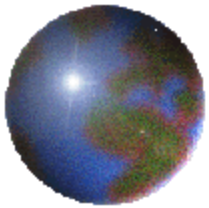

Implementing Ethical Standards in the Context of Global Clinical Trials

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International Programs
U.S. Food and Drug Administration

Presidential Commission for the Study of Bioethical Issues
New York, NY
18 May 2011

FDA – where does it fit in?

- Assess the benefit-to-risk profile of a product based on the totality of the data submitted, including pre-clinical, clinical, and manufacturing process data.
- If the demonstrated benefits of the product outweigh the known risks of the product for the intended population when used as directed, it can be authorized for marketing, provided the manufacturer can produce it consistently in accordance with good manufacturing practices.

FDA

- Scientific validity of the data
- Clinical relevance of the data
- Completeness of the data
- Ethics of the data – we can’t authorize a product based on unethically obtained data

FDA

- What does it mean for the data to have been obtained in an “ethical” manner?
- Was much easier to answer 20 years ago

Globalization of Clinical Research: Realities for FDA

- The proportion of FDA-regulated CIs based in North America has steadily declined from 96% of the total global pool in 1990 to 54% in 2007[1]
- Non-U.S. and multinational studies are an increasing proportion of submissions to FDA
  - In 2007: over 60% of pivotal studies submitted to CDER NDAs contained data from one or more non-US study sites
  - Non-U.S. studies/data are also increasing in biologics and medical device applications

[1] Ken Getz, Applied Clinical Trials, 2009

What the IG Tells Us*

- In FY 2008, sponsors submitted marketing applications to CDER/CBER with over 230,000 subjects enrolled at over 6500 non-US sites in 68 countries
  - Western Europe accounted for 60% of total non-US sites
  - The other 40% was nearly evenly divided:
    - Eastern Europe: 11%
    - Asia/Pacific: 10%
    - Non-U.S. North America: 8%
    - Central/South America: 8%
- IG Study/2010 Report: "Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials"

European Union 2005-2009

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

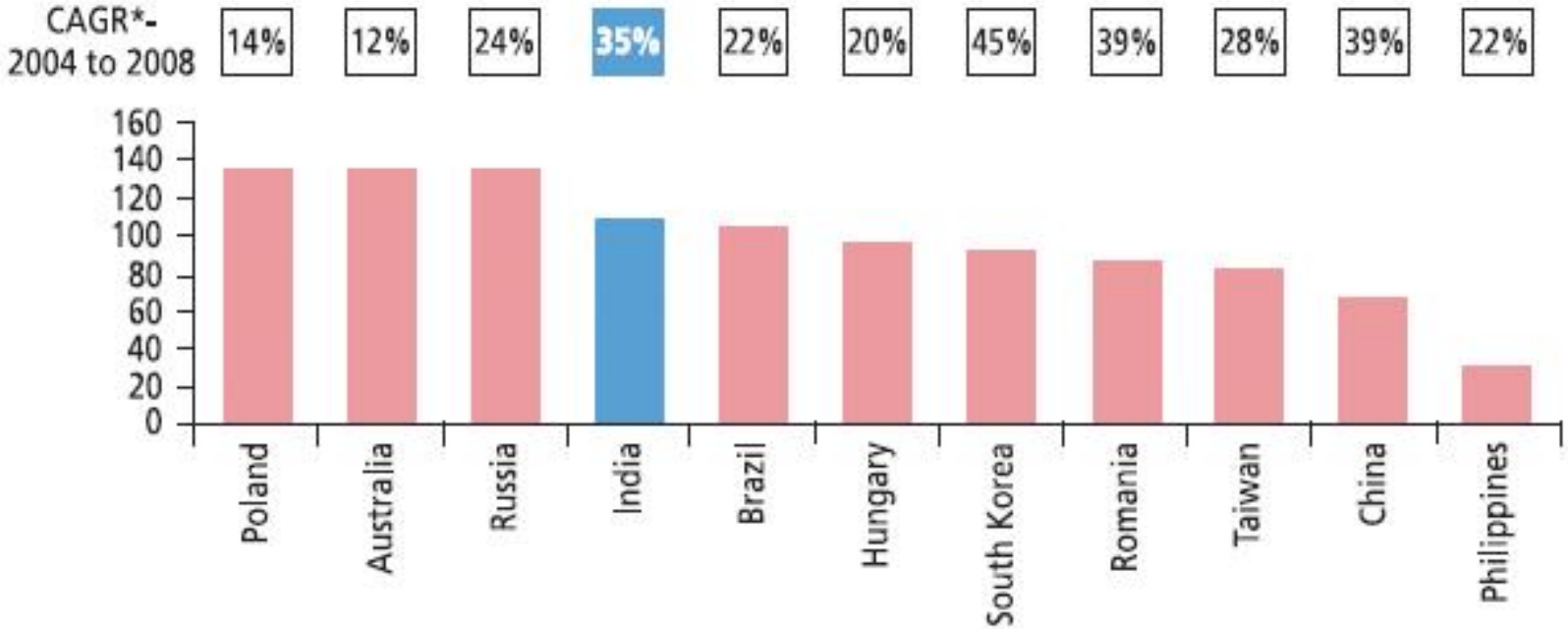
Wherever you stand, the majority of clinical trials are being conducted elsewhere, and yet we all as regulators use these data to allow or disallow marketing of a product, and physicians and patients use these data to decide to use or not use a medicine. Fergus Sweeney, EMA

