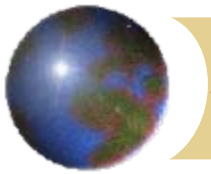


HOW TO REGULATE PHARMACEUTICALS IN A GLOBAL VILLAGE?

Murray M. Lumpkin, M.D., M.Sc.
Deputy Commissioner
International Programs
U.S. Food and Drug Administration

College ter Beoordeling van Geneesmiddelen
Utrecht
08 June 2011

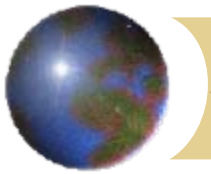




Murder and Martyrdom of St Lambert of Maastricht



- “Lumpkin” first in 1277 in England amongst wool traders from Flanders
- Pet or diminutive form of the personal name "Lambert". St Lambert of Maastricht was object of special veneration.
- Yielded surnames - Lambert, Lampreth, Lambkin, Lampkin, Lumokin, and Lumpkin.

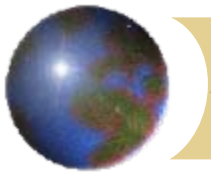


Welcome to the 21st Century

**In the world of sourcing our
pharmaceuticals and clinical trials
data,**

– it's a GLOBAL SUPERMARKET –

and people are shopping everywhere.



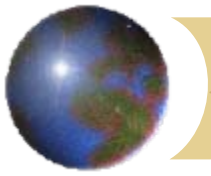
The Facts of Globalisation

- Our regulated products are global commodities
- The clinical and manufacturing data bases that support these products have global pedigrees
- Company messages and regulatory submissions about these products are global, whether intended to be or not

- **Bottom line:**

Medical product discovery, development, manufacturing, authorisation, marketing, promotion, and use by consumers, practitioners, and patients in geographic *isolation* simply does not exist in the world of the 21st century.

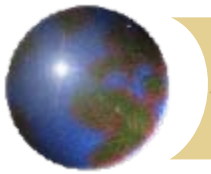
Therefore, regulation of these products cannot occur in geographic isolation.



Globalisation

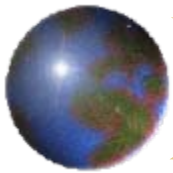
Themes You've Heard

- **Globalisation and the global supermarket for regulated pharmaceutical products have multiplied the scale of regulators' responsibilities and the challenges we face.**
- **They have created unique regulatory challenges for regulators globally – how do we all operate in and contribute to the global regulatory enterprise and help protect and promote the public health of our citizens?**

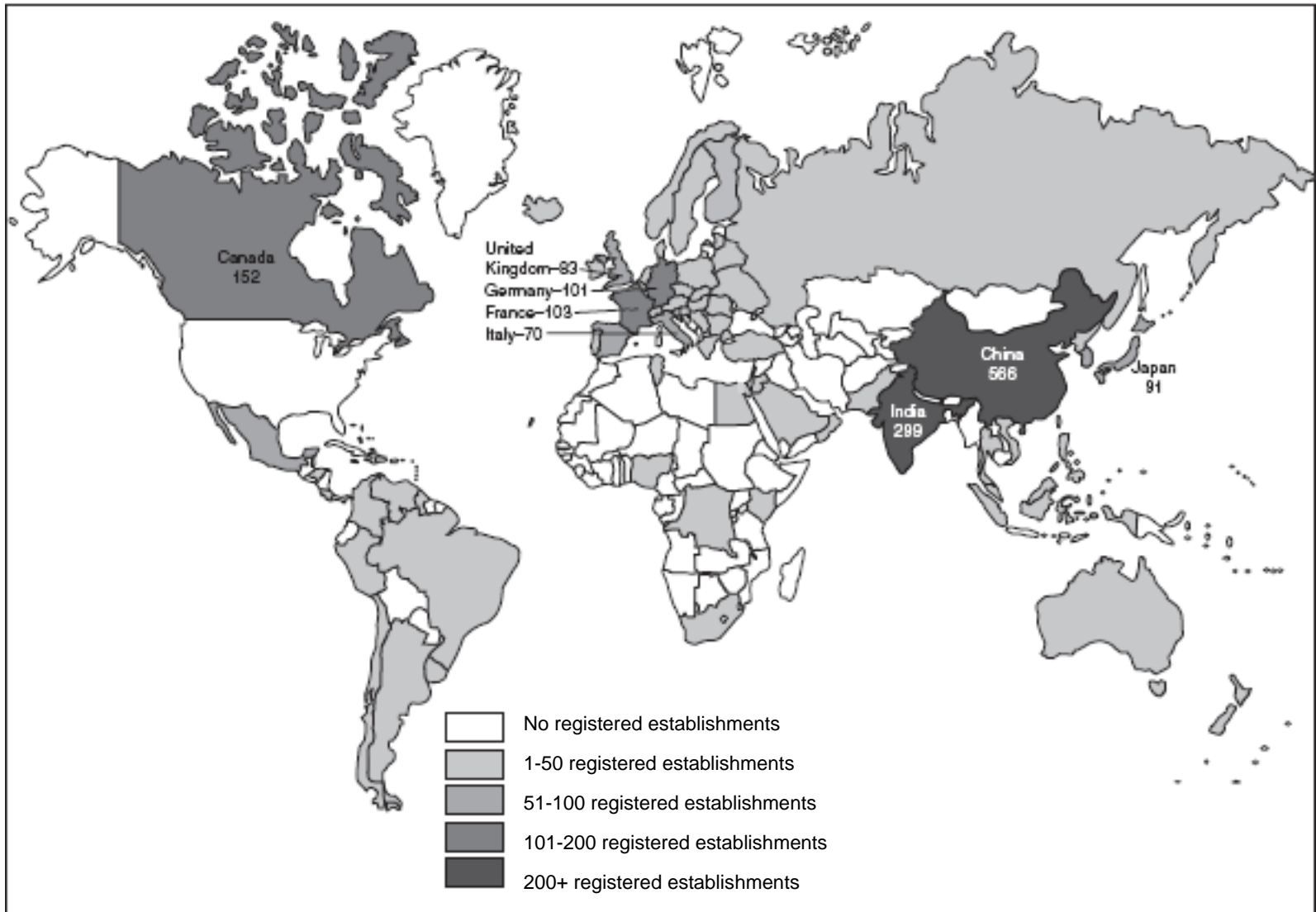


- **The United States, for example, imports annually approximately US\$2 billion worth of FDA-regulated products:**
 - ❑ **150 countries**
 - ❑ **130,000 importers**
 - ❑ **300,000 foreign establishments**
 - ❑ **300 U.S. ports-of-entry**

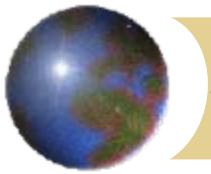
- **Many of these (primarily foods and OTC drugs) have no pre-market authorisation requirement.**



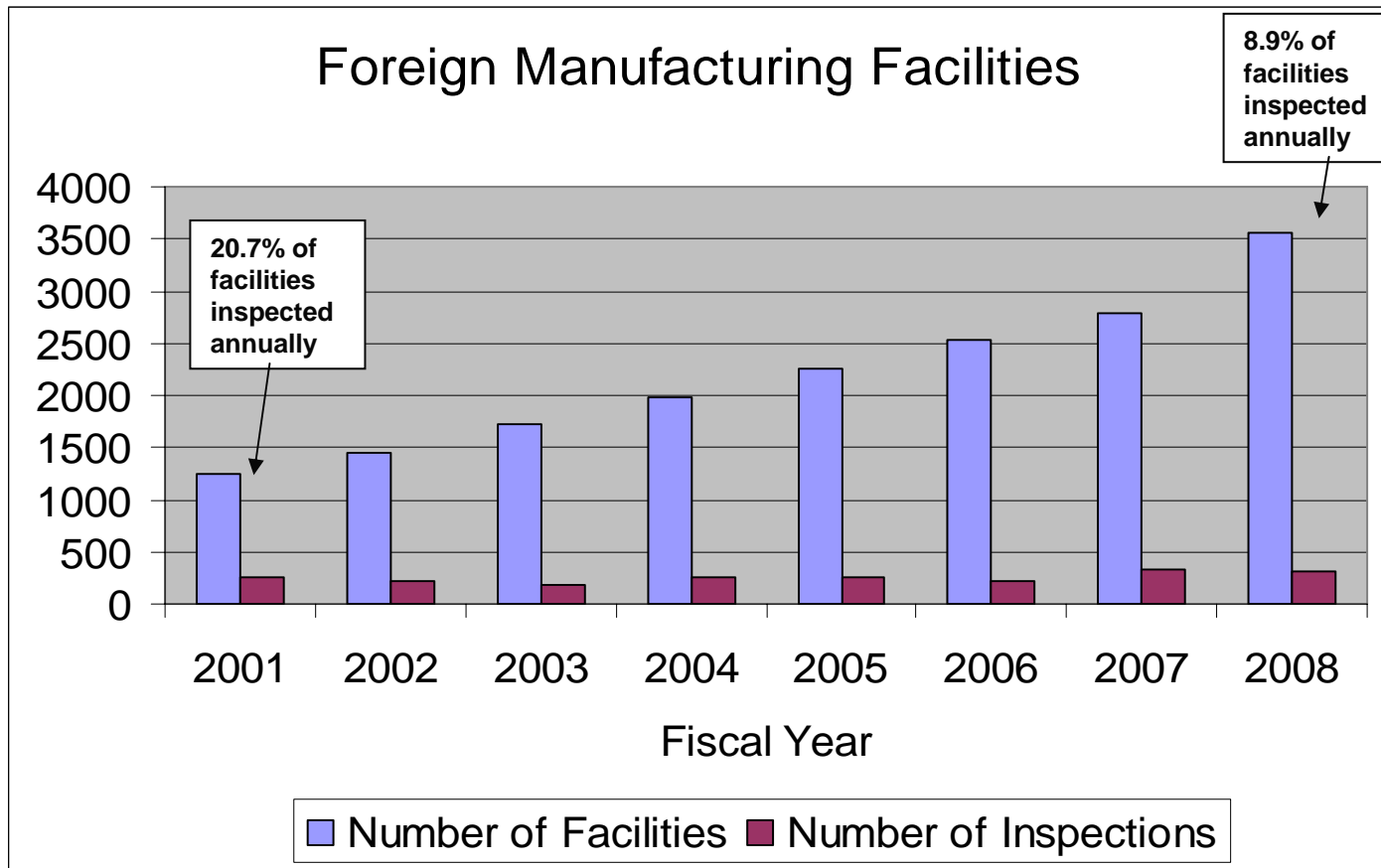
Challenges of Globalization: Many Drugs Are Produced Abroad



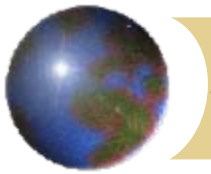
(Source: GAO Report 08-224T on Drug Safety. Foreign firms registered to manufacture drugs for the U.S., FY2007)



Industry trends in foreign manufacturing



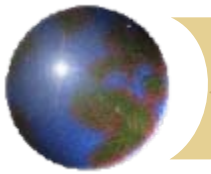
- Foreign facilities have grown by 185%
- Inspections have increased by 23%
- Inspection rate has dropped by 57%



The Global Supermarket

The Common Challenges

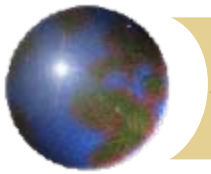
- **More foreign facilities and clinical trials sites supplying primary data for US and EU marketing applications**
- **Increasing volume in our domestic markets of imported finished products and components – both traditional imports and internet imports**
- **More outsourcing of manufacturing and clinical trials to foreign entities not historically engaged with FDA and EU**
- **IT systems and data to have accurate inventory controls**
- **Greater complexity in supply chains and in manufacturing processes for newer products**
- **How do we assure that quality is “built in” – can’t inspect quality in**



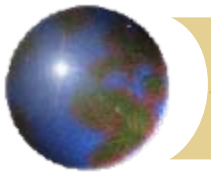
The Global Supermarket

The Common Challenges

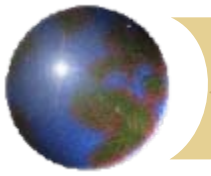
- **Increasing products and data coming from countries with less developed regulatory systems and little ability to provide the regulatory oversight needed to assure the safety of products or robustness of clinical data exported from their country.**
- **Lax oversight in many foreign locales presents opportunities for contamination, falsification, or production of other substandard products because of economic “gain” by cutting corners**
- **Cargo and warehouse theft – domestic and foreign**
- **Helping assure drugs to meet needs where market forces don’t – domestically and internationally**



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

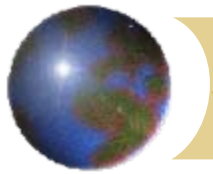


This shift has significant implications for how regulators operate and for what is needed to maintain a secure, stable drug supply domestically and internationally



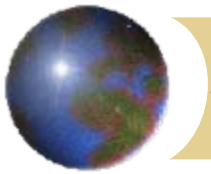
Regulators' Current International Lens

- **Fundamentally missioned as *domestic* public health protection and promotion agencies**
 - ❏ *this hasn't changed*
 - ❏ *how do we focus on our domestic mission while thinking and acting and engaging globally without appearing self-serving, self-centered, or arrogant*



Regulators' Current International Lens

- **Pharmaceutical Regulators are not missioned or funded as development agencies**
 - ❏ *but not everyone understands this*
 - ❏ *how can we leverage our meager resources with development agencies and others to actually leave a capacity building footprint (technical expertise to the table -> translate it)*



21st Century Health Care Systems

● Three pillars:

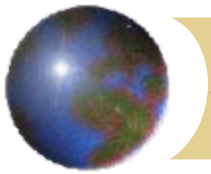
- ❑ **21st century personnel**

- ❑ **21st century regulatory authority**

 - **Underfunded / under-appreciated**

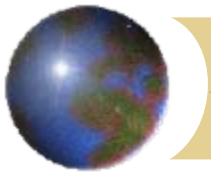
 - **Maintains the quality of the tools the other pillars use**

- ❑ **21st century infrastructure**



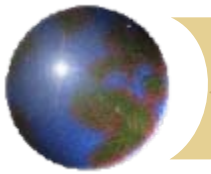
Implications for Regulators

- **Maintaining a high-quality pharmaceutical supply – when a great deal of the process is beyond one's own borders**
- **Dealing with evidence of drug bioavailability, safety, and efficacy that has been collected from sites all over the world**
- **Our changing, evolving roles – specific and implicit - in the global environment in which we work**



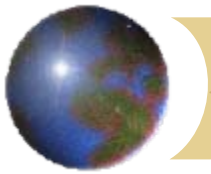
Implications for Regulators

- **Continuing lack of adequate resources to perform all of the tasks expected of us, especially in a time of economic challenges**
- **Changing views within our larger communities on expectation from regulatory authorities**
 - ❏ **Especially with respect to comparative efficacy in our decision-making processes**
 - ❏ **Changing from an ASSESSOR of knowledge to a GENERATOR and COMMUNICATOR of knowledge**



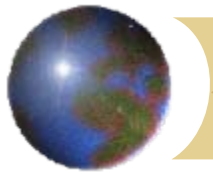
Way Forward

- **In order to accomplish our mission and be even more effective at home today we have to engage more effectively abroad**
 - ❏ *but what we need to do, we cannot do alone*
 - ❏ *what are the appropriate metrics by which we measure the domestic impact of our international work*



