FDA Perspective on International Clinical Trials

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Disclaimer

The Views expressed in this presentation are those of the speaker and not necessarily those of the Food and Drug Administration

Outline

1. Background
2. International Clinical Investigators & Clinical Trials
3. Drivers to Conduct Clinical Trials Outside the USA
4. Law Governing International Clinical Trials
5. Challenges
6. Addressing the Challenges

Foreign Clinical Trials (FCTs)

BACKGROUND

Foreign Clinical Trials (FCTs)

- Prior to the 1962 Kefauver-Harrison Amendments, it was uncommon for a Sponsor to submit FCTs data
- In 1975 provisions that permit submission of FCTs data not conducted under an IND were codified in 21CFR312.120
- Since then medical product discovery & development have become increasingly globalized

Past 3 Decades & FCTs

- In the past three decades, drug development, production & distribution moved from a national and regionally-centered activity to a global one

- This increase in shift has significant implications on FDA's perspective on international clinical trials

International Clinical Investigators & Clinical Trials

METRICS

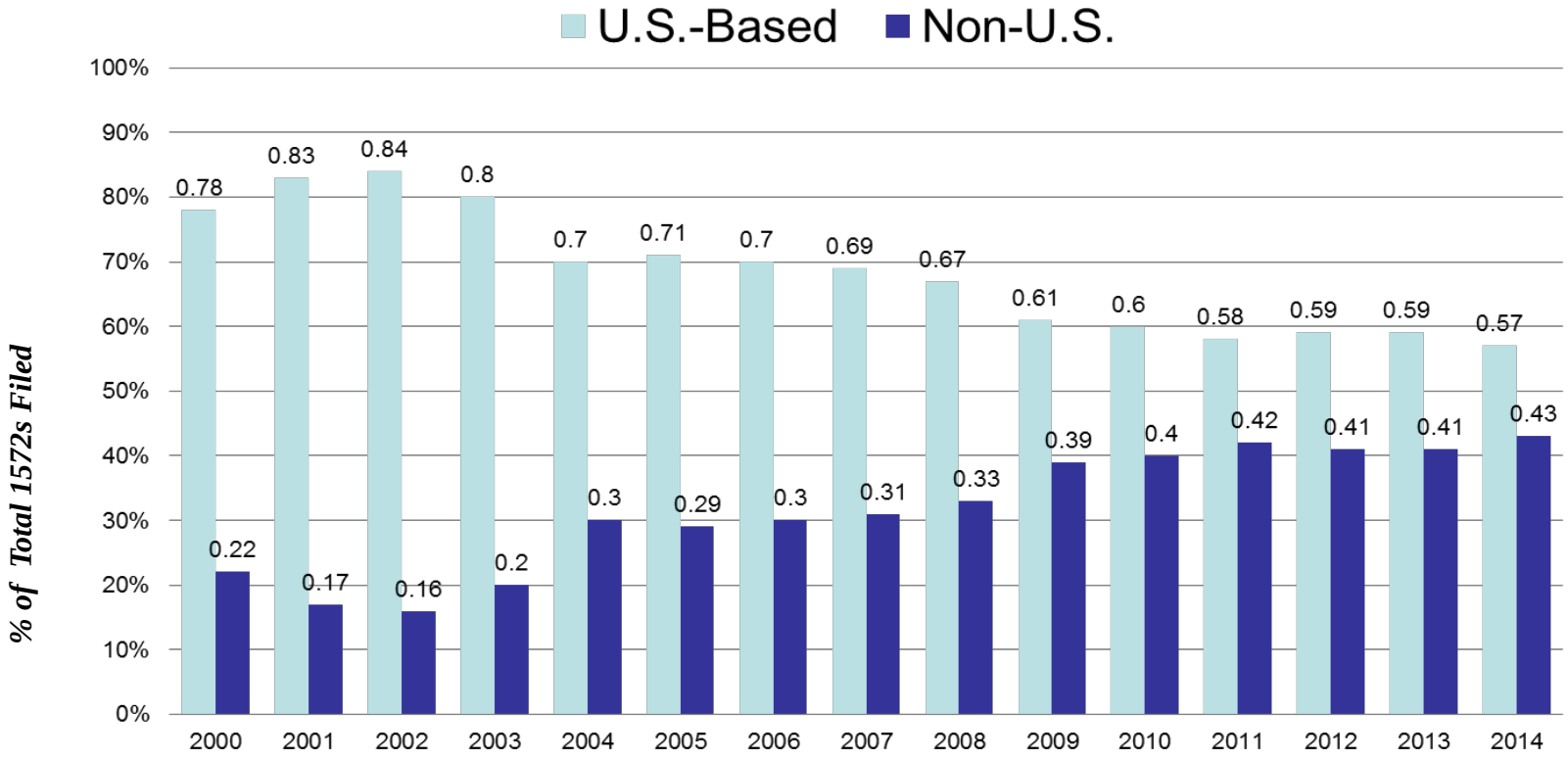
Rate of Increase for FDA Regulated Investigators: 1996-2006

	1996	Percent of Total	2006	Percent of Total	Annualized 10-year Growth Rate
North America	12,174	83.65%	14,555	63.18%	1.80%
Western Europe	1899	13.05%	3923	17.03%	7.52%
Central and Eastern Europe	56	0.38%	1793	7.78%	41.4%
Latin America	98	0.67%	1095	4.75%	27.3%
Asia	108	0.74%	1054	4.58%	25.6%
Rest of World	218	1.50%	617	2.68%	11.0%
TOTAL	14,574		23,089		

Source: Tufts Center for the Study of Drug Development.

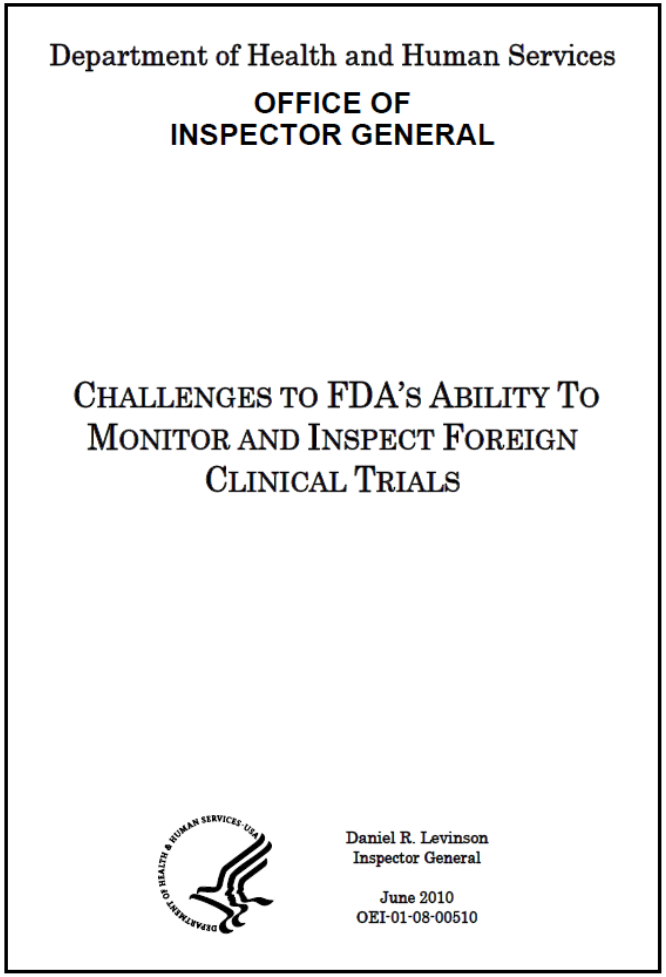
- **During the 10 year period, the % of total for U.S. based investigators declined by 20% (annual growth rate 1.8%)**
- **The number of active FDA–regulated investigators who are based outside the United States has grown**

Rate of Increase for FDA Regulated Investigators: 2000-2014



OIG Report:

- Over half of all clinical trial sites are outside the U.S.
- % of non-U.S. clinical investigators conducting trials under INDs has doubled over the last decade



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CHALLENGES TO FDA'S ABILITY TO MONITOR AND INSPECT FOREIGN CLINICAL TRIALS

Daniel R. Levinson
Inspector General

June 2010
OEI-01-08-00510

OIG Report:

- 80 % of applications for drugs & biologics contain data from ex-U.S. studies
- 78 % of all subjects were enrolled outside the U.S.
- 87 % of all subjects in recent biologics trials were enrolled outside the U.S.

Department of Health and Human Services

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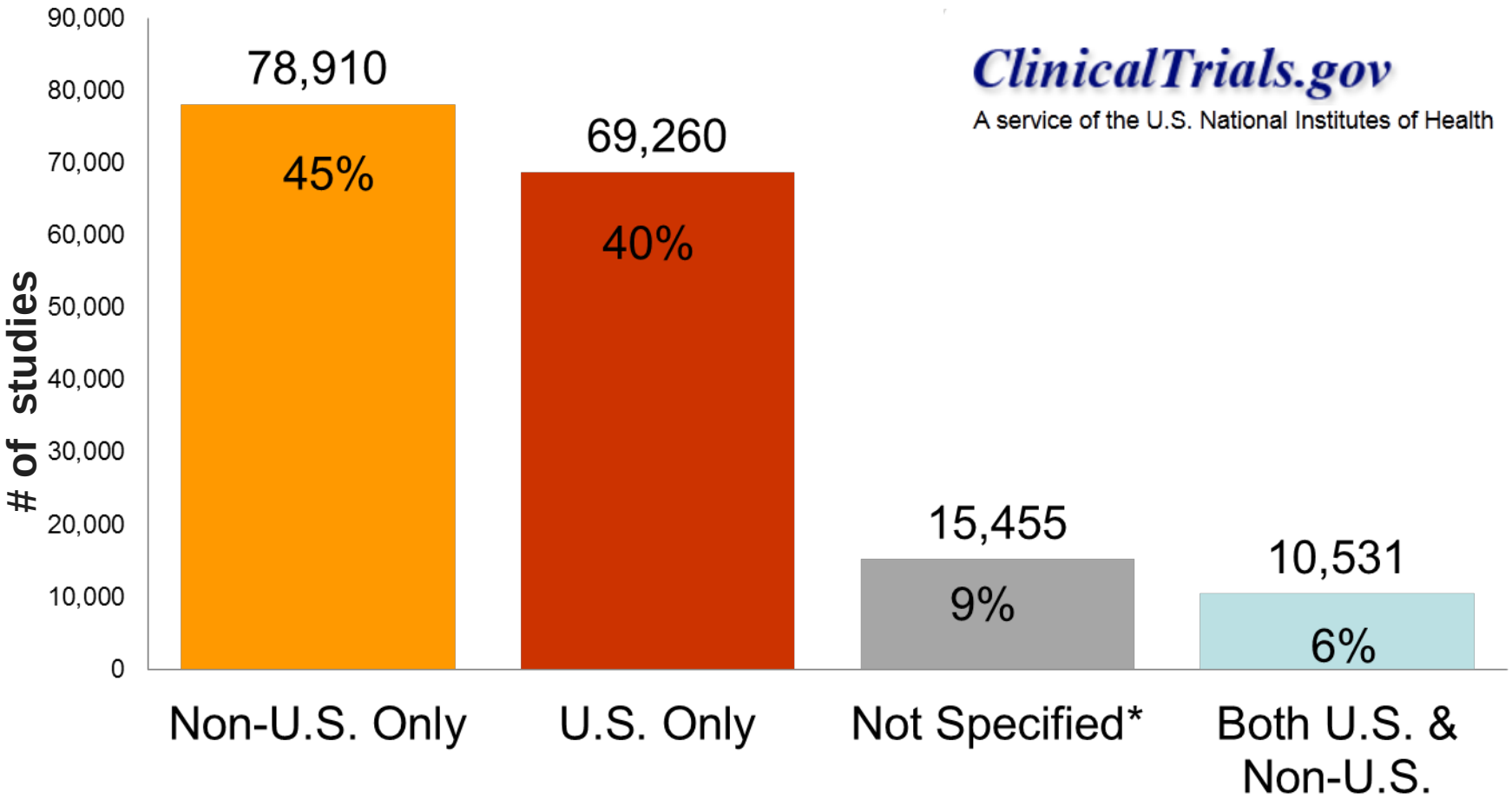
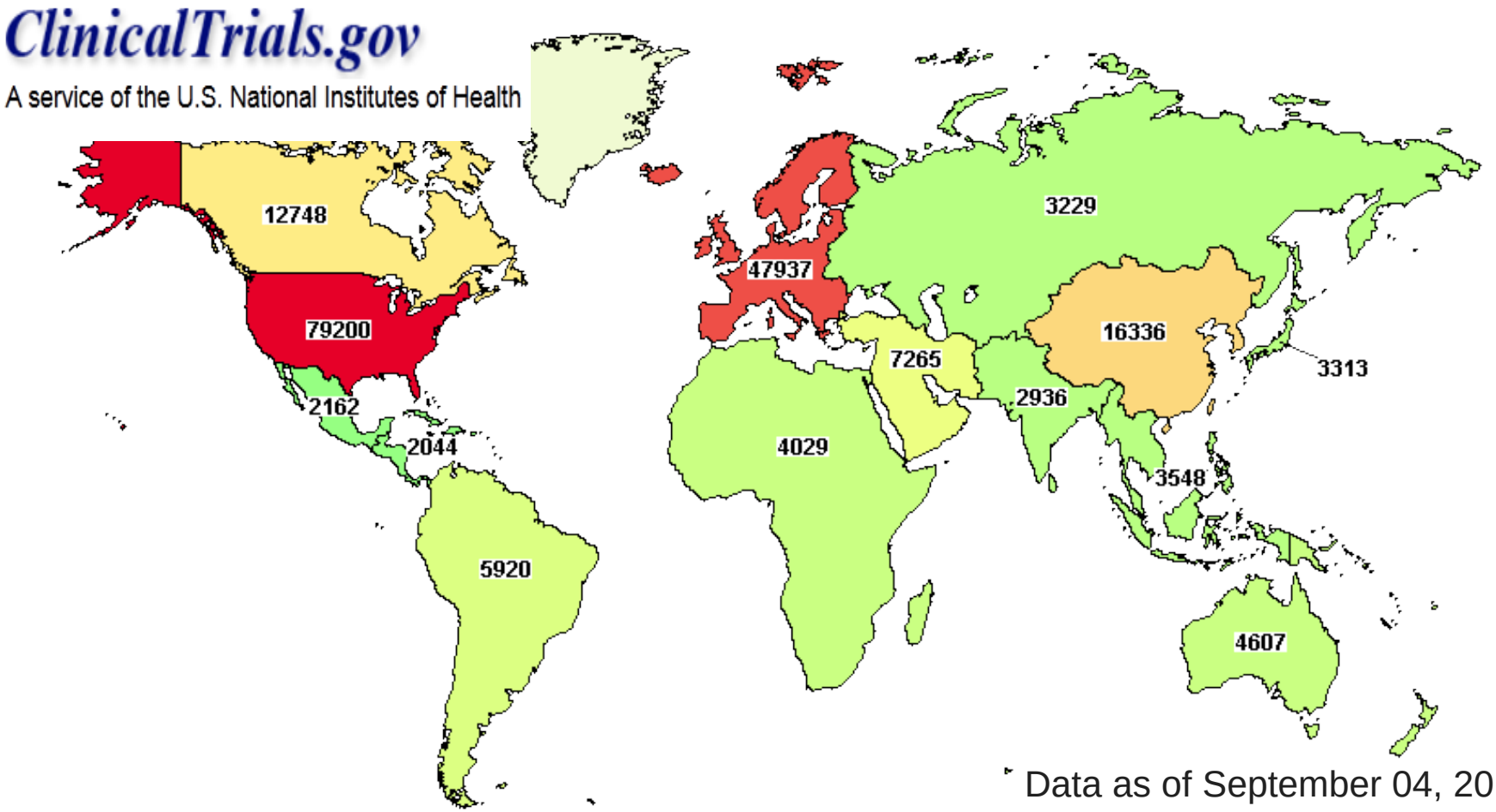
Distribution of Studies



All studies registered on ClinicalTrials.gov: Data as of September 04, 2014

Studies Distribution Map



Data as of September 04, 2014

ClinicalTrials.gov currently lists 174,156 studies with locations in 187 countries

What Drives Companies to Conduct Clinical Trials Outside the USA?

