores from previous visits if there is no change instead of conducting the ratings as instructed
- DSI recommended to review division to reject data
- Non-approvable letter was sent to the U.S. sponsor in 2005



Helpful Websites

- FDA Homepage: http://www.fda.gov
  - Links to Code of Federal Regulations, Federal Register Notices, FDA guidance documents
- DSI Homepage
  - http://www.fda.gov/cder/Offices/DSI/
- CDER guidance (including ICH documents):
  - http:www.fda.gov/cder/guidance/index.htm
- Compliance Programs:
  - http://www.fda.gov/ora/compliance_ref/default.htm

Helpful Websites (cont.)

- IRB information sheets and other documents:
  - http://www.fda.gov/oc/gcp
- Lists of Clinical Investigators who have been disqualified, restricted or provided assurances:
  - http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm