



U.S. Food and Drug Administration

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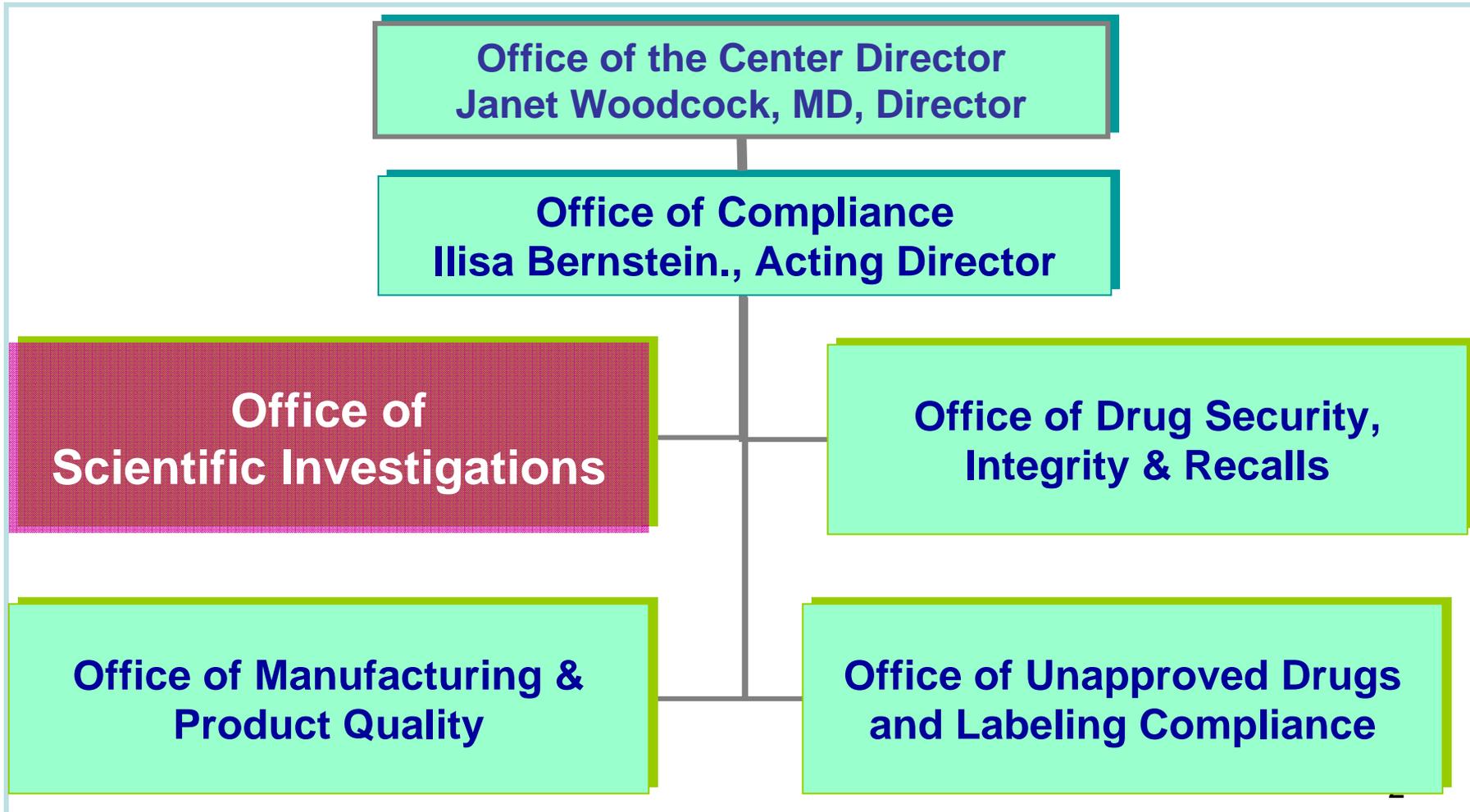
# What FDA Expects in a Pharmaceutical Trial

Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations (DSI)  
Center for Drug Evaluation and Research





# Center for Drug Evaluation and Research





# Drug Development and Review Process

*It takes a decade on average for an experimental drug to travel from lab to medicine chest. Only five in 4,000 compounds screened in preclinical testing make it to human testing. One of these five tested in people is approved.*

## Preclinical Testing

## Phase I

## Phase II

## Phase III

## FDA

## Approval

YEARS	1	2
Test Population	Laboratory and Animal Studies	
PURPOSE	Assess toxicity and biological activity	
% of all new drugs that pass		

FILE  
IND

3	4	5	6	7	8
20 to 80 Healthy Volunteers	100 to 300 Subject Volunteers		1,000 to 3,000 Subject Volunteers		
Determine Acute Toxicity and Dosage	Evaluate effectiveness. Look for Side effects.		Verify effectiveness, monitor adverse reactions from Cumulative dosing and delayed Toxicity		
	Expedited Review: Phases II and III combined to shorten approval process on new medicines for serious & life-threatening diseases.				
~70% of INDs	~33% of INDs		~27% of INDs		

FILE  
NDA

9	10	→
Review usually takes about ½ - 1 year		Post-marketing safety monitoring
		Distribution
		Education
~20% of INDs		



# Office of Scientific Investigations

**Director (Acting)**  
**Leslie Ball, M.D.**

**Immediate Office**

**Program Management and Organizational Strategy (Tanya Clayton, Acting)**  
**Risk Science, Intelligence & Prioritization (Ann Meeker, Acting)**  
**Policy & Communication (Karena Cooper, Acting)**

**Division of  
Bioequivalence & GLP**  
**Joe Salewski**  
**(Acting)**

**Division of  
GCP Compliance**  
**Tejashri Purohit-Sheth, M.D.**  
**(Acting)**

**Division of  
Safety Compliance**  
**Kevin Prohaska, M.D.**  
**(Acting)**

# What does DSI do?

- Assigns and Performs inspections through the Office of Regulatory Affairs (**ORA**) to verify data submitted to FDA and ensure the protection of the rights and welfare of human research subjects
- Investigates allegations of regulatory non-compliance
- Provides a scientific and medical review of Establishment Inspection Reports (**EIRs**) generated by ORA
- Makes recommendations regarding data reliability to Review Divisions
- Takes appropriate regulatory action

# IND Regulations

- Definitions
- Scope
- Applicability

# FDA Definitions

- ***Drug:***
  - Articles intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in man [21 U.S.C § 312(g)(1)(B)]
  - Articles (other than food) intended to affect the structure or any function of the body of man [21 CFR U.S.C. § 312(g)(1)(C)]

## FDA Definitions: [21 CFR 312.3]

- ***Investigational New Drug***: a new drug or biological drug, to include a biological product that is used in vitro for diagnostic purposes
- ***Clinical Investigation***: any experiment in which a drug is administered to human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

## FDA Definitions: Con't

- ***Sponsor:*** individual or entity responsible for and who initiates a clinical investigation. May be an individual or a pharmaceutical company, government agency, academic institution, or other organization.
- ***Clinical Investigator:*** an individual who actually conducts a clinical investigation. In the event of a team, the investigator is the responsible leader of the team.
- ***Sponsor-Investigator:*** an individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is administered or dispensed. (Term does not include any person other than an individual.)

# FDA Definitions: Con't

- **Contract Research Organization (CRO)**

“ . . . a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.”

# IND Regulations: Scope

## 21 CFR 312

- Contains procedures and requirements governing the use of investigational new drugs, including
  - Procedures and requirements for submission of an investigational new drug to the FDA
  - FDA's review of the IND
- Allows for the lawful interstate shipment of investigational drugs under an IND

## **Applicability** [21 CFR 312.2]

- 21 CFR 312 applies to all clinical investigations of products that are subject to Section 505 of the FD&C Act, unless IND exemption requirements are met

## IND Requirements [21 CFR 312.20]

- A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug product (unless an exemption applies)
- FDA's objectives in review of an IND
  - Assure the safety and rights of subjects in studies
  - Assure that the quality of the scientific evaluation of the drugs is adequate to permit an evaluation of the drug's effectiveness and safety

# Exemption from IND Requirements [21 CFR 312.2(b)]

- **A clinical investigation of a lawfully marketed drug product is exempt if all of the following apply**
  - **The investigation is not intended to be reported to the FDA as a well controlled study in support of**
    - **New indication**
    - **Significant change in labeling of the product**
    - **Significant change in the advertising of the product**
  - **The investigation does not involve a new route of administration or dosage level that significantly increases the risk with the use of the investigational product**
  - **The investigation complies with**
    - **IRB regulations (21 CFR 56)**
    - **Informed Consent regulations (21 CFR 50)**
    - **Promotion and charging for investigational product regulations (21 CFR 312.7)**

## IND Exemption: con't

- A clinical investigation involving an in vitro diagnostic biological product that confirms the diagnosis made by another, medically established, diagnostic product or procedure
  - Blood grouping serum
  - Reagent red blood cells
  - Anti-human globulin
- Investigation of a drug intended solely for tests in vitro or in laboratory research animals
- A clinical investigation involving placebo (if the study doesn't otherwise require submission of an IND)
- Use of an approved product used in the practice of medicine for an unlabeled indication



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# Guidance for Industry Investigational New Drug Applications (INDs)— Determining Whether Human Research Studies Can Be Conducted Without an IND

## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joe Griffin (CDER) 301-796-2270, or the Office of Communication, Outreach and Development (CBER) 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

October 2010  
Clinical/Medical



# IND/IDE Center Contact Information

## Drugs - CDER

Call: 888-463-6332 or 301-796-3400

Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)

Internet: <http://www.fda.gov> and select “Drugs”

## Biologics – CBER

Call: 800-835-4709 or 301-827-1800

Email: [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

Internet: <http://www.fda.gov> and select  
“Vaccines, Blood, & Biologics”

## Devices – CDRH

Call: 800-638-2041 or 301-796-7100

Email: [dsmica@cdrh.fda.gov](mailto:dsmica@cdrh.fda.gov)

Internet: <http://www.fda.gov> select “Medical Devices”

IDE Inquiries: 301-796-5640



# Bioresearch Monitoring

# FDA's BIMO Program

- FDA's Bioresearch Monitoring Program - A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

# **BIMO Program Objectives**

- To verify the quality and integrity of research data
- To ensure that the rights and welfare of human research subjects are protected
- To ensure that FDA regulated research is conducted in compliance with applicable regulations

# DSI/CDER's BIMO Program Responsibilities

- Ensure adherence to applicable regulations with respect to:
  - Good Laboratory Practice (GLP)
    - *In vivo* Bioequivalence
  - Good Clinical Practice (GCP)
    - Institutional Review Boards
    - **Clinical Investigators**
    - Sponsor-Monitors, CROs



# FDA/CDER GCP Regulations

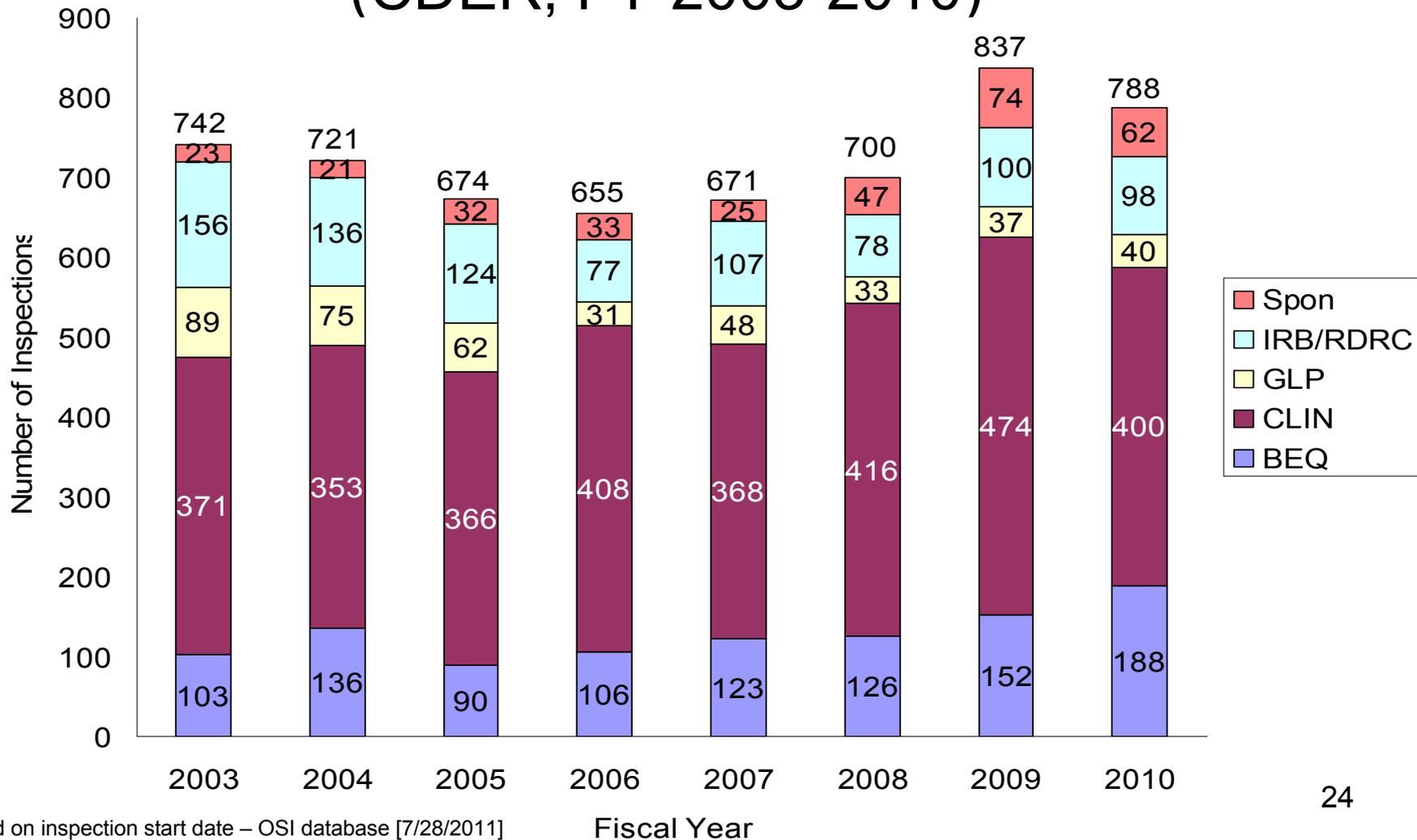
<b>Inspections apply to:</b>	FDA regulated <b>CLINICAL</b> and non-clinical research
<b>Regulatory oversight</b>	Institutional Review Boards (IRBs), Sponsors, CROs/Monitors, Clinical Investigators
<b>Relevant Regulations include (but not limited to)</b>	<b>21 CFR</b> <ul style="list-style-type: none"><li>•Part 50: Protection of Human Subjects</li><li>•Part 54: Financial Disclosure</li><li>•Part 56: Institutional Review Boards (IRB)</li><li>•Part 312: Investigational New Drugs (IND)</li><li>•Part 314: New Drug Applications (NDA)</li></ul>

# FDA Inspections

- FDA will often assess the **validity of data** and **safety and protection of human subjects** through *on site inspections* of clinical investigators and sponsors



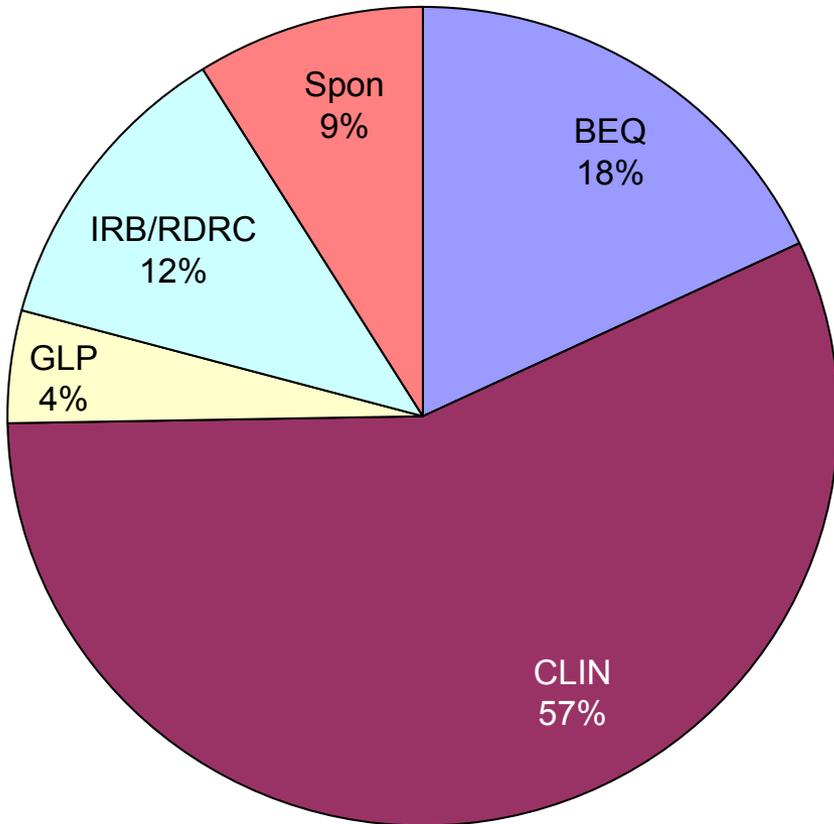
# Bioresearch Monitoring Program Inspections\* (CDER, FY 2003-2010)



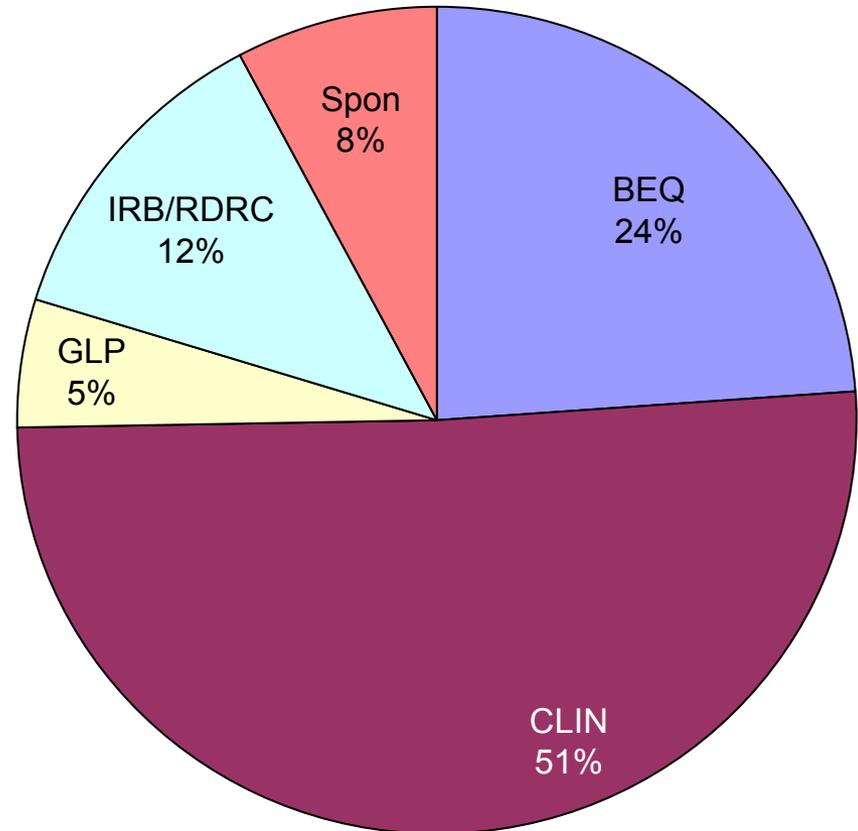
\*Based on inspection start date – OSI database [7/28/2011]  
IRB/RDRC no longer includes CBER/CDRH related Inspections

# Bioresearch Monitoring Program Inspections\* (CDER, FY 2009-2010)

FY2009 (N=837)



FY2010 (N=788)



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

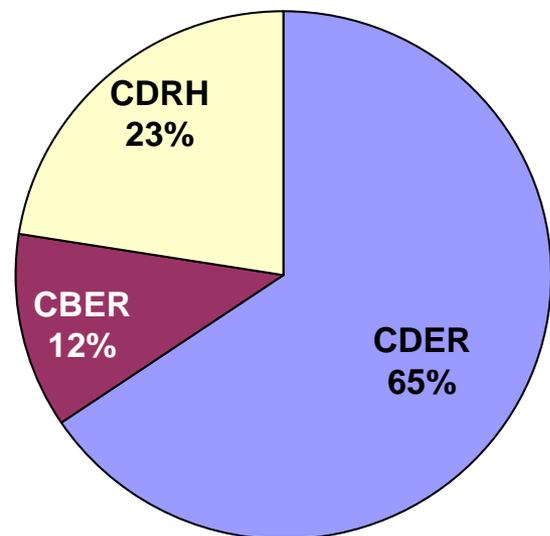
# Regulatory Authority to Conduct Inspections/Audits

- 21 CFR 312.68
  - “An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator...”

# Clinical Investigator Inspections\*

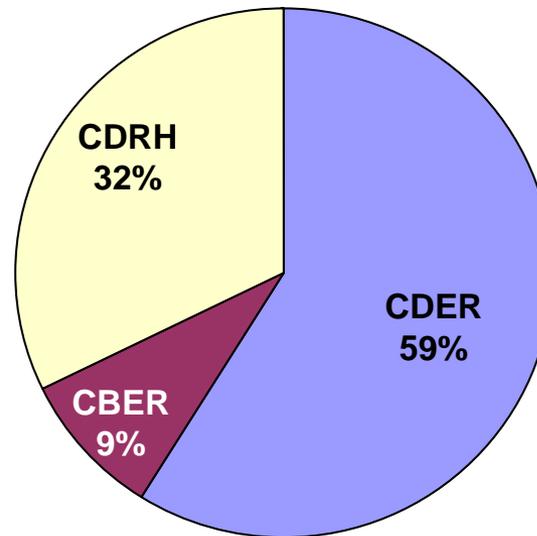
## (All Centers, FY 2009-2010)

FY2009 (N=722)



CDER	=	474
CBER	=	85
<u>CDRH</u>	=	<u>163</u>
<b>Total</b>		<b>722</b>

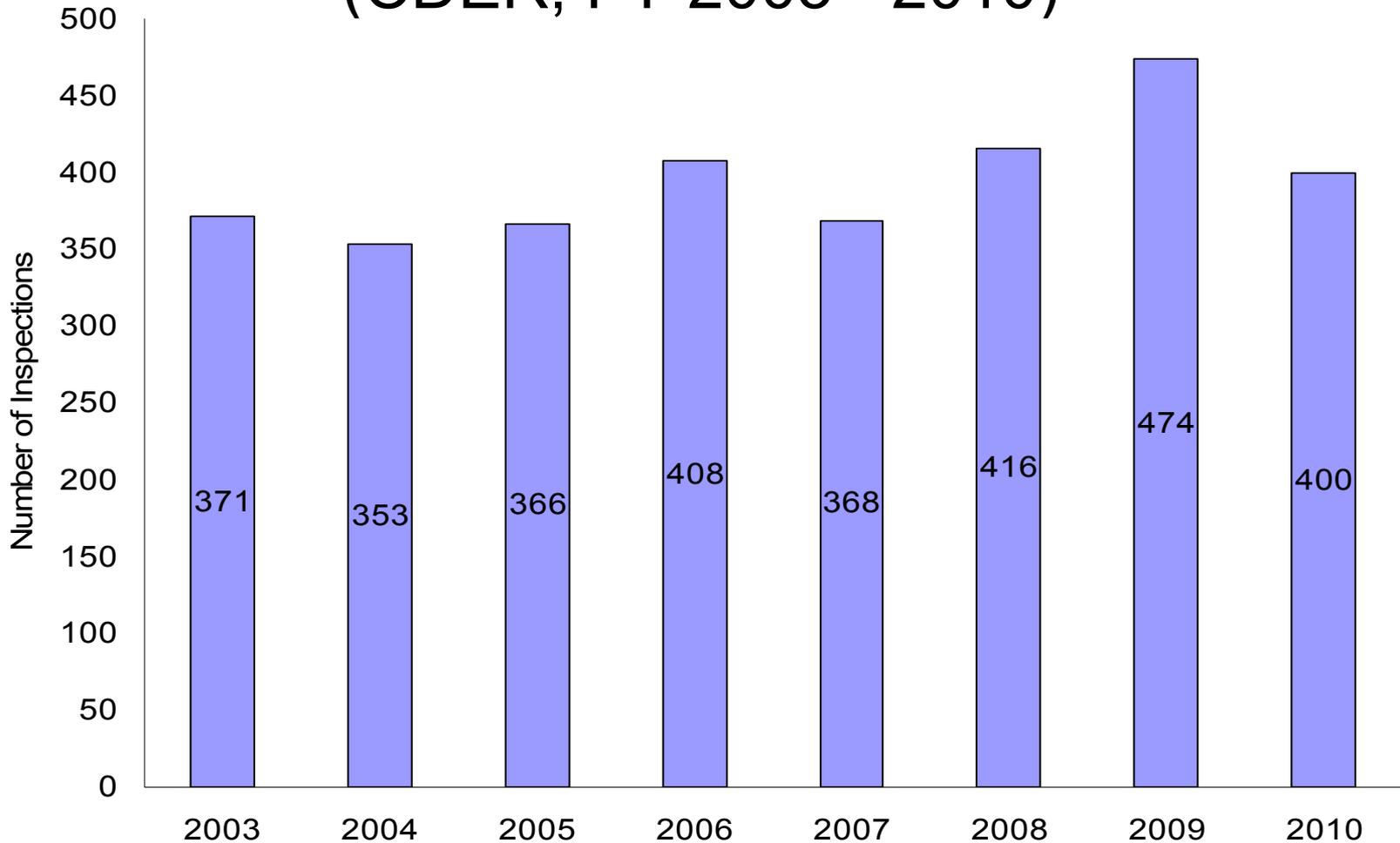
FY2010 (N=678)



CDER	=	400
CBER	=	60
<u>CDRH</u>	=	<u>218</u>
<b>Total</b>		<b>678</b>

\*Based on inspection start date, CDER data [7/28/2011]

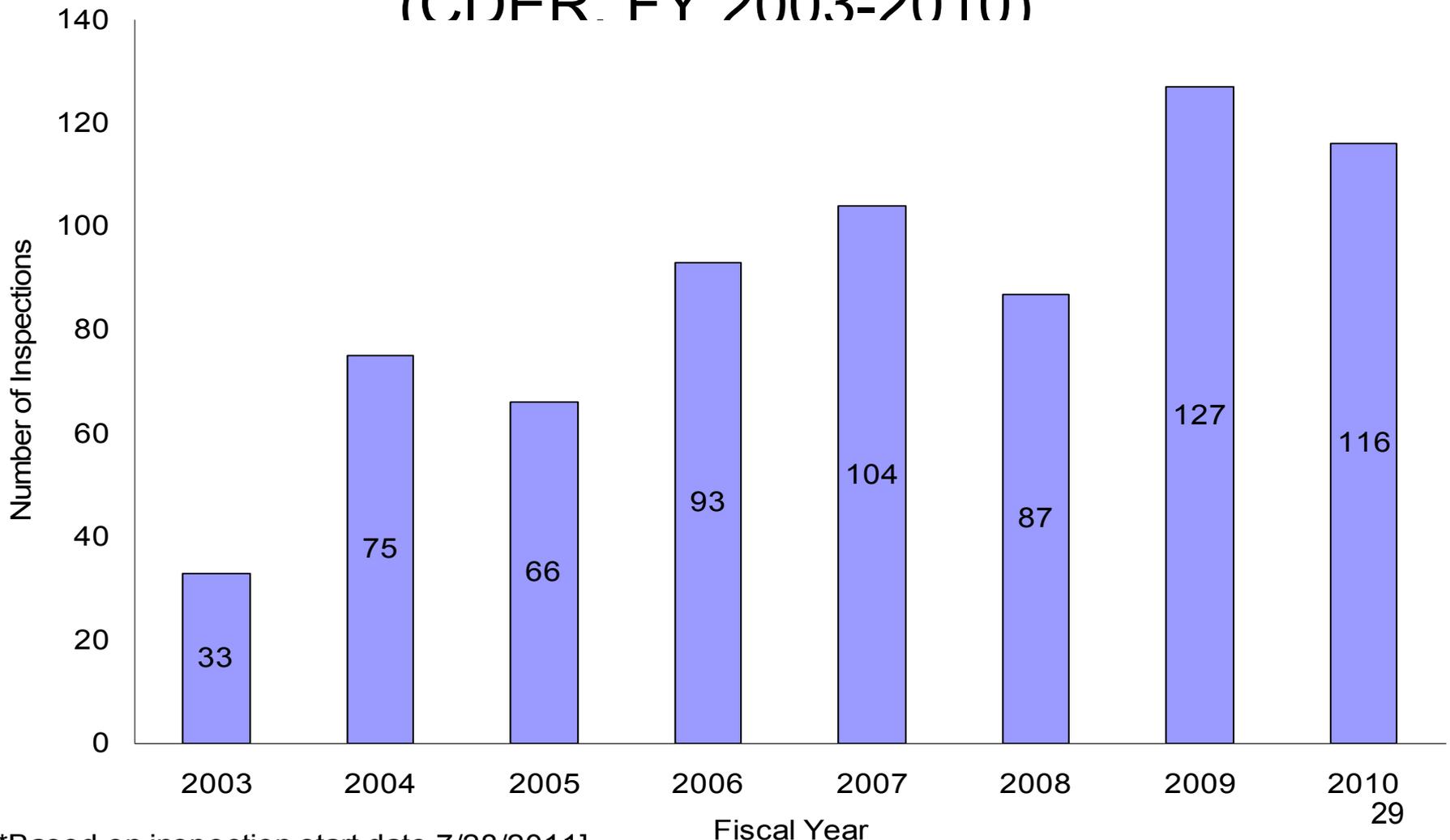
# Clinical Investigator Inspections\* (CDER, FY 2003 - 2010)