DRIVERS

Pushing & Pulling Forces

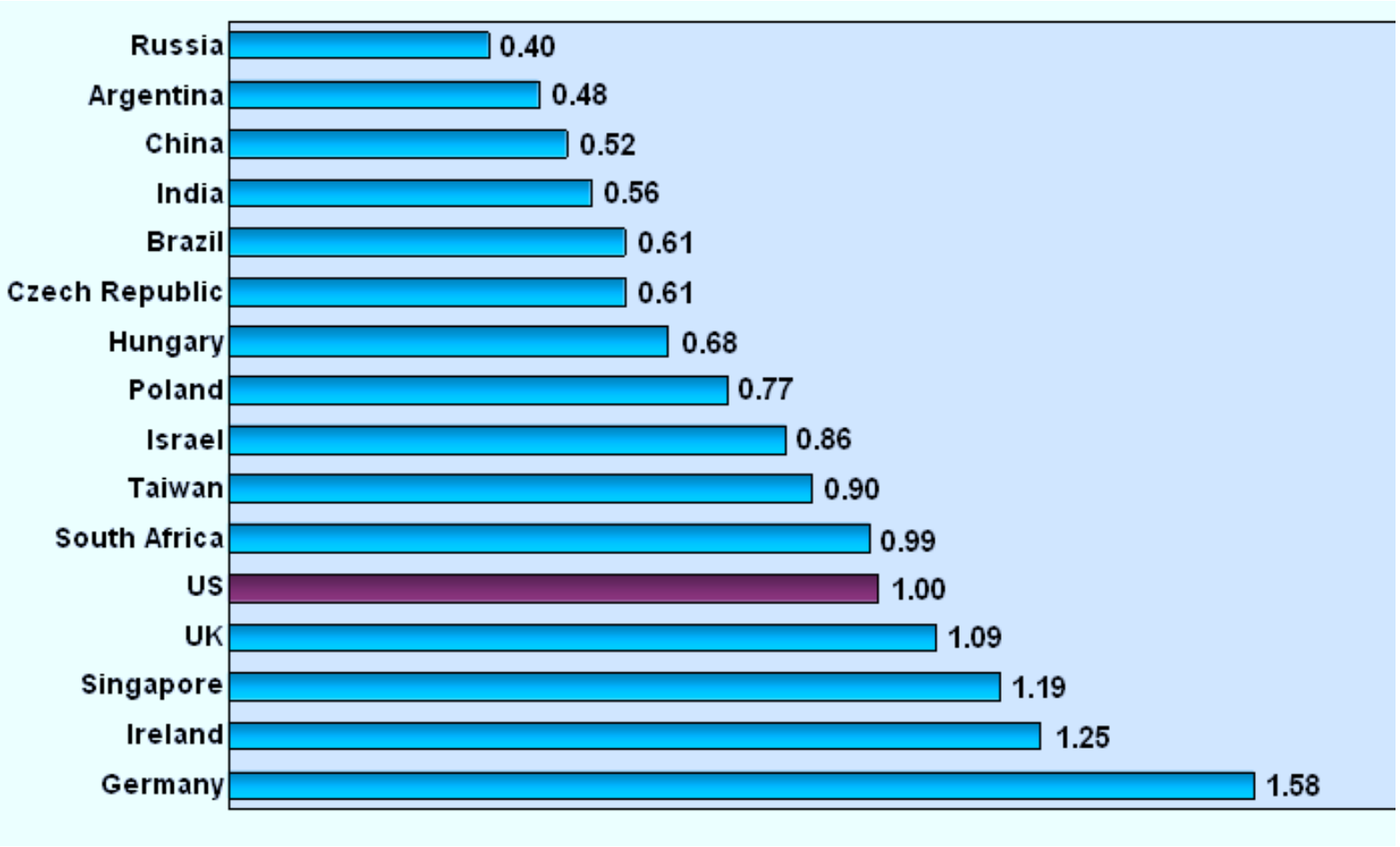
U.S.

- Difficulty recruiting patients
  - Fewer feel need to participate
- Higher standard of care
- Mistrust (historical infamy Tuskegee trial)
- Requirement for larger # of Pts
- Insurance precluding participation/HIPAA
- Higher costs: clinical care/Operational/ documentation & training)

Non U.S.

- Reduced cost or economic drivers (clinical care/Operational/training)
- Motivated subjects & investigators
- Rx naïve subjects willing & eager to participate
- Faster recruitment rates/ short timeline
- Availability of large # of patients
- Countries and institutions trying to attract research and clinical trials
- Availability of CROs focused on global trialsr
- Less regulatory red tape

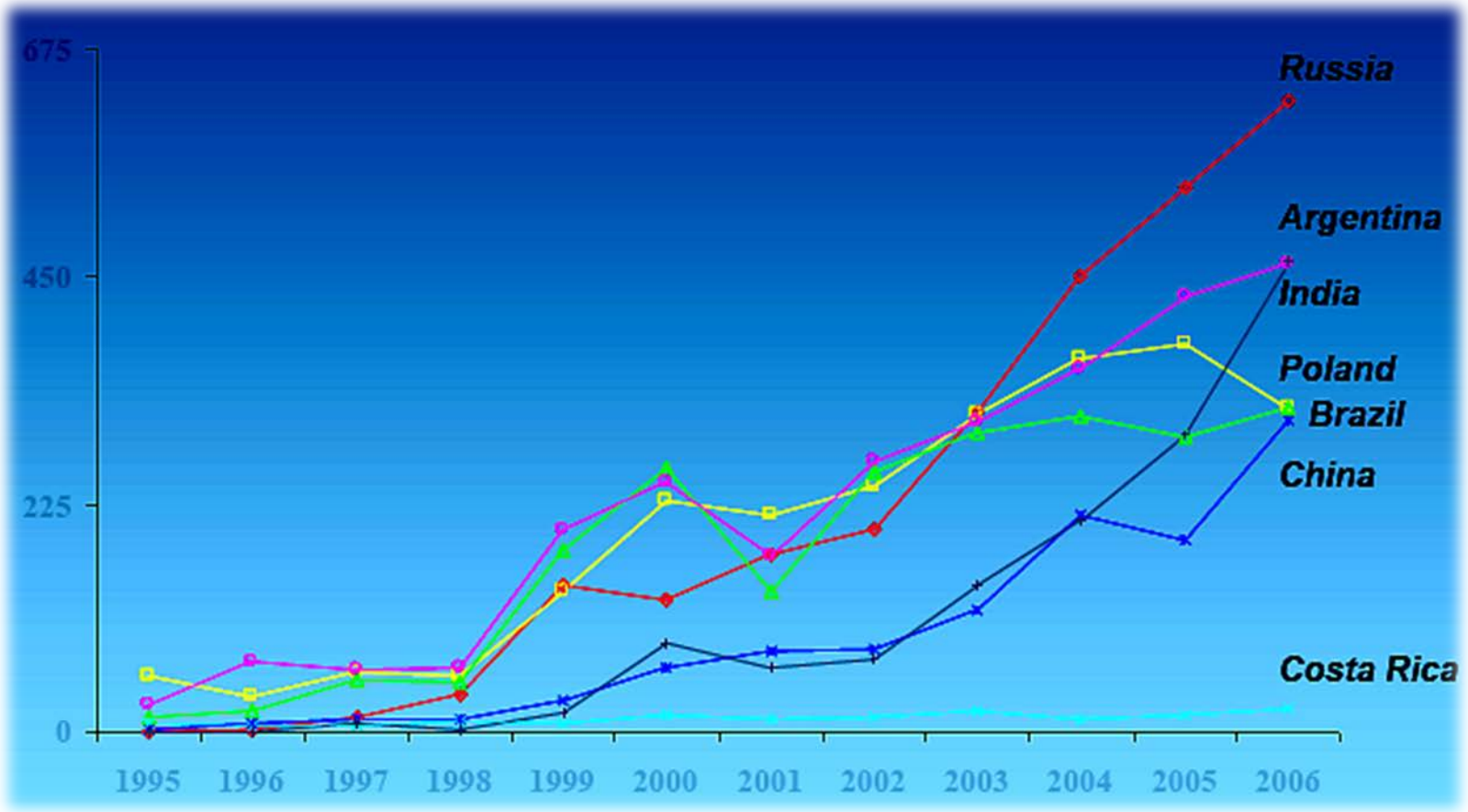
Overall Clinical Trial Costs



The cost of conducting CR in Russia, Argentina, China & India is about half the cost to the US (manpower, rental, IT & operational costs)