What the Academics Tell Us*

- Change in Global Clinical Trial Site Distribution (2003-2007)
  - Asia Up 15%
  - Eastern Europe Up 10%
  - Latin America Up 7%
  - Middle East Up 6%
  - Western Europe 0% (No Change)
  - North America Down 4%

- From Fabio Thiers, MIT, "Where are the Clinical Trials Going and Why", Presented to 35th Brazilian Congress of Pharmaceutical Medicine, Nov 2009

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.

Philip Ward, Applied Clinical Trials, Sept 1, 2009

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

312.120

- Rule links to “GCP” and acknowledges GCP as a global standard for conduct of clinical research
- Reflects FDA’s legal/regulatory authority
- Articulates FDA’s expectations for BOTH the quality and integrity of scientific data AND the protection of subjects
- Requires not just certification but submission of descriptions/documentation to FDA (which might be verified on inspection) that studies were conducted according to GCP

Required Descriptions

- Name and address of the IEC and statement that the IEC meets definition in the rule
  - Review panel responsible for ensuring protection of the rights, safety, and well-being of subjects
  - Adequately constituted to provide assurance of that protection
- A summary of the IEC's decision to approve or modify and approve the study

Required Descriptions

- A description of how informed consent was obtained
- A description of what incentives, if any, were provided to subjects to participate
- A description of how the sponsor monitored the study and ensured that the study was carried out consistently with the protocol

ICH GCP: A "First" Unified GCP Standard

- ICH (International Conference on Harmonization): Drugs/Biologics
  - Regulators and Industry from U.S., European Union, Japan – with multiple public consultation
  - WHO, Canada, Switzerland
  - Lengthy process: 1991-1997
  - ICH GCP Consolidated Guideline (May 1997) is "official" FDA guidance, published in the FR
  - http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf

The Result: Other Internationally Harmonized GCP Guidelines

- Regionally/globally for drug/biologics studies
  - PAHO/PANDRH (Pan American Network on Drug Regulatory Harmonization) GCP: Document of the Americas (2004)
  - WHO: Handbook for Good Clinical Research Practice (2005)
- For medical device studies
  - ISO 14155: Clinical Investigations of Medical Devices for Human Subjects (2006)
  - [Global Harmonization Task Force (GHTF) for medical devices: May 2007 final document, “Clinical Evaluation”]

International GCP Guidelines: Take-Home Messages

- Each addresses the fundamental expectations of FDA for acceptance of OUS studies/data
- Differences between GCP guidelines are generally minor, reflecting implementation issues/priorities
  - WHO GCP vs. ICH GCP
    - Includes role/responsibilities of regulators
  - Document of the Americas vs. ICH GCP
    - Greater elaboration on Ethics Committees
    - Annex on inspecting clinical investigators

CGP Inspections outside the USA

Algeria**	1
Argentina	35
Australia	10
Austria	11
Bahamas	1
Bangladesh	1
Belgium	28
Brazil	24
Bulgaria	6
Canada	169
Chile	9
China	13
China, Taipei	4
Colombia	3
Costa Rica	8
Croatia	13
Czech Republic	15
Denmark	19
Dominican Rep.	1
Ecuador	1
Egypt	1
Estonia	6
Finland	15
France	62
Gabon	1
Germany	82
Ghana	1
Greece	4
Guatemala	3
Hong Kong	8
Hungary	21
India	18
Ireland	1
Israel	7
Italy	42
Japan	7
Kenya	1
Latvia	9
Lithuania	2
Malawi	1
Malaysia	5
Mexico	25
Morocco	1
Netherlands	31
New Zealand	6
Nigeria**	1
Norway	6
Panama	2
Paraguay	1
Peru	8
Philippines	7
Poland	56
Portugal	4
Romania	9
Russia	76
Serbia	3
Singapore	1
Slovenia	1
South Africa	37
South Korea	8
Spain	23
Sweden	31
Switzerland	2
Tanzania	3
Thailand	7
Tunisia	1
Turkey	6
Ukraine	11
United Kingdom	109
Venezuela	2
Zambia	1

*Conducted for FDA/CDER from 1980 through 12/10; total: 1148
**data reviewed in U.S.

Present Impacts

- Increased interactions with counterpart regulatory authorities around the world
  - Confidentiality Arrangements
  - CGP inspections and training Collaborative Initiatives – esp with the EU
  - Formal CGP training with counterpart agencies in China, Vietnam, southern Africa, Russia, etc
  - FDA permanent staff in 13 overseas posts – started 2009

GCP检查国际培训班
International Training Course For GCP Inspection
主办单位：国家食品药品监督管理局
美国食品药品监督管理局
Organizers: State Food and Drug Administration(SFDA)
U.S. Food and Drug Administration(US-FDA)
承办单位：四川省食品药品监督管理局
Chengdu Sichuan
April 1 2010

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