International Engagement

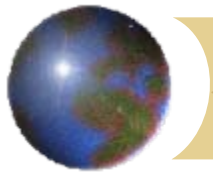
- **International engagement is no longer discretionary; it is an integral, daily part of how we accomplish our domestic mission – part of global regulatory community**
 - ❏ *explore ways to get recognition of value added to their daily work*
 - ❏ *how do we get from “receiving” information from trusted regulators to “relying” on the information to make our own regulatory decisions – true leveraging / work sharing – next big hurdle – go from “confidence building” to “confidence in”*



Current Engagements:

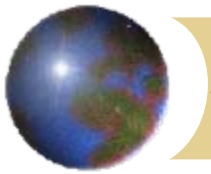
Why we are able to do them

- **Shared commitment to public health**
- **General agreement on the underlying principles of efficacy, safety, and manufacturing quality as the criteria for product market authorisation**
- **Fairly common statutory missions**
- **Not like some commodities where culture and trade dominate, rather than science and public health**



International Engagement Better Information

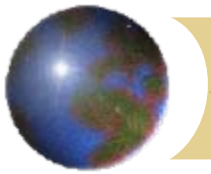
- **Through several broad initiatives, many of which are specific to certain areas, *obtain better and more robust information* to help officials make better entry decisions about the products that are presented for marketing in and entry into our countries**



International Peer-to-Peer Engagement

Leveraging of Resources

- **Bilateral and multilateral efforts to *leverage* the human, scientific, financial, and inspectional resources of and the knowledge and experience of other key regulatory authorities and others so as to avoid duplication of effort, to make our activities more efficient, and to allow us to focus our limited resources on higher-risk areas of concern.**



International Engagement Styles

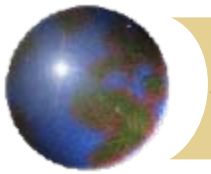
- **Bilaterally**

- **Multilaterally**

- ▣ **Multilateral International Organizations**

- ▣ **Harmonization Initiatives**

- ▣ **Product Specific Regulatory Coalitions**

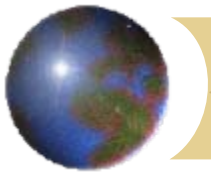


FDA's Collaborations (Agreements)

- **Over 100 bilateral agreements**

- **Confidentiality Commitments**
 - ❑ **20 Countries**
 - ❑ **European Commission (DG - SANCO)**
 - ❑ **EMA and EFSA**
 - ❑ **EDQM**
 - ❑ **World Health Organization (drugs / biologics)**

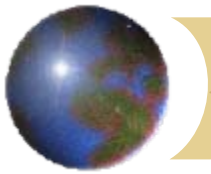
- **Most tools for information exchange; others developed affirmative collaborations.**



Confidentiality Commitments

(counterpart agencies in)

- **Australia**
- **Austria**
- **Belgium**
- **Brazil**
- **Canada**
- **Denmark**
- **EDQM**
- **EFSA**
- **EMA**
- **EU – SANCO**
- **France**
- **Germany**
- **Ireland**
- **Israel**
- **Italy**
- **Japan**
- **Mexico**
- **Netherlands**
- **New Zealand**
- **Singapore**
- **Sweden**
- **Switzerland**
- **South Africa**
- **United Kingdom**
- **World Health Organization**

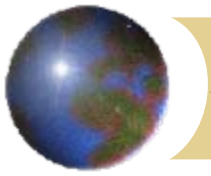


Confidentiality Arrangements

● Legal Framework

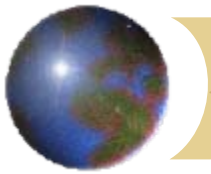
- ❑ Commercial confidential
- ❑ Pre-decisional
- ❑ Investigative – compliance
- ❑ **NOT** Trade Secret

- ❑ **NO** requirement to exchange anything



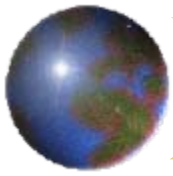
Specific Initiatives

- **Depends on agency and issue being addressed**
 - ▣ level of capability,
 - ▣ history of interactions,
 - ▣ level of confidence
 - ▣ bilateral vs. unilateral benefit
 - ▣ is the juice worth the squeeze?
- **API with TGA and EMA**
- **GCP with EMA**
- **Paediatric product development plans with EMA, Health Canada, and Japan's PMDA**
- **EMA and EFSA personnel embeds at FDA (and vice versa)**



Product Specific Regulatory Coalitions

- **Summit of Heads of Medicines Regulatory Agencies**
- **Medicines Regulators Forum (ICH fringe)**
- **ICDRA (WHO)**
- **ICCR (cosmetics)**
- **Vaccine Regulators Forum (WHO)**
- **Paediatric Medicines Regulators Forum (WHO)**
- **Combination Products Coalition (medicine/device)**
- **Medical Devices Regulators Coalition**
- **Tobacco Regulators**
- **PIC/S (GMP Inspectorates)**
- **Special Cooperative Agreements with WHO and OIE**



Harmonisation Initiatives

● Technical Requirement Harmonisation Bodies

- ICH

- VICH

- ICCR

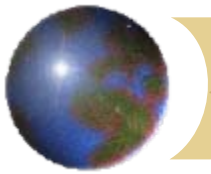
- GHTF

- Codex Alimentarius



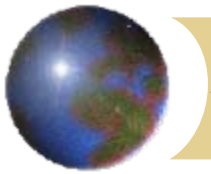
HARMONISATION: WHAT

- **Technical Requirements**
- **Study Designs**
- **Endpoints**
- **Assessment Tools and Metrics**
- **Analytical Tools**
- **Statistical Approaches**
- **Application Content and Format**