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)

Annual Growth in Clinical Investigations



Increasing Annual Growth of Clinical Trials Outside the US

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)

Current Law Governing Foreign Clinical Studies

21CFR312

Foreign Study Conducted Under IND

- When a study is conducted under an IND but is located outside of the United States, the study still must comport with all relevant FDA regulations as if it were being conducted within the United States
- A Sponsor is not required to conduct an FCT under an IND in order to use it as support for an NDA or IND

Foreign Clinical Trials Not Conducted Under An IND

21CFR312.120

Acceptance of Foreign Clinical Data

- FDA Accepts Foreign Clinical data from studies not conducted under an IND if the following conditions are met:
  I. Study was conducted in accordance with Good Clinical Practice (GCP)
  II. FDA is able to validate the data from the study through an onsite inspection

GCP

- Sponsor shall submit to FDA a description of actions taken to ensure research conformed to GCP:
  - Defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data &reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected

Supporting information

1. CI's qualifications
2. Description of the research facilities
3. Summary of the protocol & results of the study &, should FDA request, case records
4. Description & details of the product/drug used
5. Information showing that the study is adequate & well controlled
7. Name & address of the IEC, a summary of the IEC's decision
8. A description:
   - how IC was obtained
   - what incentives, if any, were provided to subjects in the study
   - how the sponsor(s) monitored the study
   - how CIs were trained to comply with GCP

Validation of Data: Onsite Inspections

- Help to ensure the protection of rights, safety and welfare of research participants
- Help to ensure data that are submitted in marketing applications are fit for purpose
  - For regulatory decision making (Approval)
  - As evidence base for clinical use of drug (Label)
- Allow evaluation of compliance with FDA regulations

Assigning International Inspections

- Clinical sites likely to be audited when:
  - only foreign data are submitted to support an application
  - insufficient domestic data
  - domestic and foreign data show conflicting results pertinent to decision-making
  - there is a serious issue to resolve (e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations)

Useful Guidance

- FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions
  - Issued March 2012
  - Provides clarifications for sponsors and applicants on how to demonstrate compliance with the requirements of 21 CFR 312.120

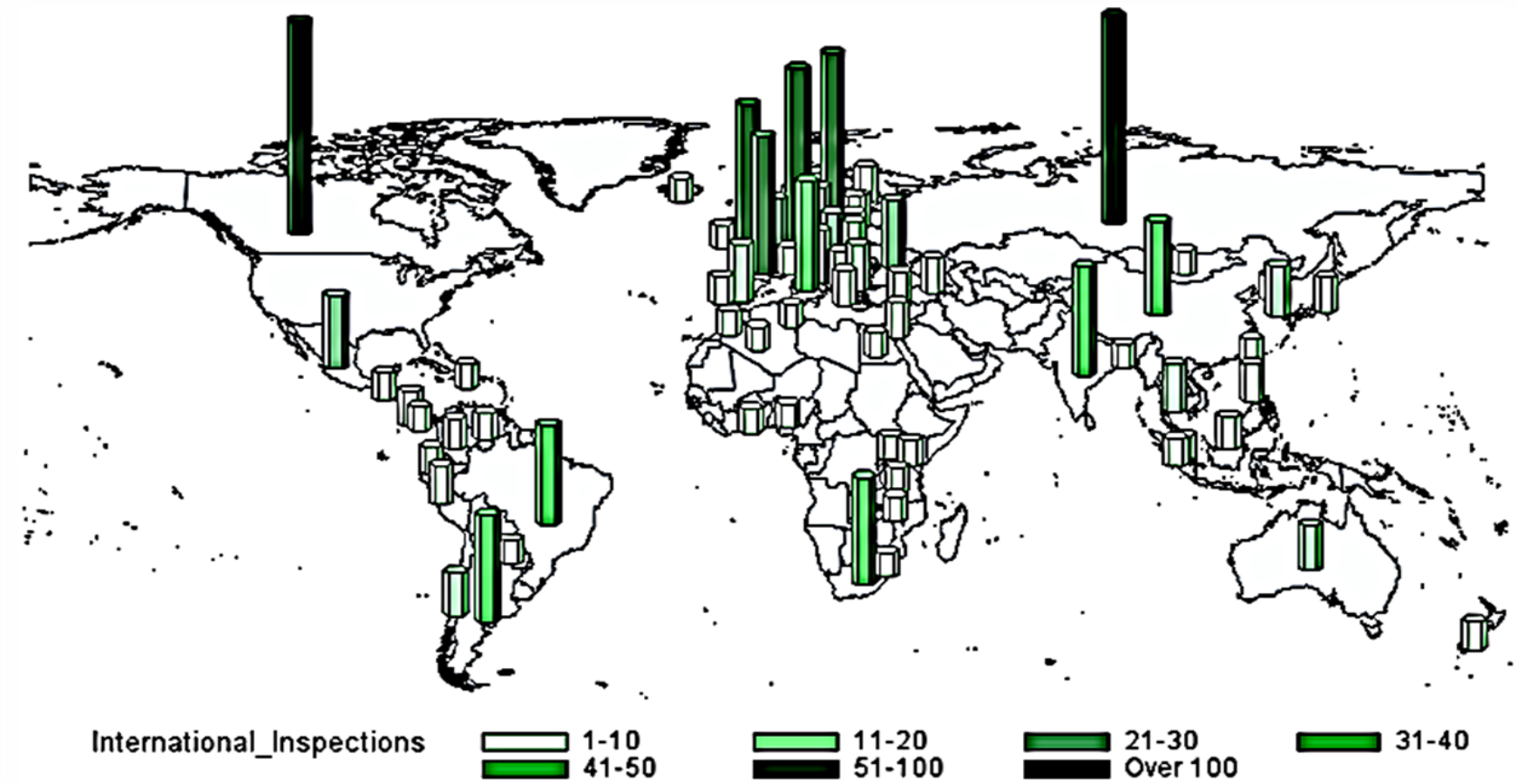
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294729.pdf