\*Based on inspection start date [7/28/2011] Fiscal Year



# International Clinical Investigator Inspections\* (CDER, FY 2003-2010)



\*Based on inspection start date 7/28/2011]

# FDA Expectations of Clinical Investigators

- Adherence to Code of Federal Regulations
  - Knowledge of Clinical Investigator regulations
  - Understanding Clinical Investigator responsibilities

[21CFR312.60-69]

# Investigator Regulatory Requirements

[21 CFR 312.60-69]

- Follow the current protocol [21 CFR 312.60]
- **Personally** conduct or supervise investigation(s) [21 CFR 312.60]
- Ensure that all persons assisting in conduct of studies are informed of their obligations [21 CFR 312.60]
- Obtain informed consent of each human subject to whom the drug is administered [21 CFR 312.60 and 21 CFR 50]
- Notify the sponsor before making changes in the protocol [21 CFR 312.60]
- Administer investigational drug only to subjects authorized to receive drug under the investigator's supervision (or subinvestigator) [21 CFR 312.61]
- Maintain adequate and accurate records
  - Disposition of drugs [21 CFR 312.62 (a)]
  - Case histories [21 CFR 312.62 (b)]
- Maintain Records for a period of 2 years following the date a marketing application is approved [21 CFR 312.62(c)]
- Report adverse events to the sponsor and IRB [21 CFR 312.64 & 312.66]
- Ensure IRB review/approval and reporting requirements are met [21 CFR 56 & 312.66]
  - Notify the IRB and obtain IRB approval before making changes in the protocol [21 CFR 312.60 & 312.66]
- Make records available for inspection [21 CFR 312.68]
- Comply with all other requirements in 21 CFR 312

# Helpful Websites

- DSI Homepage:**  
<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090085.htm>

Includes links to the Clinical Investigator Inspection List (NEW), Bioresearch Monitoring Information Systems (BMIS) files (NEW), Warning Letters, NIDPOE Letters, Lists of Disqualified or Restricted or Debarred Investigators, Code of Federal Regulations, etc.
- FDA Homepage:** [www.fda.gov](http://www.fda.gov)

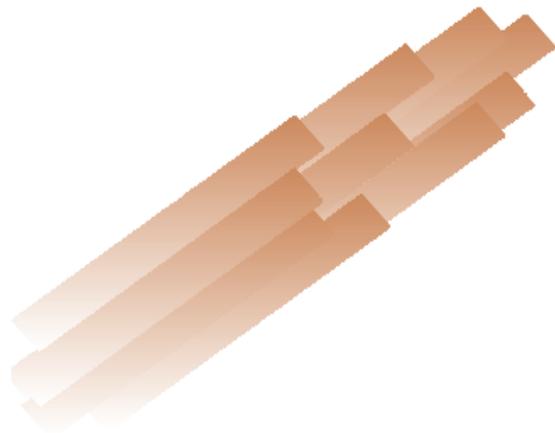
Includes links to the Federal Register Notices, CFR, FDA guidance documents.
- Compliance Programs and Manuals:**  
[www.fda.gov/ora/compliance\\_ref/default.htm](http://www.fda.gov/ora/compliance_ref/default.htm)

# Helpful Websites

- **Good Clinical Practices: [gcp.questions@fda.hhs.gov](mailto:gcp.questions@fda.hhs.gov)**  
<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm134493.htm>
- **Clinical Trials Guidance documents**  
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm>
- **ICH E6 Good Clinical Practice**  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf>
- **Frequently Asked Questions – Statement of Investigator (Form FDA 1572)**  
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf>

## 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>



## Contact Information

Tejashri Purohit-Sheth, M.D.  
Acting Division Director  
Division of GCP Compliance  
Office of Scientific Investigations/FDA  
White Oak, Bldg. 51, Rm. 5358  
10903 New Hampshire Ave.  
Silver Spring, MD 20993  
[Tejashri.purohit-sheth@fda.hhs.gov](mailto:Tejashri.purohit-sheth@fda.hhs.gov)  
PH: 301-796-3402