HARMONISATION: WHAT NOT

- **Assessment of Local Risk tolerance**
- **Availability and Use of Local Risk Management tools**
- **Dictated by local medical practice, cultures, and laws**
 - **Not uncommonly dissimilar**
- **Can lead to dissimilar regulatory decisions – and that's ok, if these are the reasons!**



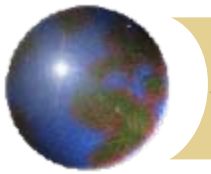
Harmonisation of Standards

- **Global industry sees various standards and inconsistencies worldwide**
- **Huge progress has been made in ICH—needs to keep widening the circle as other regions/areas of industry mature**
- **Regulators also need to align implementation of established standards—a huge challenge**



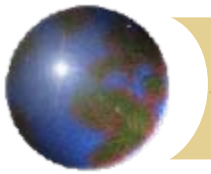
FDA Foreign Posts

- **Response to the Problems of 2007**
- **Special Congressional Appropriation in 2008**
- **Stood up from zero in 12 months**
- **Now mandated in FSMA**
- **Chosen strategically based on problems in the past and on ability to leverage expertise and to build on past experiences**



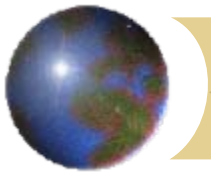
FDA In-Country Presence Locations

- **China – Beijing, Shanghai, Guangzhou**
- **India – New Delhi, Mumbai**
- **Latin America – San Jose, Santiago, Mexico City**
- **Europe – Brussels, EFSA / EMA (FDA embeds)**
- **The Middle East - Amman**
- **South Africa – Pretoria**



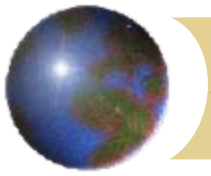
Breakdown of New Hires

- **Senior Technical Experts in foods, medicines, or devices**
- **Inspectors with expertise in either food/feed or medical products**
- **Locally employed staff**



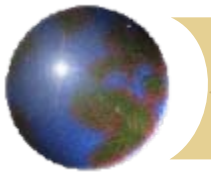
Present In-Country Focus Better Collaboration

- **Through several broad initiatives, many of which are specific to certain areas, initiate and strengthen areas in which we can better collaborate with our counterpart agencies and engage with export industries**
- **Have people in-country whose “full time, day job” it is to foster these relationships and to champion these efforts**



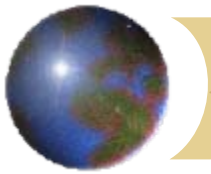
FDA In-Country Presence: Activities

- **(1) Working with counterpart agencies in-country / full time focus on the country's issues / championing agreed initiatives**
- **(2) “Environmental scanning” to gather better knowledge about issues that may affect the quality and availability of products to be exported to the US → Analytical papers**
- **(3) Engage with mature counterpart agencies overseas to leverage/create synergies with scientific, inspectional, and other resources**



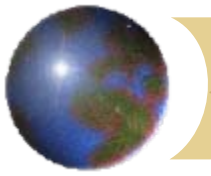
FDA In-Country Presence: Activities

- (4) When requested, engage with counterpart agencies in specific technical cooperation projects
- (5) Engage private- and public-sector *trusted third parties* to provide helpful information about regulated industry compliance with FDA standards (third party auditors)



FDA In-Country Presence: Activities

- **(6) Engage with *regulated industry* to provide greater information about expectations and standards for their products to be admitted to the USA**
- **(7) Engage with *USG agencies already in-country* with complementary missions**



FDA In-Country Presence: Activities

- (8) Have the capacity to perform *more overseas inspections of high risk facilities*



Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

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

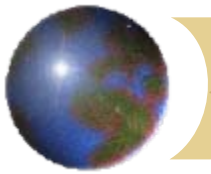


Daniel R. Levinson
Inspector General

June 2010
OEI-01-08-00510

Findings: In FY 2008

- 80% of approved marketing applications contained data from foreign clinical trials
- NDAs contained data from 200,000 patients at > 6500 sites outside the US.
- FDA inspected only 1.2 % of clinical trial sites
 - 1.9 % of domestic sites
 - 0.7 % of foreign sites
- Challenges to conducting foreign inspections inhibit FDA's ability to monitor foreign trials



European Union 2005-2009

- **39% of clinical trials data in MAAs came from within the EU**
- **44,000 patients in 89 countries**

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



Use of Foreign Data to Support Marketing Applications in the USA

- **Governed by 21 CFR 314.106 and 21 CFR 312.120**

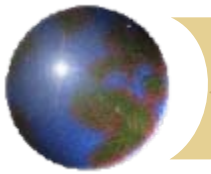
- ❏ **FDA able to validate data through on site inspections**

- ❏ **Clinical investigators with recognized competence**

- ❏ **Conducted in accordance with GCPs, including independent ethics board review, approval, continuing oversight**