THE CHALLENGES

Increase in Breadth of Inspections

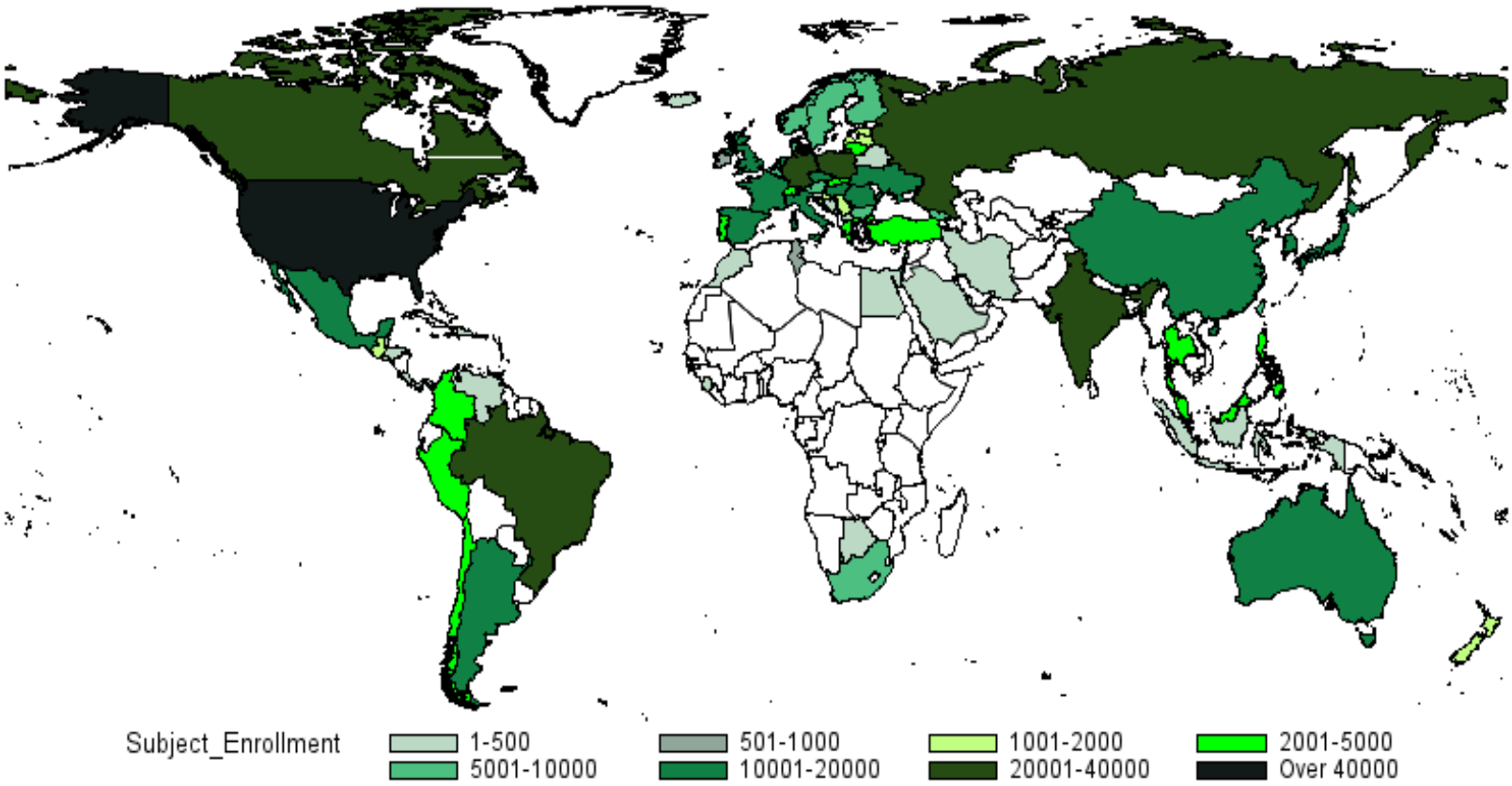
- Increasing volume to data from other regions submitted in support of marketing submissions submitted to FDA
- Increase in breadth of international inspections

Global Coverage of GCP Inspections



Conducted for FDA/CDER from 1984 through Sept 3, 2013; Based on Inspections with a start date in CDER/OC/OSI database

