Regulatory, Scientific, and Ethical Issues in the Global Harmonization of Clinical Trials

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Society of Clinical Trials
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AGENDA

- The Facts of Globalization
- The Challenges of Globalization
  - Clinical Trials Data
- The Regulatory Response
The Fact of Globalization

- FDA-regulated products are a global commodity
- The databases that support these products are a global resource
- The company messages and regulatory submissions about these products are global, whether intended to be or not

Bottom line:
Medical product discovery, development, manufacturing, authorization, marketing, promotion, and use by consumers, practitioners, and patients in geographic isolation simply does not exist in the world of the 21st century.
Fact of Globalization

- In the world of sourcing our food and drugs and clinical trials data, – it’s a GLOBAL SUPERMARKET – and people are shopping everywhere.

- In 2007, the United States imported more than $2 billion worth of FDA-regulated products, from roughly 200 countries or territories, using 130,000 importers, through over 300 U.S. ports-of-entry.
The Challenges of Globalization

- Globalization presents patients, practitioners, regulators, and companies with both positive opportunities and negative challenges.

- The challenges are consuming an ever larger amount of regulators’ time and effort.
**Number of Phase III Trials Started in 2008**

*CAGR*= Compound annual growth rate

**Source**: www.clinicaltrials.gov.

India’s Phase III is growing seven times faster than the global average.
Clinical Trials

- Cost
  - Cost per patient

- Cost
  - Time of accrual
  - Number of treatment naïve patients

- Cost
  - Competition in Quality site available
Off-Shoring To Reduce Costs of RCTs

**Overall Indexed Clinical Trial Costs**

Within the next 3 years, up to 65% of clinical studies in FDA regulatory submissions will be conducted outside the US.

- RCT results depend on:
  - drug
  - study design
  - study conduct
  - subgroups
  - local culture

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Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)
Annual Growth in Clinical Investigations (by country)

41% of principal investigators in FDA regulatory submissions were based outside the US (2007)

Dr. Ken Kaitin, Tufts Center for the Study of Drug Development (2008)
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 if needed
- 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
CDER Clinical Investigator Inspections – Intl* FY 2000–’08

*Based on Inspection Start Date
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*Conducted for FDA/CDER from 1980 through 08/4/08; total:889

**data reviewed in U.S.
Drugs GCP Inspection Experience By Region

1980-2008
n=889

17%

15%

45%

11%

11%

7%

11%

12%

12%

31%

31%

1%

4%

*CI inspections performed for CDER

2006-2008
n=252

11%

3%

12%

11%
GCP Compliance in U.S. and International Inspections (2008)

- United States: n=303
  - NAI: 49%
  - VAI: 41%
  - OAI: 9%

- International: n=70
  - NAI: 57%
  - VAI: 43%
  - OAI: 0%
Non-U.S. GCP Inspectorates

- European Medicines Agency (EMA)
  - European National Inspectorates
- Health Canada
- Japan’s PDMA
- Korea’s KFDA
- China’s SFDA
- Singapore’s HSA
- Argentina’s ANMAT
- New Zealand, South Africa, Israel
- On the Horizon: India, Jordan, Thailand, Others
EMA: CHMP-Requested GCP Inspections
(Slide courtesy of Dr. Fergus Sweeney, EMA)

INSPECTIONS CARRIED OUT (To Sep 2008)
Present Impacts

- CGP inspections in all parts of the world
  - Increased resources

- Assessing “qualifications”
  - Increased knowledge of various medical qualifications and medical practice legislation

- Increased interactions with counterpart regulatory authorities around the world, especially if safety issues during clinical trials
  - Confidentiality Arrangements
FDA’s Collaborations (Agreements)

- Over 100 bilateral agreements

- Confidentiality Commitments
  - 19 Countries
  - European Commission (2 different DGs)
  - EMA and EFSA
  - EDQM
  - World Health Organization (drugs / biologics)

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

- Ethical standards, ethics committees, and documentation
  - How does one define “exploitation” and does it disqualify data – individual ethics versus population ethics. Are patients the “end” or a “means to an end”?
  - How does one define “standard of care” and what if it is “no treatment” because therapies are not available
  - How does one define legitimate “consent” in many social contexts different from one’s own
  - What is the perspective by which this is judged – local or reviewing authority
  - Especially when we get to the situation where the great majority of the data come from areas new to the clinical trials arena
Present Impacts

- Relevance of the treated population in the clinical trial to the US population and medical practice

- Intrinsic / Extrinsic factors
  - Not a new issue. ICH E5 has grappled with this for years. (Is bridging the answer to the questions?)

- Comparator products

- Appropriate primary endpoints for desired claims, especially as we get into new biomarkers – must they population validated?

- Underlying illnesses
- Concomitant therapies

- Cultural issues – food, dietary supplements, herbals
An Example of the Type of Problem That Off-Shoring Can Render

**Antiviral Agent:** Pivotal clinical trial enrolled primarily Asians. At baseline, patients had HBV of either genotype B (26%) or genotype C (51%). Viral genotype plays a major role in treatment response. Genotype A is the major genotype in Caucasians.

**Comparability:** what are the differences in response among Asians within the RCT assuming them to be identical?

**Generalizability:** can the efficacy in Asians be extrapolated to those in the USA who were not enrolled in the RCT?

*Fung et al, Hepatology 2004;40:790-792*
Challenges of Globalization

Globalization has fundamentally changed the environment for regulating medical products and the data that support them.

Created unique regulatory challenges for FDA:

- More foreign facilities and clinical trials sites supplying the U.S.;
- Increasing volume of imported products and data;
- More outsourcing of manufacturing and clinical trials;
- Greater complexity in supply chains and clinical trials;
- Imports of products and data coming from countries with less well developed regulatory systems; and
- Greater opportunities for fraud.
Challenges of Globalization

- How do we begin to get an handle on something of this scope – that just keeps on growing?
- How do we get better information to make better decisions?
- How do we focus the historically nationally focused resources we do have?
- How do we leverage resources of others – domestic and foreign?
- How do we go from receiving information from trusted counterparts to relying on information from trusted counterparts?
- How do we go from cooperation with trusted counterparts to confidence in trusted counterparts?
Regulatory Globalization

- Today regulators talk with each other earlier, more often, and more in depth than ever before
- Common mission -- To promote and to protect the public health of our citizens when it comes to the products for which we are responsible within our jurisdictions
FDA-EMA Collaboration

- In August 2009, FDA and the EMA initiated a bilateral GCP pilot initiative that, over the course of the next 18 months will expand GCP information-sharing together, better coordinate inspection planning, collaborative GCP inspections.

- To conduct periodic information exchanges on GCP-related information in order to streamline sharing of GCP inspection planning information, and to communicate timely and effectively on inspection outcomes.

- To conduct collaborative GCP inspections by sharing information, experience and inspection procedures, cooperating in the conduct of inspections, and sharing best-practice knowledge.

- To share information on interpretation of GCP, by keeping each regulatory agency informed of GCP-related legislation, regulatory guidance and related documents, and to identify and act together to benefit the clinical research process.
FDA In-Country Presence
Initial Locations

- China
- India
- Latin America
- Europe – EFSA / EMA / FDA embeds
- The Middle East
Breakdown of New Hires

- **50 US Nationals – new FDA FTEs**
  - 5 Regional/Country Directors
  - 21 Senior Technical Experts in foods, medicines, or devices
  - 9 inspectors with expertise in either food/feed or medical products
  - 15 support personnel at Headquarters (OM, OIP)

- **19 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.

- Have people in-country whose “full time, day job” it is to foster these relationships and to champion these collaborative efforts.
Apertura de las oficinas de la FDA en México
Opening of FDA Offices in Mexico

Mexico, D.F. 15 de Diciembre, 2009
Mexico City, December 15, 2009
Present In-Country Focus
Better Information

Through several broad initiatives, many of which are specific to certain areas, obtain better and more robust information to help FDA officials in the centers and at the borders make better entry decisions about the products that are presented for entry into the US.
THANK YOU

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