- ❏ **Applicable to the US population and US medical practice**

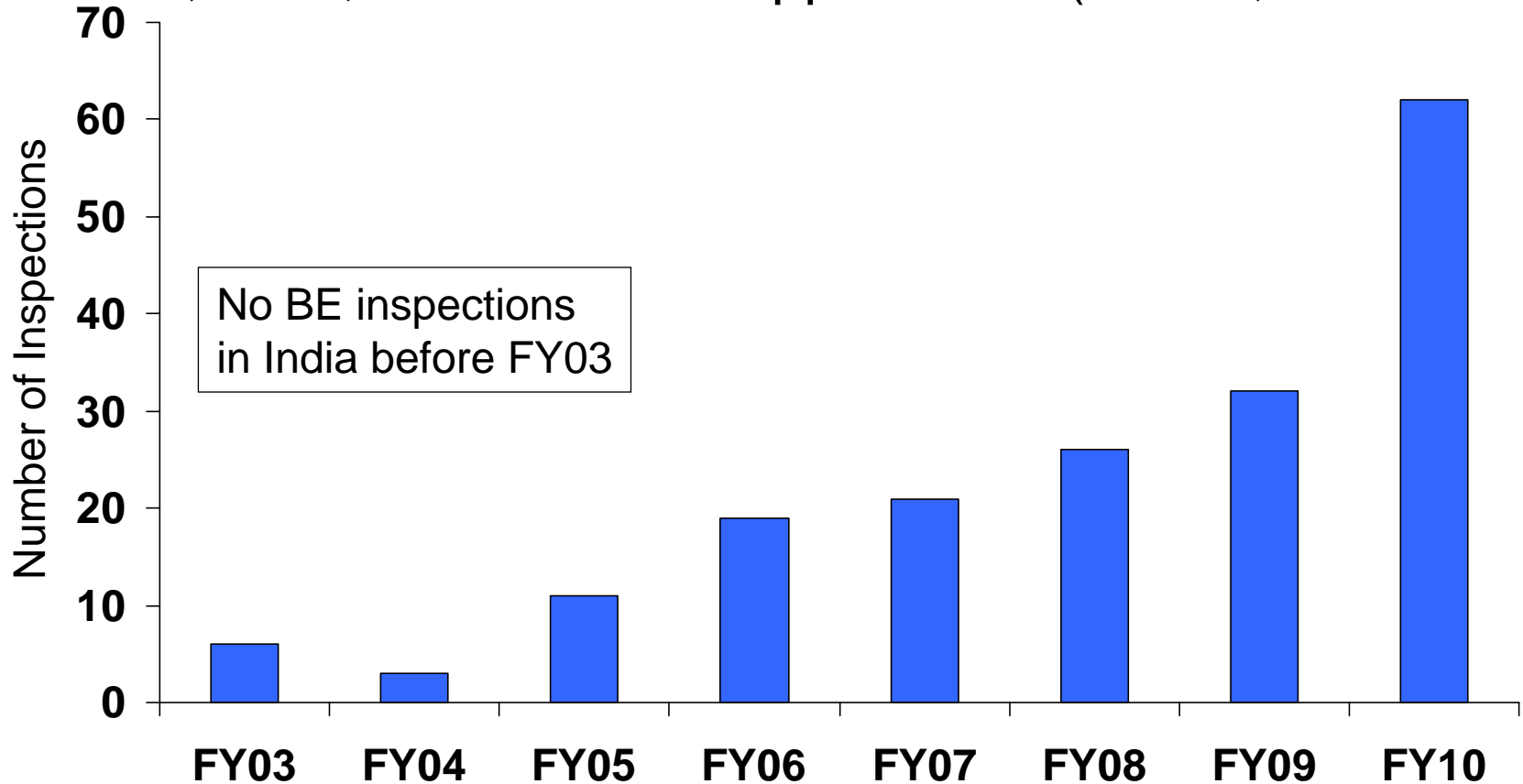
- **Do not have to be conducted under a US IND**



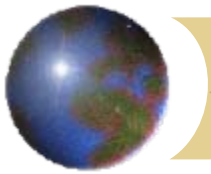
Increased BE/BA Inspections* in India

Clinical and analytical sites

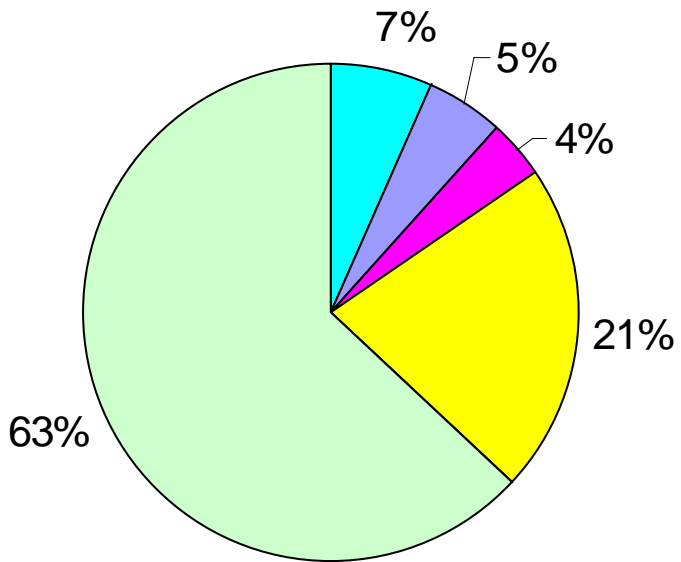
ANDA, NDA, and PEPFAR applications (CDER, FY 03-10)