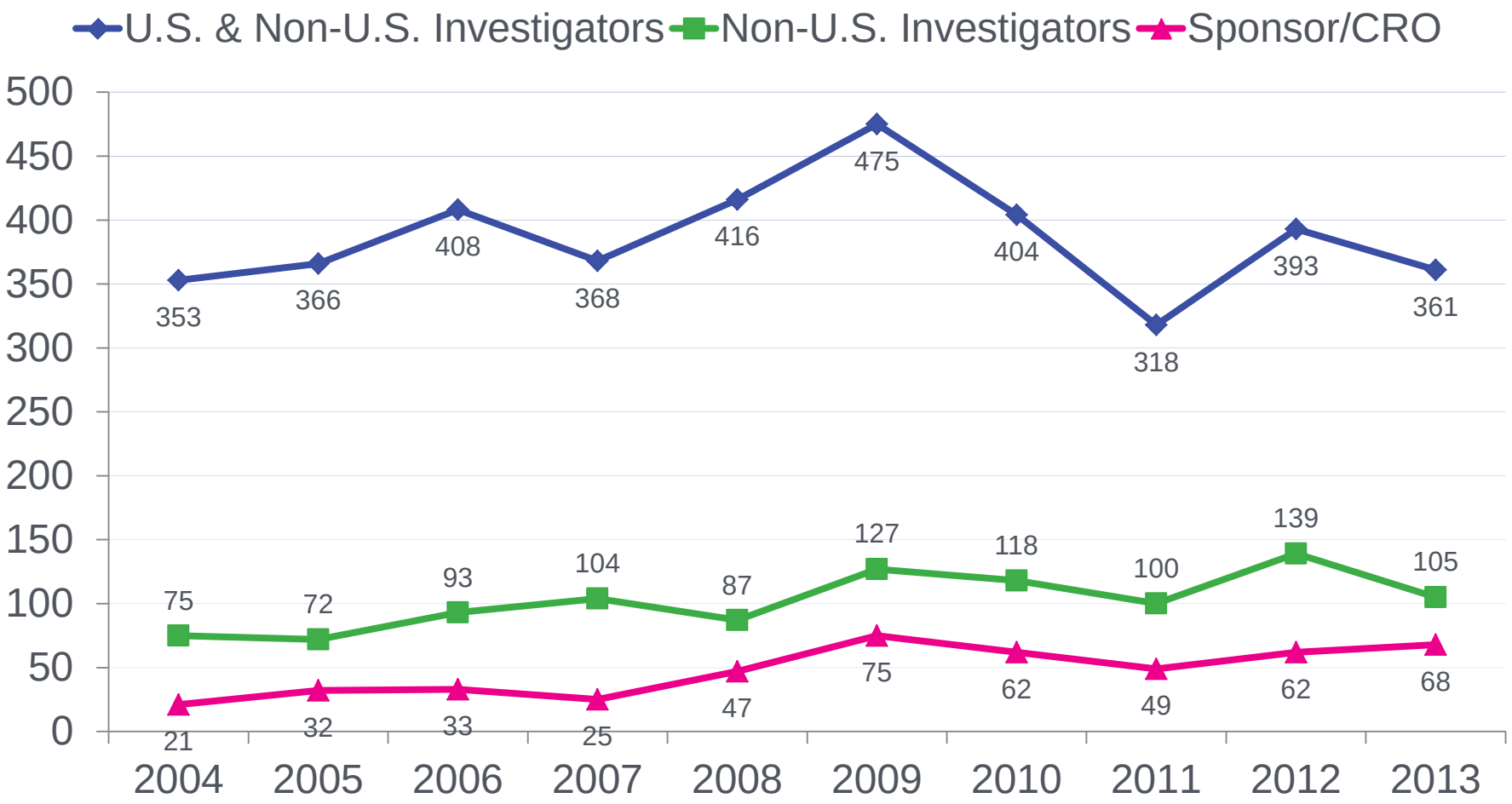
Distribution of Subject Enrollment



Finite inspection resources

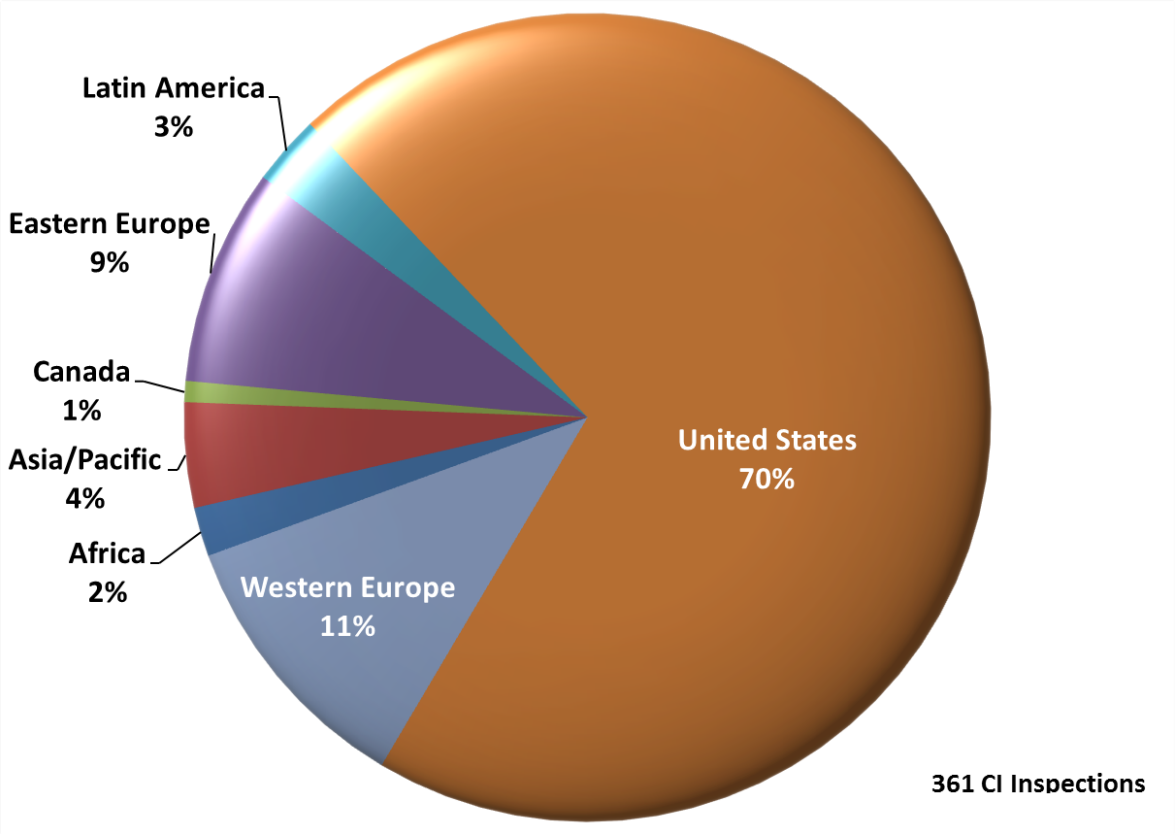
- Breadth of international inspections coupled with finite inspection resources result in inspection of a limited number of sites
- Despite the large portion of clinical studies being conducted abroad, the OIG 2010 Report found that the FDA only inspected 0.7% of all foreign clinical sites in 2008, compared to 1.9% of all domestic clinical sites.

Clinical Inspections*: CDER 2004-2013



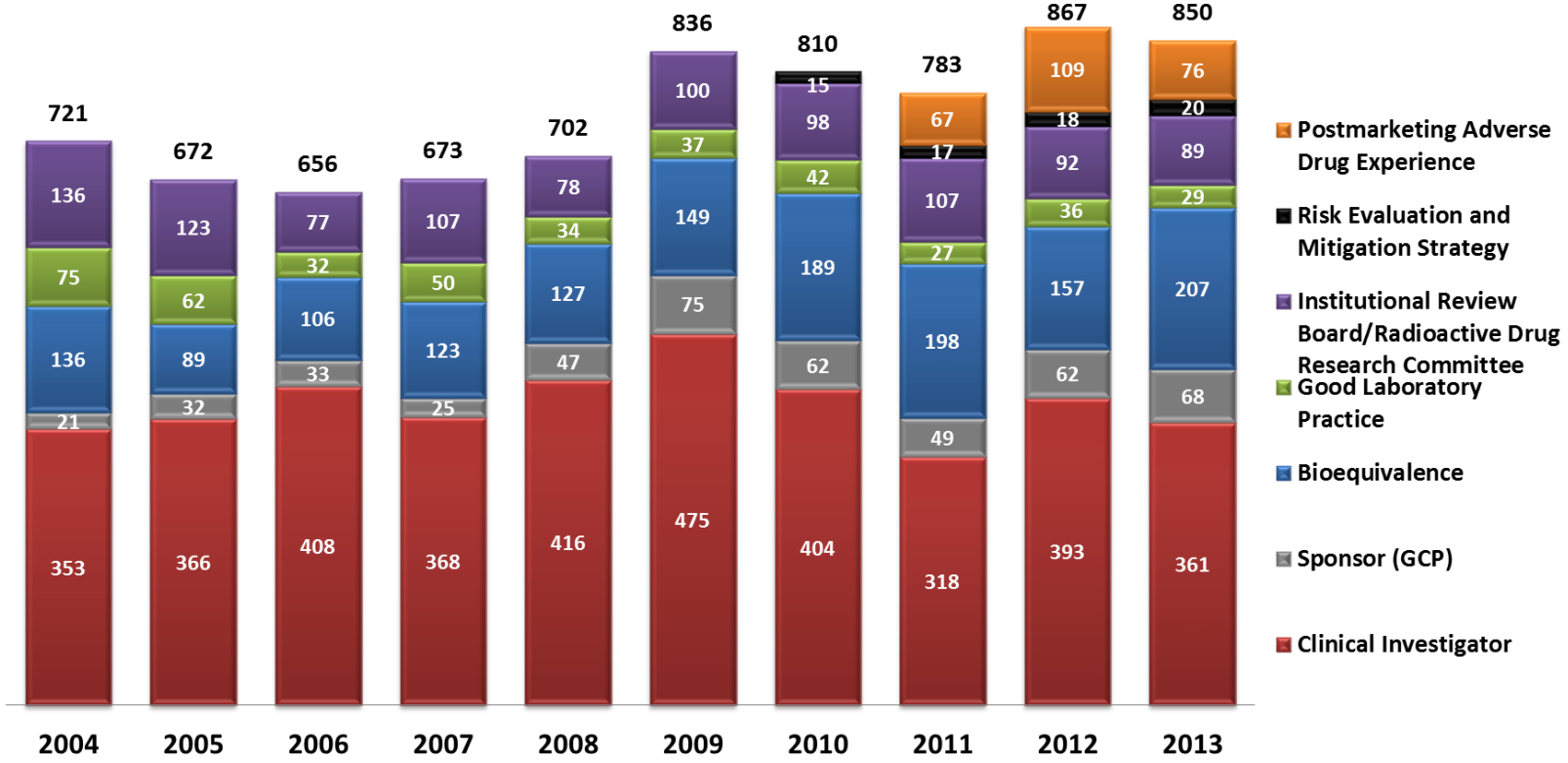
Clinical Investigator Inspections by Location*

(CDER, FY 2013)



*Based on inspection start date – [OSI database as of January 31, 2014]

Inspections Overseen by CDER, OSI* (CDER, FY 2004 - FY 2013)



*Based on inspection start date – [OSI database as of January 31, 2014]
IRB includes only CDER numbers – previously reported metrics may have used combined data across CDER, CBER and CDRH
Sponsor (GCP) includes Sponsor/CRO/Sponsor-Investigator
Postmarketing Adverse Drug Event and Risk Evaluation and Mitigation Strategy inspection programs incorporated into OSI June 2011

Strategies

ADDRESSING THE CHALLENGES

Leveraging Knowledge/ Resources

- Utilize finite resources strategically and efficiently and leverage inspection
  - **EMA-FDA Collaboration GCP Inspection Initiative**:
    - Initiated in Sept. 2009 as pilot to:
    - Develop a joint GCP program
      - Plan, coordinate, schedule, and conduct collaborative GCP inspections
    - Establish joint procedures
      - Share information related to drug applications
  - **FDA International Offices:**
    - Provide a platform for inspection of foreign facilities
    - Offices collect & leverage local & regional knowledge

Building Quality

- Build quality in during the planning stages:
  - incorporate quality management approach into clinical studies & their oversight to prevent the critical/errors, and monitor for those errors (perhaps centrally (remotely/real time)) and focus less on the less important matters

Utilize Data Standards

- Encouraging sponsors to utilize data standards to improve analysis and site selection for inspection
- Risk-Based Monitoring and Inspection
  - Using innovative strategies & tools to identify sites for clinical inspection(ex. GCP risk-based site selection tool for clinical inspection)

Science-Based Standards

- Working to converge regulatory standards (to share a common foundation of science-based goals for product safety, quality, and efficacy).
  - Continue to work to converge regulatory standards, processes, and procedures for the pharmaceutical industry(ex. ICH, ICH Global Cooperation Group Members)
- Strengthening regulatory capacity of governments to manage, assess, and regulate drug development (such as providing information, tools, training & exchange programs)

Final Thought

"Wherever you stand, the majority of clinical trials are being conducted elsewhere, and yet we all as regulators use these data to allow or disallow marketing of a product, and physicians and patients use these data to decide to use or not use a medicine."

Fergus Sweeney, EMA

"Today we recognize that to successfully protect U.S. public health, we must think, act, and engage globally. Our interests must be broader than simply those within our own borders."

Margaret Hamburg, FDA Commissioner

Helpful Link

- Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions
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