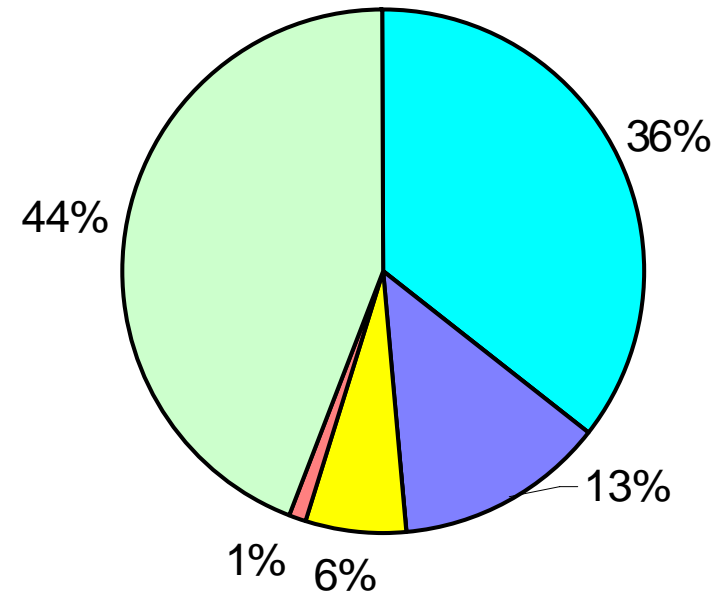
*Based on Inspection Start Date - Each application is counted as an inspection - Several applications may be covered during a single site visit
[BE Database 1/21/2011]



BE/BA Inspections* by Location (CDER, FY 03 vs. 10)



2003



2010

*Based on Inspection Start Date - Each application is counted as an inspection – Several applications may be covered during a single site visit
[BE Database 1/21/2011]

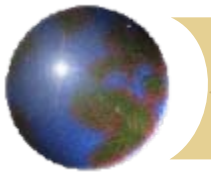


Global Coverage of FDA CDER GCP

Inspections*

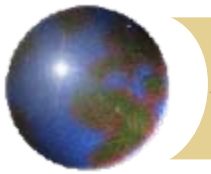
Argentina	30	Estonia	6	Latvia	9	Romania	10
Australia	5	Finland	3	Lithuania	2	Russian Federation	79
Austria	10	France	46	Malawi	1	Serbia and Montenegro	2
Bangladesh	1	Georgia	1	Malaysia	2	Singapore	1
Belgium	16	Germany	53	Mexico	22	Slovakia	2
Brazil	23	Ghana	1	Mongolia	1	South Africa	24
Bulgaria	7	Greece	4	Morocco	1	Spain	10
Canada	83	Guatemala	1	Netherlands	10	Sweden	7
Chile	9	Hungary	15	New Zealand	1	Switzerland	4
China/Hong Kong	20	Iceland	1	Norway	7	Taiwan	2
Colombia	3	India	23	Panama	1	Thailand	8
Costa Rica	5	Ireland	1	Paraguay	1	Tunisia	1
Croatia	13	Israel	2	Peru	8	Turkey	7
Czech Republic	15	Italy	27	Philippines	6	Ukraine	12
Denmark	14	Japan	6	Poland	58	United Kingdom	44
Ecuador	1	Kenya	1	Portugal	2	United Rep of Tanzania	1
Egypt	1			Republic of Korea	8	Zambia	1

*Conducted for FDA/CDER from FY2001 through FY2010; total: 802 – Source DSI Database, [1/21/2011]



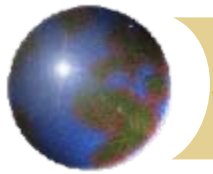
Ethical Issues

- **Ethics committees – especially on-going oversight, conflicts of interest, and documentation**
- **Individual ethics versus population ethics**
- **How does one define “standard of care” and what if it is “no treatment” because therapies are not available**
 - **Can we use data from a trial design considered ethical in another setting that would not be considered ethical in ours?**



Ethical Issues

- **How does one define legitimate “consent” in many social contexts different from one’s own**
 - ❏ **Where men and women have different legal rights**
 - ❏ **In societies that are hierarchical with “elder” decision- making models**
 - **In societies with high levels of illiteracy**
- **What constitutes “coercion” in situations where access to “standard” medical care is limited to non-existent**
- **What is the perspective by which this is judged – local or reviewing authority**

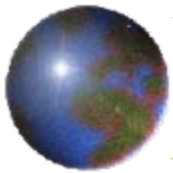


“Smarter” regulation:

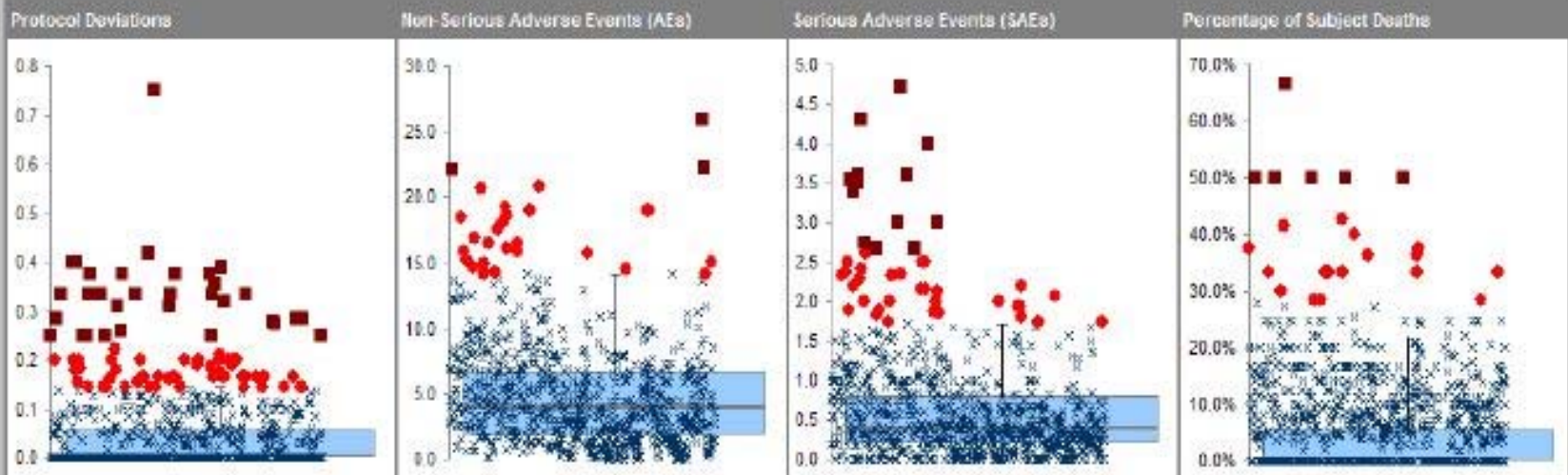
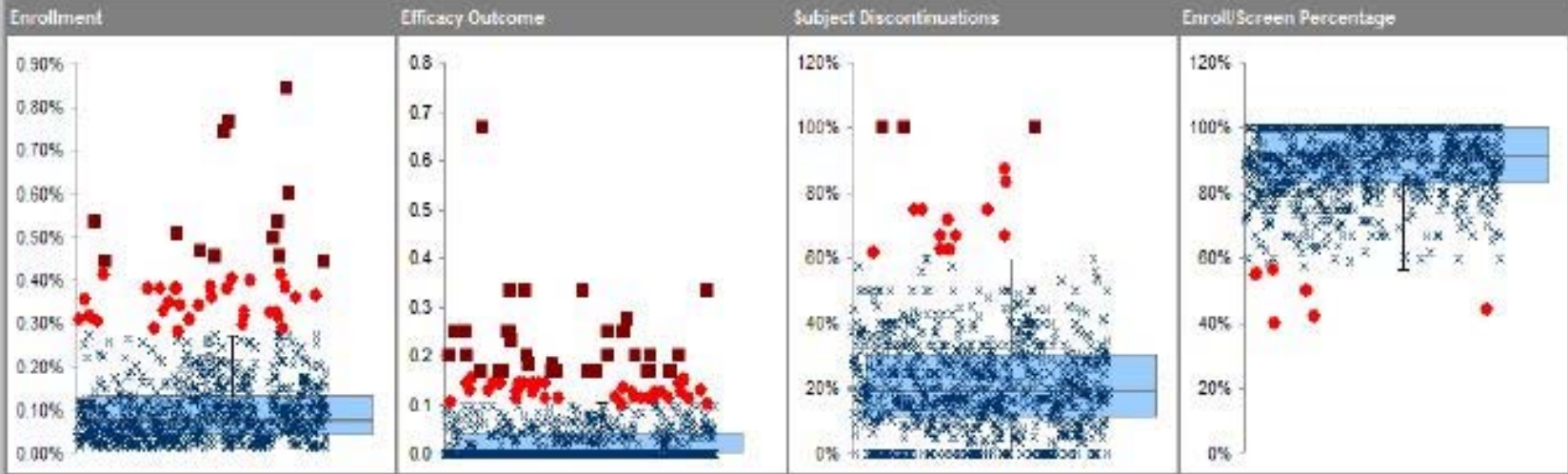
Focus on areas with maximum impact to public health

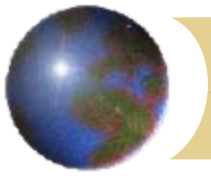
✚ Risk-based oversight

- Site selection tool for clinical trials sites, ethics committee, and bioequivalence studies**



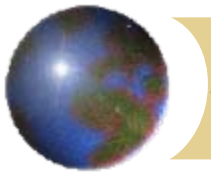
Site Selection Tool for GCP Inspections



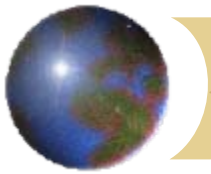


What We've Learned

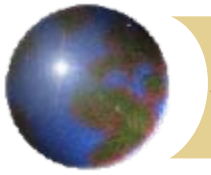
- **None of us has the financial, human, or scientific resources to do all that our parliaments and people ask and expect of us**
- **Cannot meet our mission by only looking within one's own borders**



- **No national or regional regulatory authority has a monopoly on good science or good regulatory practices.**
- **The sum of our parts (as regulatory authorities) is clearly superior to their individual value.**



- **Regulatory cooperation is no longer discretionary.**
- **Regulatory cooperation must become the standard operating procedure of 21st century medicinal and food products regulatory authorities**



Dank U zeer!